GLAUCOMA THERAPY

Current Issues and Controversies

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FOREWORD

It is a pleasure to be asked to write a foreword to a new book written by European, Far Eastern and US colleagues who are currently at the forefront of their area of interest. I consider it a compliment to have been asked to do so having been in love with the enigma of glaucomas and its management for over half a century.

It is an even greater pleasure when the book deals with the controversies in the treatment of glaucoma. Without such controversy there would be no progress only stagnation. Controversy arises when traditional thoughts and practices are questioned or when new concepts are challenged. The lack of understanding of the causes, pathogenesis and often the natural history of the diseases underlies what seems controversial. Research generating new knowledge then resolves most these controversies.

Controversy in the treatment of glaucoma can also arise when reputable investigators claiming to do similar studies obtain different results and arrive at different conclusions. A good example of this occurred when timolol the then ‘magic glaucoma potion’ was found, in almost identical studies, to favourably influence glaucomatous progression by some and yet not by others in spite of the excellent pressure reduction in all of the studies. The natural history of the disease nor its risk factors were not known at that time nor was the concept that there maybe individuals who have a pressure dependent glaucoma while others have a similar clinical picture which is much less dependent, or even totally independent, of intraocular pressure. It might easily have happened that 60% pressure sensitive individuals were recruited by chance in one study and only 40% of such individuals in the other which would have resulted in the controversy. Now that the natural history of the chronic glaucomas is better understood the likely causes of the controversy can be easily explained and understood.

I am impressed by many of the authors who were chosen to highlight the new and old controversies in the book. I look forward to reading what they have to say.

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1. ALTERATIONS OF THE OPTIC NERVE IN GLAUCOMA

Selim Orgül

Introduction

Historically, the term glaucoma has been used to describe conditions associated with increased intraocular pressure (IOP) leading to optic nerve and visual field damage. Today, because not all patients with increased IOP suffer from neuronal damage, and not all patients with glaucomatous optic neuropathy have an increased IOP, the term glaucoma refers to a syndrome of retinal ganglion cell loss manifested as retinal nerve fiber bundle loss and excavation of the optic nerve head with corresponding visual function defects. Morphological alterations of the optic nerve in glaucoma have long been described. Today, because of the perspective to identify the disease or the progression thereof earlier than by means of functional loss assessment,1 major efforts are being invested into the development of techniques that can quantify the clinical alterations of the optic nerve in glaucoma.2–10 Even more vivid is the research in the field exploring the pathway leading to the observed changes. A higher awareness of these mechanisms may enhance our understanding of the pathophysiology of glaucomatous optic neuropathy and foster the development of new therapeutic modalities.

Clinical changes

The various clinical alterations at the glaucomatous optic nerve head (ONH) can be appraised by quantitative methods, such as vertical cupping and neuroretinal rim loss, or qualitatively, for example by vessel baring, notching, retinal nerve fiber layer (RNFL) loss and disc hemorrhage. Clinical experience teaches that, without the help of sophisticated technical means, qualitative morphological criteria have a higher diagnostic power compared to quantitative criteria.

The essence of glaucoma is a chronic loss of ganglion cell axons.11 This loss must be distinguished from a physiologic decrease in nerve fibers with advancing age.1 Physiologic loss of retinal nerve fibers does not seem to alter markedly the aspect of the ONH cupping.12–14 Based on clinical features of the ONH in glaucoma, four major types of disc
damage have been defined: the focal ischemic disc, the senile sclerotic disc, the myopic disc, and the disc with a generally enlarged cup.15

Peripapillary atrophy

As well as ONH alterations, peripapillary changes have been described in glaucoma, but seem not to occur in other optic neuropathies.16 Peripapillary atrophy is characterized by a region of atrophy of the retinal pigment epithelium, centrally, adjacent to the scleral ring, the beta zone, and a region of pigment mottling, lying more peripherally, the alpha zone (Figure 1.1). Many studies have confirmed that peripapillary atrophy, especially the beta zone, can increase in glaucomatous optic neuropathy17 and that peripapillary alterations may even precede functional loss in patients with ocular hypertension converting to glaucoma.18,19 It may also be helpful in differentiating normal-tension glaucoma from glaucoma-like discs.20 Even in experimental glaucoma, the development of peripapillary atrophy has been described.21 Careful scrutiny of the published figures in the latter study suggests, however, that the zone where peripapillary atrophy develops can already be outlined on baseline pictures. A possible interpretation hereto is that peripapillary atrophy

Figure 1.1 Peripapillary atrophy is characterized by a central region of total atrophy of the retinal pigment epithelium (the beta zone), and a peripheral zone of pigment mottling (the alpha zone). 1=optic cup; 2=rim of the optic disc; 3=beta zone; 4=alpha zone; 5=scleral ring.
does not develop, but is unveiled during glaucomatous atrophy. This is in line with the observation that histological evidence for peripapillary Bruch’s membrane devoid of RPE (atrophy) can be seen in nearly 90% of non-glaucoma eyes. Furthermore, Curcio et al could not find any evidence that atrophy of the choriocapillaris may precede peripapillary atrophy of the retinal pigment epithelium. These observations suggest that peripapillary atrophy simply reflects neuronal atrophy and connective tissue alterations in glaucoma, unveiling pre-existing atrophy of the retinal pigment epithelium. With atrophy of the axons, pre-existing atrophy of the retinal pigment epithelium becomes visible. Interestingly, such an exposure of pre-existing atrophy of the retinal pigment epithelium seems not to occur in non-glaucomatous optic neuropathies, suggesting that part of the unveiling process is also due to structural alterations at the level of the connective tissue.

**Optic disc hemorrhage**

Optic disc hemorrhages (Figure 1.2) are detected in around 4–7% to 20% of eyes with glaucoma, often herald progression in damage, and indicate faster progression of damage compared to eyes without disc hemorrhage. Such a development appears to be independent of the absolute level of IOP. Optic disc hemorrhages are signs of microvascular damage. Close associations between optic disc hemorrhages, retinal vein
**Figure 1.2** Optic disc hemorrhages accompanying a glaucomatous atrophy.
occlusions, and glaucoma,29 between optic disc hemorrhages and high systemic blood pressure,30 and between optic disc hemorrhages and generalized vascular disease31 have been described. A small size of the neuroretinal rim of the ONH seems to be the only clinically identifiable morphologic predictive factor for the development of optic disc hemorrhages.32,33 The pathogenesis of this feature remains, however, unclear. In some cases, disc hemorrhages seem to precede a rise in IOP.25 A likely pathway of optic disc hemorrhage is endothelial damage/dysfunction.34

**Peripapillary arteriolar narrowing of retinal vessels**

Although not exclusive to glaucomatous eyes, a peripapillary focal arteriolar narrowing of retinal vessels35 is seen in nearly half of the affected eyes, where it locates in 90% of the cases to the disc sector with the greatest cupping,36 and correlates in 90% with the presence of a visual field defect in the corresponding superior or inferior hemifield. Although the degree of constriction does not necessarily correlate with the severity of visual field defect,37 an increasing narrowness of retinal peripapillary focal arteriolar constriction appears to indicate progressive glaucomatous optic nerve damage.38 Consequently, this feature may, independently of whether these vascular changes occur primarily or secondarily to glaucomatous damage, be a potential marker of progression.

**Alterations of the lamina cribrosa in glaucoma**

Alterations in a glaucomatous ONH are not limited to neural elements, but also include the surrounding connective tissue, especially the lamina cribrosa. The mechanical properties of the macromolecules of the extracellular matrix of the lamina cribrosa may make this tissue compliant and sensitive to intraocular pressure.39 The cribriform plates of the lamina cribrosa consist of a core of elastin fibers and collagen type III, coated with collagen type IV and laminin. The insertion of the lamina cribrosa in the sclera demonstrates concentric, circumferential elastin fibers that surround the lamina cribrosa and are continuous with the elastin in the cribriform plates. In eyes with glaucomatous optic neuropathy, these characteristics change markedly, including an upregulation of the synthesis of extracellular matrix components such as collagen, proteoglycans, and adhesion molecules.40–53 Histological features of connective tissue in a glaucomatous optic nerve impress, as they would have been caused by direct mechanical compression, for example at the level of the cribriform plates (Figure 1.3). The latter show a disorganized and compressed arrangement and a backward bowing.54 When translaminar pressure is, however, measured at different levels of IOP in dog eyes, no change of the path along which the pressure gradient drops to retrolaminar pressure levels is observed, suggesting an
The lamina cribrosa in glaucomatous eyes, compared to a normal eye impresses mechanical compression has distorted the cribriform plates. An invariable thickness of laminar tissue when IOP is increased acutely.\textsuperscript{55,56} Consequently, rather than due to mechanical compression, the alterations in connective tissue observed in glaucoma are likely to be initiated in response to the local stress, leading to local tissue remodeling. The observation of similar changes in glaucomatous eyes without increased IOP validates this view.\textsuperscript{57}

The tissue remodeling in glaucomatous optic neuropathy results in physical alterations influencing plastic and elastic properties of the connective tissue. In early-glaucoma eyes of monkeys fixed at an IOP of 0 mm Hg, a posterior displacement and thickening of the lamina cribrosa as well as an enlargement of the scleral canal at the level of Bruch’s membrane and at the anterior laminar insertion can be observed.\textsuperscript{58} These modifications seem to be independent of the distensibility of the local tissue. Due to intrinsic distensibility of the lamina cribrosa, some posterior displacement of the lamina cribrosa, but no change in laminar thickness or scleral canal diameter, can be observed in normal eyes, confirming earlier findings in dog eyes. In contrast to this normal compliance, eyes with early glaucoma demonstrate a noticeably more marked distensibility, what Bellezza et al have called a hypercompliant deformation.\textsuperscript{58}

The observed alterations are thought to be largely brought about by activated glial cells (Figure 1.4).\textsuperscript{52,53,59} The alterations seem to be specific to the chronic stress conditions in glaucoma and not secondary to axonal loss. Upregulated matrix metalloproteinases (MMPs), proteolytic enzymes capable of degrading components of the extracellular matrix, may represent the link between glial cell reactivation and remodeling of the lamina cribrosa.\textsuperscript{60,61} Remarkably these changes occur without the formation of a scar tissue. A possible modulator hereof may be tenasin, a large extracellular matrix glycoprotein synthesized by astrocytes during development and wound healing, forming barriers and affecting neurite outgrowth. In human glaucomatous optic nerve heads there is an upregulation of tenasin mRNA and protein in reactive astrocytes. Tenasin may participate in forming a boundary to prevent migration of blood-borne cells or humoral inflammatory mediators into the optic nerve tissue during glaucoma and, thus, prevent scar tissue formation.
Elastin
Proteoglycan
Fibrillar Collagens

Basement Membranes
Tenascin/Other Reactive ECM
Cell Adhesion Molecules

RGC Axons
Normal Astrocytes
Normal ECM

↑ IOP, Ischaemia and Other Factors

Axon Damage
Reactive Astrocytes
Abnormal ECM

New/Modified Gene Expression
Autocrine Paracrine Factors
ECM Synthesis Degradation

Neurotoxic Mediators
Free Radicals
Proteases
Glycogen Reactive ECM
Proteases

RGC Death
ECM Remodeling
Figure 1.4 In glaucomatous optic neuropathy, astrocytes play a major role in the remodeling of the extracellular matrix of the optic nerve head (adapted from Hernandez MR, Pena JDO. The optic nerve head in glaucomatous optic neuropathy. Arch Ophthalmol 1997; 115:389).
Axonal transport in glaucoma

Similar to the central nervous system, a bidirectional axonal flow can be demonstrated in optic nerve axons. An anterograde transport system carries material from the cell body to the axonal terminal, and a retrograde transport system carries material in the opposite direction. The anterograde axonal flow has one fast and one slow component. The materials that are rapidly transported are those involved in synaptic function, while high-molecular-weight proteins and particulate substances that participate in structural maintenance and axonal growth are transported slowly. The velocity of retrograde axonal transport is variable, but it is generally slower than that of the fast component of the anterograde transport. The material that is transported through this system is similar to that transported by the anterograde system. In addition, the retrograde system transports proteins and small molecules that have been picked up at the axonal terminals. Axoplasmic flow is typically altered in glaucoma, leading to accumulation of cellular organelles at the level of the lamina cribrosa. Ultrastructural alterations in axons exposed to high intraocular pressure seem also to be most marked at the level of the lamina cribrosa sclerae, but axonal alterations can even be seen in the optic chiasm.

The pathway leading to blockage of axonal flow in glaucoma has not yet been clarified. The selective location of axoplasmic stasis at the level of the lamina cribrosa indicates an anatomic or a physiologic boundary. The lamina cribrosa delineates the peripheral edge of the subarachnoid space surrounding the optic nerve, and separates anatomically this compartment from the intraocular cavity. Because the two compartments exhibit different levels of pressure, alterations in the pressure gradient around the lamina cribrosa may represent a physical obstacle promoting local accumulation of intracellular elements. On the other hand, the level of the lamina cribrosa coincides with the zone of abrupt decrease of axonal density of mitochondria in the optic nerve, compared to the retina. The inverse relationship between myelination and mitochondrial distribution in optic nerve axons indicates that cellular elements may accumulate at the level of the lamina cribrosa in case of lack of oxygen.

Comparably to direct damage to the optic nerve inducing retrograde degeneration and apoptosis of the retinal ganglion cell bodies in mammals, chronic hindrance of axonal flow such as that occurring in glaucoma also leads to retinal ganglion cell death. The mechanisms that mediate the response of the neuronal cells to the axonal injury are still unknown. Antagonizing axon guidance molecules opposing axonal flow or replacing neurotrophins normally conveyed to the ganglion cell bodies favorably influence the fate of agonizing retinal ganglion cells. However, the observation of the chronology of events in rat eyes with increased IOP suggests that glial responses precede blockage of axonal flow, and that the hindrance of supply with neurotrophic factors is not the primary driving mechanism in glaucomatous atrophy.
Apoptosis in glaucoma

Apoptosis is a form of genetically programmed cell death that can be induced by a variety of different stimuli. It is often referred to as a form of cellular suicide. Typically, apoptosis is characterized by the condensation and shrinkage of the cellular nucleus and cytoplasm, followed by the complete fragmentation of the cell and subsequent phagocytosis of the debris by surrounding cells. Important during development and for the maintenance of homeostasis in some adult tissues, apoptosis is also associated with disease processes such as glaucoma. The goal of research in cell death mechanisms is to identify pharmacological means to protect retinal ganglion cells from degeneration regardless of the elevated IOP. Various approaches of pharmacological neuroprotection can be envisaged including supplying neurotrophic factors, inhibiting apoptosis, antagonizing excitotoxicity, and inhibiting the generation of neurotoxic molecules. A further approach might be boosting a protective, controlled autoimmune reaction. The clinical value of neuroprotective therapeutic strategies in human glaucoma needs still to be ascertained in clinical trials. However, an unquestionable prerequisite for such studies warrants adequate methods to evaluate progression of damage.

A potential trigger for apoptotic retinal ganglion cell death in glaucoma could be an autoimmune reaction. Arguments in favor include the following: astrocytes, which express MHC class II antigens, may function as antigen-presenting cells; elevated serum antibodies against retinal heat shock proteins can be measured in glaucoma patients; expression of heat shock proteins is increased in neuronal and glial elements of the retina and optic nerve of glaucomatous eyes; exogenously applied heat shock proteins at concentrations similar to those found in glaucoma patients facilitate apoptotic cell death. These studies suggest that, somehow, heat shock proteins, which normally serve to protect cells from damage, may become immune targets involved in the progression of the disease. These alterations have been claimed to be amenable to neuroprotection.

Reactivation of glial cells

Recent evidence suggests that glial cells may participate in damaging neurons in glaucoma. During the development and maintenance of the nervous system, glial cells are structurally and functionally linked to neuronal tissues, including in the lamina cribrosa. Glial cells control the extracellular environment of the axons and scavenge toxins. In the optic nerve, glial cells include astrocytes, oligodendrocytes (behind the lamina cribrosa), and microglia, while, in the retina, there are mainly Müller cells and astrocytes. In glaucoma, pathologic mechanisms within the anterior optic nerve include glial cell activation. The suspected primary injury site in glaucoma is the ONH. However, the observation of secondary degeneration of retinal ganglion cells in glaucoma, with widespread
neuronal damage occurring beyond the initial injury site or even beyond the eye makes the delineation of the primary injury site uncertain. Indeed, glial cells in human eyes undergo an activation process in glaucoma not only in the ONH, but also in the retina.

A potential mediator of glial cell reactivation and of extracellular matrix remodeling in the lamina cribrosa of glaucomatous eyes may be transforming growth factor beta. A further possible candidate may be endothelin-1. A study using cultured ONH astrocytes demonstrated an increased migratory ability in response to elevated hydrostatic pressure, and that the migration of ONH astrocytes is accompanied by proteolytic degradation of the environing tissue. Possibly, activation of glial cells in glaucomatous eyes occurs primarily as a supportive mechanism for neuronal function. Likely enhanced mechanisms are regulation of extracellular amino acids and toxins, as well as supply of metabolites or growth factors to the neuronal tissue. However, at some point, under the prolonged stress conditions of glaucoma, a shift seems to occur from supporting functions to the development of noxious effects on neuronal tissue by mechanical injury as well as by changes to the microenvironment.

In addition, activated astrocytes are known to produce neurotoxic substances such as nitric oxide and TNF-alpha. An alternative hypothesis is that the supporting ability of the glial cells may be exhausted with time.

**Conclusions**

In summary, the presented evidence suggests that

1. Astrocyte activation is the key-factor in glaucomatous optic nerve remodeling.
2. Withdrawal of neurotrophic support may not be the only determinant of retinal ganglion cell apoptosis in glaucoma.
3. Mechanical compression alone cannot explain the observed alterations at the level of the ONH in glaucoma.

These findings have clearly influenced our appraisal of glaucomatous disease, although therapeutic approaches often still remain limited to the lowering of IOP. However, one step following another, it can be anticipated that newer therapeutic modalities will emerge in a not so far future.

**References**


2. THE MECHANISMS OF INTRAOCULAR PRESSURE INCREASE IN PRIMARY OPEN-ANGLE GLAUCOMA

Ernst R Tamm

Introduction

Intraocular pressure (IOP) at a level that is too high for the health of the optic nerve head is the major and most critical risk factor for glaucoma. IOP is higher in the eye than in its surrounding tissues in order to maintain the overall shape and the refractive properties of the visual organ. The actual rate of IOP depends on the circulation of aqueous humor. Aqueous humor is actively secreted by the ciliary epithelium into the posterior chamber. It passes through the pupil to the anterior chamber to leave the eye via the trabecular meshwork into Schlemm’s canal, which connects by collector channels to the aqueous veins that carry aqueous humor to the episcleral veins on the surface of the eye. The trabecular meshwork provides a resistance to aqueous humor outflow and IOP builds up in response to this resistance until it is high enough to drive aqueous humor across the trabecular meshwork into Schlemm’s canal. Aqueous humor passes through the trabecular meshwork as bulk flow driven by the pressure gradient; any active transport is not involved as neither metabolic poisons nor temperature affect this flow. An alternative pathway exists by which aqueous humor exits the eye through the ciliary muscle, the supraciliary and suprachoroidal spaces and finally through the sclera into the episcleral tissue, or through reabsorption by vortex veins or uveal vessels. This unconventional or uveoscleral outflow accounts for only 10% of the total outflow in the human eye and is generally regarded as pressure-insensitive. In primary open-angle glaucoma (POAG), IOP is elevated because the resistance to aqueous humor outflow in the trabecular meshwork is abnormally high.

The structure of the trabecular meshwork

The trabecular meshwork consists of three regions that differ in structure: the inner uveal meshwork, the deeper corneoscleral meshwork and the juxtacanalicular tissue or cribriform
region that is localized directly adjacent to the inner wall endothelium of Schlemm’s canal. The uveal meshwork is an irregularly arranged porous structure that consists of one to three layers of trabecular beams or lamellae. Each lamella has a core, which is formed by extracellular collagenous and elastic fibers and which is covered by flat trabecular cells resting on a basal lamina. Comparable lamellae that extend from the scleral spur to the cornea are found in the corneoscleral meshwork (Figure 2.1). Here, the lamellae form several interconnected layers. The cribriform region does not form lamellae or connective tissue beams, but rather appears as a typical loose connective tissue with relatively free cells that are embedded in a loosely arranged fibrillar extracellular matrix (Figure 2.1). Cribriform cells are not in contact with a basal lamina. The cribriform cells form elongate processes by which they attach to one another, to extracellular matrix fibrils or to the inner endothelial cells of Schlemm’s canal. The lumen of Schlemm’s canal is lined by vascular endothelial cells that form at its inner side a barrier with very high hydraulic conductivity (Figure 2.1). Based on the aqueous humor flow rate and a pressure drop of approximately 5 mm Hg, the hydraulic conductivity of the inner wall endothelium is the highest of any endothelium in the body, including fenestrated structures such as the renal glomerulus. Compared with non-fenestrated endothelia, the inner wall endothelium has a hydraulic conductivity that is at least 100 times larger. To allow this high hydraulic conductivity, the inner wall endothelium is specialized by the formation of large pores that range in size from 0.1 μm to 3 μm, with an average diameter of a little less than 1 μm. Most of the pores appear to be intracellular openings, but a significant number of intercellular pores have been observed that may form a paracellular pathway across the inner wall. Pores are often associated with structures called giant vacuoles, which are outpouchings or invaginations of inner wall cells that extend into the lumen of the canal. It is generally agreed that giant vacuoles form passively due to the pressure drop across the inner wall, since the number of these invaginations increases in parallel to a rise in IOP.

Localization of outflow resistance

The openings between the network of the lamellae in the uveal and corneoscleral trabecular meshwork are too large in size and number to contribute to outflow resistance. Accordingly, cutting of the proximal parts of the trabecular meshwork does not affect outflow resistance. There is also considerable evidence that the endothelial lining of Schlemm’s canal does not significantly contribute to aqueous humor outflow resistance. The size and number of pores in the inner wall endothelium appear to be high (between 1000 and 2000 pores/mm²) and more than adequate to allow unhindered flow of aqueous humor. Indeed, by using scanning electron microscopy and hydrodynamic calculations, Bill and Svedbergh concluded that inner wall pores would generate, at most, 10% of the observed aqueous humor outflow resistance, a result that has been confirmed in independent studies. A recent report challenged this point of view by showing that the
Figure 2.1 Schematic drawing of the outer parts of the trabecular meshwork (TM) in normal eyes and in those with POAG. Aqueous humor enters the cribriform region through the large openings between the lamellae of the corneoscleral TM. It passes the extracellular pathways of the cribriform region and flows into Schlemm’s canal through pores in the endothelial lining that are often associated with giant vacuoles (arrows). In POAG, the pathways for aqueous humor in the cribriform region become smaller, as there is an increase in extracellular ‘plaque material’ that mainly derives from the thickened sheaths of cribriform elastic fibers (asterisks).

characteristics of inner wall pores depend on fixation conditions. The density of inner wall pores increases with the volume of fixative perfused through the outflow pathway and decreases with post-mortem time.\textsuperscript{23}

Nevertheless, there is also other experimental evidence that argues for the presence of pores and against Schlemm’s canal endothelium as the major site of outflow resistance. Johnson and coworkers perfused enucleated human eyes with 0.18-μm microspheres and found that approximately 50% of microspheres successfully passed through the outflow pathways.\textsuperscript{24} There was no indication of a build-up of microspheres near the inner wall
endothelium. It is hard to understand how such a high fraction of particulates could
successfully pass through the outflow pathway, except through pores. This leaves the juxtacanalicular meshwork or cribriform meshwork as the most likely site of trabecular outflow resistance. This assumption is supported by experimental studies reported by Mäepea and Bill, who measured pressure at different locations in the cribriform region of monkeys with a micropipette tip. They found that most of the outflow resistance is located in the cribriform region, at a distance of approximately 7 to 14 μm from the inner wall endothelium. Moreover, in monkey eyes a positive correlation has been observed between resting facility and the area of optically empty spaces in the cribriform meshwork, which should serve as pathways for aqueous humor.

Still, theoretical calculations of the resistance in the cribriform flow passages as viewed using conventional electron microscopy (EM) indicated that the cribriform region could not generate a significant outflow resistance, unless the assumption is being made that areas which appear optically empty are filled with extracellular material that is poorly visualized or is lost during the embedding procedures that are required for EM. Indeed, experimental evidence for the role of the extracellular material in generating outflow resistance comes from studies in perfused human anterior segment organ cultures. Bradley and coworkers showed that perfusion with matrix metalloproteinases, enzymes that degrade extracellular matrix moieties, causes a significant decrease in outflow resistance. In a more recent study, however, the trabecular meshwork and the inner wall of Schlemm’s canal were examined using quick-freeze deep-etch EM. This technique should preserve extracellular moieties that are lost by conventional EM. Although significantly more extracellular matrix was observed in the cribriform region using quick-freeze deepetch EM than by conventional EM, some micron-sized open spaces were still present immediately beneath the inner wall of Schlemm’s canal. In conclusion, as of today, specific components that account for normal outflow resistance in the cribriform region and their specific location within this region have not been identified.

**Structural changes with POAG**

The two major structural changes that occur in eyes with POAG are a loss of trabecular meshwork (TM) cells and a significant increase in extracellular material in the cribriform region of the TM. The predominant component of the extracellular material that is increased in POAG has been termed ‘plaque material’ and derives from thickened sheaths of elastic fibers in the cribriform TM (Figure 2.1). Plaque material consists of banded fibrillar elements that are embedded in different glycoproteins. The molecular nature of plaque material is unclear, but there is some evidence that collagen type VI is associated with it. The increase of plaque material in POAG correlates with the degree of axonal damage in the optic nerve head. Still, eyes with ocular hypertension or early glaucoma do not show a substantial increase in this material, indicating that plaque material is rather a symptom than a cause of increased outflow resistance in POAG.
Other components of the extracellular matrix that have been reported to be present in higher amounts in the TM of eyes with POAG are collagen type IV, laminin and fibronectin, but again it is far from clear whether this increase causes elevated TM outflow resistance. An extracellular molecule that might act more specifically on TM outflow resistance in patients with POAG is myocilin, a secreted glycoprotein of the olfactomedin family, which is expressed in very high amounts in the trabecular meshwork. Mutations in myocilin cause some forms of POAG that are often associated with high pressure. The immunoreactivity for myocilin has been found to be increased in the TM of eyes with POAG. Moreover, perfusion of human anterior segment organ cultures with recombinant myocilin made in bacteria increased the resistance of trabecular outflow. Still, these results need to be interpreted with caution, since proteins made in bacteria do often differ substantially from that made in eukaryotic cells. Bacteria lack an endoplasmic reticulum and all its control mechanisms that facilitate protein folding, which is required to obtain the proper three-dimensional structure of proteins. Indeed, in a more recent study on organ cultures that were perfused with a myocilin fragment, which contained the critical olfactomedin domain and was purified from a eukaryotic non-bacterial expression system, no significant effects on outflow resistance were observed.

The factors that control extracellular matrix turnover in the normal TM and its increase in POAG are largely unclear. In other tissues and disorders, for example in pulmonary or hepatic fibrosis, systemic sclerosis, glomerulosclerosis in the kidney or in dermal scarring, there is considerable evidence that transforming growth factors-β1 and 2 (TGF-β1 and 2) mediate a pathological increase in extracellular matrix deposition and the development of tissue fibrosis. A similar role for the increase in TM extracellular matrix in POAG has been proposed for TGF-βs in the eye. Human TM cells in culture have been shown to secrete TGF-β and to express mRNA of TGF-β receptors. Treatment of TM cells with TGF-β in vitro causes an increase in fibronectin synthesis and a substantial cross-linking of fibronectin by the action of tissue transglutaminase. Moreover, elevated amounts of TGF-β2 have been found in the aqueous humor of patients with POAG.

The role of the TM cytoskeleton and contractility

While the quality and quantity of the extracellular matrix are certainly critical for the major function of the TM, which is to provide optimal conditions for aqueous humor outflow, the TM by no means acts like a passive filter. As with any other connective tissue, there is certainly a constant remodeling of the extracellular matrix, a process that requires active de novo synthesis of extracellular matrix compounds and continuous degradation of those by the action of matrix metalloproteinases and other enzymes that contribute to extracellular matrix turnover. It also appears to be very likely that the TM extracellular matrix is organized and sensed by TM cells via integrins, which are membrane-spanning
heterodimeric receptors that mediate communication between the extracellular matrix and cells in connective tissues. Integrins in cell-matrix adhesions transmit information in a bidirectional manner between extracellular matrix, cytoplasm and cytoskeleton, which become dynamically linked and are able to interact continuously with each other.\textsuperscript{56,37} Indeed, agents that interfere with the TM cytoskeleton can induce dramatic changes in TM structure and outflow resistance.\textsuperscript{58} In addition, considerable and convincing evidence has been accumulated in recent years that TM cells have smooth muscle-like properties and are able to actively contract.\textsuperscript{59} Contraction of TM cells appears to modify the outflow pathways in a way that increases outflow resistance, while relaxation appears to do the opposite. These mechanisms do certainly provide highly interesting pathways for novel therapeutic approaches that may lower IOP in patients with POAG. Still, so far there is no evidence that lack of TM contractility or changes in the cytoskeletal organization of TM cells causes or contributes to the increase of IOP in POAG.

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3. PATHOGENESIS OF GLAUCOMATOUS OPTIC NEUROPATHY

Josef Flammer

Introduction

Glaucomatous optic neuropathy (GON) has been known clinically for more than 150 years as optic nerve head excavation. We are, however, only beginning to understand the corresponding changes at the cellular and molecular levels. More information can be expected in the next few years from studies using immunohistochemistry and in situ hybridization. The main problems are the difficulty of obtaining fresh human material and the lack of good animal models, especially for normal-tension glaucoma.

This chapter summarizes both present knowledge and its application to the pathogenesis of GON in primary open-angle glaucoma (POAG), including normal-tension glaucoma (NTG).

In order to understand a disease at least three steps are usually considered: the risk factors, the pathomechanism, and the damage (Figure 3.1). In some diseases there is a fourth step, the recovery. Before discussing the pathophysiology of GON the present knowledge of the damage and the risk factors involved will be described. The pathomechanisms leading to increased intraocular pressure (IOP) will not be delineated, but rather the mechanisms leading to GON will be focused on.

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Figure 3.1 A disease is characterized by its risk factors, by the pathomechanism, and by the damage (from Hernandez, with permission).
The phenomenology of GON

Whereas the ophthalmologist sees the optic nerve head (ONH) excavation (Figure 3.2a), the pathologist sees, besides a loss of neural tissue, an elongation, stretching and collapse of the lamina beans and their posterior displacement (bowing) (Figure 3.2b). The damage is demonstrated schematically in Figure 3.2c and summarized in Table 3.1. The loss of retinal ganglion cells is non-specific and occurs in a number of other retinal and optic nerve diseases as well. What is specific for glaucoma, however, is the tissue remodeling leading to excavation. Therefore a concept of pathogenesis of GON needs to explain tissue remodeling as well. The optional changes listed in Table 3.1 are also non-specific, but clearly occur in glaucoma patients more often than in healthy controls.

In addition to these local changes in the eye a number of systemic symptoms and signs are found, again not specific but occurring more often in glaucoma than in healthy controls (Table 3.2). Most consistent are ocular hemodynamic changes, often accompanied by systemic vascular dysregulation. For a detailed description, refer to the review by Flammer et al.¹

Risk factors for GON

From a scientific point of view the true risk factors are separated from risk indicators. In practice this is often not easy. As an example: increased optic nerve head excavation is

![Figure 3.2 Glaucomatous optic nerve atrophy: (a) through an ophthalmoscope; (b) the histological picture; (c) a schematic presentation of GON (from Hernandez,² with permission).](image)

<table>
<thead>
<tr>
<th><strong>Table 3.1 Morphology of GON</strong></th>
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<tbody>
<tr>
<td><strong>Obligatory changes</strong></td>
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<tr>
<td>Retinal ganglion cell loss</td>
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<tr>
<td>decrease in neuroretinal rim</td>
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<tr>
<td>thinning of the retina</td>
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<td>loss of axons</td>
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<tr>
<td>Tissue remodeling</td>
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<td>excavation</td>
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<td>stretching and of beans</td>
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Table 3.2 Optional systemic findings in glaucoma

<table>
<thead>
<tr>
<th>Hemodynamic alterations</th>
<th>Autoimmunity</th>
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<tr>
<td>Leukocyte activation</td>
<td>Autonomous nervous dysfunction</td>
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<tr>
<td>Endocrinological dysfunction</td>
<td>Neurodegenerative diseases</td>
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<tr>
<td>Psychological instability</td>
<td>Infections with helicobacter pylori</td>
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<tr>
<td>Increased plasma level of endothelin-1</td>
<td>Increased level of MMP-9</td>
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associated with an increased probability of further progression. This could mean that an excavation is a risk factor in itself—in other words, if the optic nerve head is excavated its vulnerability increases. However, it could also mean that a patient who has acquired damage in the past (due to whatever risk factors) obviously has a higher probability of progressing in the future (unless the relevant risk factors have been eliminated meanwhile). As a clear separation is often not possible, the term risk factors is used in a broad sense to mean factors that are statistically associated with the occurrence or with the progression of GON (Table 3.3). Of clinical relevance, however, is the question of whether or not a risk factor can be influenced.

Three risk factors will be considered: IOP, vascular dysregulation, and blood pressure (Figure 3.3). According to the author’s experience, these three factors are the most important ones and can, at least partially, be influenced.

Pathomechanism of GON

It must be emphasized that the mechanisms leading to the damage are not yet fully understood. The current concept will be summarized. Although there is a complex interplay of

Table 3.3 Factors associated with progression of GON

<table>
<thead>
<tr>
<th>Cannot be influenced</th>
<th>May be influenced</th>
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<tr>
<td>Ethnic background</td>
<td>IOP</td>
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<tr>
<td>Gender</td>
<td>Vascular dysregulation</td>
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<tr>
<td>Age</td>
<td>Blood pressure</td>
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<td>Refraction</td>
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<tr>
<td>Morphology of the optic nerve head (including hemorrhages)</td>
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Autoimmune diseases
Figure 3.3 The three most important and influenceable risk factors for GON.

different factors, for didactic purposes we will discuss it step by step, artificially breaking it down to a number of different aspects.

The concept of cell stress

A disease (including glaucoma) is based on functional and structural damage to cells. In general a number of factors can damage cells, including hypoxia, toxins, ionizing radiation, bacteria, viruses, immune processes, etc. These factors often also damage the cells via an increase in production of free radicals.

A cell has a limited repertoire to response to injury. If the stress is high, the cell dies either by necrosis or apoptosis. If the stress is less intensive, the cell survives, but changes temporally its gene expression. This may lead, for example, to an increased production of the so-called heat shock proteins. A repeated or chronic cell stress leads to a chronic ‘response to injury’ which, depending on the tissue involved, manifests as metaplasia, dysplasia, or tissue remodeling, for example. These changes are often accompanied by some cell loss.

It has been demonstrated in vitro that mechanical and ischemic stress induce in astrocytes very much the same response (Table 3.4). These changes are also the ones that can be observed in human GON.2

In the past two theories for the pathogenesis of GON were presented, the mechanical and the vascular. The mechanical theory supposed that GON is a direct consequence of IOP damaging the lamina cribrosa and the neural axons. The vascular theory considered GON as a consequence of insufficient blood supply due to either increased IOP or other.

Table 3.4 Upregulated genes in astrocytes

<table>
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<th>Genes</th>
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<tr>
<td>NOS-2</td>
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<tr>
<td>COX-2</td>
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<tr>
<td>TNFα</td>
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<td>MHC-II</td>
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• MMPs
factors reducing ocular blood flow. In the early 1980s the author proposed that both the mechanical and vascular theories might be correct and that in most cases the two mechanisms might act synergistically. The above described activation of astrocytes supports such an assumption.

Is GON an ischemic lesion?

Research supports the view that ocular blood flow is indeed reduced in the majority of glaucoma patients. Reduction was found in all ocular tissues tested so far, but specially in the choroid, the optic nerve head, and the peripapillary retina. It is known that a marked reduction in blood flow leads to infarction. Such a marked reduction in the ONH blood flow leads to ONH infarction and as a consequence to a ‘simple’ ONH atrophy. Although such an anterior ischemic neuropathy (AION) occurs more often in patients with increased IOP than in normals, an atrophy after AION (Figure 3.4a) is distinctly different from a glaucomatous atrophy (Figure 3.4b).

If reduced blood flow is involved in both conditions how can the differences be explained? Hypothetically there are three possibilities:

• Ischemia may only lead to GON together with damaging IOP. The occurrence of NTG, however, makes such an explanation unlikely.

• A chronic ischemic lesion may lead to a different type of damage compared to the acute ischemic lesion. The fact that ocular ischemic syndrome (as seen in patients with occlusive carotid artery disease, for example) does not lead to GON makes this hypothesis also unlikely.

• The damage may rather be a consequence of a reperfusion injury than of a pure ischemia.

GON as a consequence of repeated reperfusion damage

It has been known for a long time that IOP fluctuations are more damaging than a steady increase in IOP. Likewise blood pressure fluctuations are more damaging than a steady hypo- or hypertension. Furthermore, a constant reduction in blood flow by arteriosclerosis is only weakly related to GON, whereas blood flow fluctuations in patients with vascular dysregulations are highly related to GON. Such fluctuations of ocular perfusion
Figure 3.4 ONH atrophy (a) after AION; (b) in glaucoma.
do occur if autoregulation is disturbed and therefore compensation for IOP and blood pressure fluctuation is insufficient. It has been clearly shown that autoregulation is indeed disturbed in patients with progressive GON. To explain these observations the author has suggested that the relevant mechanism of damage in glaucoma is not the hypoxia but rather the reperfusion injury.\textsuperscript{1} Reperfusion leads to an increased production of free oxygen radicals, especially in the mitochondria.

The role of oxidative damage

Oxygen, ironically the molecule on which we depend for our life, is also the molecule that can harm us. A free radical is defined as a chemical species that has an odd number of electrons and that is therefore thermodynamically instable and highly reactive. Free radicals seek to combine with other molecules to pair off their free electron. They are produced in cells by various mechanisms including reperfusion. Most of the free radical production occurs in the mitochondria, explaining why many of the naturally occurring defense mechanisms are concentrated about or in the mitochondria. The net damage done is the result of several factors such as the type of free radical, the rate of production, the structural integrity of the cells and their compartments, and the activity of the antioxidant defense system. There are many indications (including the activation of lymphocytes) that oxidative stress is indeed involved in the pathogenesis of GON. An increased production of NO in the astrocytes is the consequence of chronic cell stress. If at the same time a reperfusion injury leads to increased production of superoxide anions in the mitochondria of the axons the very damaging peroxynitrate (Figure 3.5) is produced.\textsuperscript{5}
Figure 3.5 Hypothesis for t ion caused by NO (from Hernandez,² with permission).
Is GON a mitochondriopathy?

It has been suggested by some authors that normal-tension glaucoma might be a mitochondriopathy. This hypothesis was formulated on the basis of the observation that a known mitochondriopathy like Morbus Leber or dominant optic atrophy leads to GON-like atrophy.

The energy consumption in the optic nerve head is indeed extremely high and therefore the mitochondria are crowded in the axons of this part of the nerve. Mitochondria are also the organelles that produce most of the free radicals during the reperfusion stage and are damaged themselves, especially if the balance between production and repair is shifted towards production. It is, however, unlikely that glaucoma is a result of a not yet detected mutation of the mitochondrial DNA. Nevertheless, it can be assumed that the mitochondria do play a major role in the pathogenesis of GON. The mitochondria, including the mitochondrial DNA, may be damaged by free radicals and such damage may cumulate over time, especially if the repair systems are no longer working properly.

The role of endothelin-1

A number of studies have shown that in the majority of glaucoma patients endothelin-1 is slightly increased. Such an upregulation can also be explained by reperfusion damage which in glaucoma patients obviously does occur not just in the optic nerve head but (subclinically) in many organs. Can the increased level of endothelin in itself lead to GON? Although the increased level of endothelin is an interesting sign of involvement of the vascular system and although endothelin-1 reduces OBF and renders the vessels more sensitive to other vasoconstrictive factors like angiotensin II or catecholamines, the increased level in itself does not explain GON. The reason for this is that endothelin is even more increased in a number of systemic diseases such as multiple sclerosis, rheumatoid arthritis or fibromyalgia, and Susac syndrome, diseases in which a pale ONH is often seen, but GON not significantly more often than in an average population. It is, however, also increased in patients with giant cell arteritis, which can lead to some excavation.

The role of MMP-9

MMP-9 expression in the lymphocytes of glaucoma patients is increased. Such an increase can also be explained by reperfusion damage. This increase of MMPs in the lymphocytes corresponds to the local increased expression in astrocytes in the optic nerve head. Furthermore, MMP-9 is involved in apoptosis of retinal ganglion cells. In MMP-9 knockout-mice apoptosis of retinal ganglion cells is inhibited. The increase in MMP-9 furthermore may at least partially explain the reduced blood-brain barrier, the tissue remodeling leading to excavation, and finally the thinning of the cornea in NTG.

The role of optic nerve head hemorrhages

It has been suggested that the hemorrhages might be a consequence of IOP. This is unlikely,
however, as it occurs more often in normal-tension glaucoma than in high-tension glaucoma. It has also been suggested that it might be a sign of a local microinfarction. The fact, however, that the corresponding visual defects normally occur weeks after
the hemorrhage is a clear sign that the hemorrhages precede the axonal loss. It can be assumed that these hemorrhages originate from small venoles as a consequence of dysregulation of the blood—brain barrier. Dysregulation of the barrier might be another sign of a generalized vascular dysregulation\textsuperscript{17} and may also be a consequence of increased activity of MMPs and of PGE\textsubscript{2}. A hemorrhage may, in turn, lead to local vasoconstriction and thereby to a small infarction.\textsuperscript{18}

**The present concept**

Based on the facts described above it is assumed that IOP may damage both mechanically and by inducing hypoxia. Increased IOP or decreased blood pressure is especially damaging if it is not compensated for by a sufficient autoregulation. This leads to a fluctuating oxygen tension and therefore to repeated reperfusion injury, which leads to oxidative stress of both the local astrocytes and the circulating lymphocytes.\textsuperscript{19,20} Whereas the astrocytes are directly involved in the pathogenesis of GON, the changes in the lymphocytes might be used for diagnostic purposes. Reperfusion leads to an increase in MMPs, which in turn are involved in the apoptosis of the retinal ganglion cells, in the disruption of the blood—brain barrier, and in tissue remodeling leading to GON. This concept is summarized in Figure 3.6.
**Figure 3.6** Present concept of the pathogenesis of GON.
Conclusion

GON is characterized by the loss of retinal ganglion cells and their axons combined with a specific tissue remodeling. Both mechanical stress and repeated ischemia lead to activation of astrocytes. A reperfusion injury leads furthermore to an increased production of superoxide anions in the mitochondria of the axons and to an upregulation of MMPs. This cell stress can also be observed in the lymphocytes, which in glaucoma patients change their gene expression pattern. The examination of lymphocytes gives insight into the pathogenesis and might be helpful for diagnostic purposes.

The cause of the reperfusion damage is the fluctuating oxygen tension, which in turn is due to fluctuating IOP and fluctuating blood pressure, not sufficiently compensated for by autoregulation.\(^\text{21}\) The autoregulation is obviously disturbed in patients with a primary generalized vasospastic syndrome.

References


4. GLAUCOMA: THE FORGOTTEN MASSES

Ghada Ibrahim and Tarek Shaarawy

Introduction

The World Health Organization (WHO) states that nine out of ten blind people live in the
developing world and that more than two thirds of blindness can be avoided if the right
mechanisms are in place to do so. It is now without a doubt that glaucoma is the second
leading cause of blindness after cataract.1 Quigley’s2 extensive review in 1996 revealed the
number of people with primary glaucoma to be 66.8 million, while the WHO put the total
number of suspect cases of glaucoma at around 105 million. The number of people suffering
from bilateral blindness as a result of primary glaucomas alone has been estimated to be 6.7
million. A more recent article3 with updated calculations, shows that the number of people
bilaterally blind from the two glaucomas, open-angle (OAG) and angle-closure (ACG), has
increased to 7.6 million, while Goldberg4 in 2000, estimated the burden of bilateral blindness
(including secondary glaucoma) to be 9.1 million individuals. According to the WHO more
than 80% of blind and suspect cases of glaucoma live in the developing world. Even so,
glaucoma is not included in the 5-year program of the vision 2020 initiative. The WHO
exclusion of glaucoma from its 2020 initiative is based on the feasibility and affordability of
glaucoma interventions. It is a fact that, after decades of glaucoma research, we possess
neither cost-effective screening nor early diagnostic tools and the majority of glaucoma
therapies, available to us as glaucoma specialists, are not affordable to the majority of our
patients. In this chapter we will discuss the magnitude of the problem, the limitations of our
resources, and the possible means of tackling the situation.

The magnitude of the problem

The study and analysis of glaucoma epidemiology is fundamental in order for relevant, timely
and efficient therapy to be realized. Proper screening is still hampered by inadequate methods
for both detecting and treating the disease and a lack of a consensus on well-defined
standardized diagnostic screening criteria. Once established, the generation
of additional, sufficient data would offer more comprehensive, tangible results for prevention and treatment of this visually threatening disease. The incidence of disease would be more accurately foreseen and risk factors delineated.

Glaucoma is a disease whose manifestations encompass a large number of conditions united by the common end result of characteristic damage to the optic nerve. Traditionally, glaucoma referred to mechanisms that cause an elevation in intraocular pressure (IOP), however there is a current bias to ignore IOP as a causative factor. Glaucoma forms are now divided, according to the mechanism of damage to the optic nerve, into open-angle glaucoma (OAG) and angle-closure glaucoma (ACG), and further divided according to whether the cause is primary or secondary. Open-angle glaucoma is a slowly progressive atrophy of the optic nerve, characterized by loss of peripheral visual function and an excavated appearance of the optic disc. Foster defines it for epidemiological research as ‘end-organ damage’: characteristic optic neuropathy of structural abnormality combined with a significant visual field defect. Even though the causes of OAG are not known, IOP seems to be a major risk factor. The iris (unlike with ACG) does not occlude the trabecular meshwork, the site of impediment to outflow.

Because, hitherto, the main emphasis has been on the form most commonly found in European and North American populations, namely primary open-angle glaucoma (POAG), there has been limited research on primary angle-closure glaucoma (PACG). It is now more widely recognized that PACG may affect more people because of its higher prevalence in the populous regions of Southeast Asia. The definition and classification of PACG are still currently being assessed. PACG, unless in its acute form, is often an asymptomatic disorder. It refers to conditions in which the iris occludes the trabecular meshwork, thus impeding outflow. Case definition depends on gonioscopic identification of occludable drainage angles together with either elevated IOP or glaucomatous optic neuropathy. Damage to the optic nerve in ACG often results from extreme elevations in IOP. The presence of primary angle closure (PAC) confers an increased risk of developing glaucomatous optic neuropathy, in the same way as raised IOP does. The distinction between PAC and PACG should be noted when considering public health initiatives aimed at reducing blindness from PACG, even though both require treatment. People with trabecular obstruction and glaucomatous damage to the optic nerve have primary angle closure glaucoma, with closure of the angle being the primary disease.

By definition, for screening purposes, early glaucoma has no associated visual field loss. Instead, the presence of characteristic glaucomatous field loss automatically makes glaucoma of at least moderate severity. Optic nerve changes precede visual field damage in the majority of patients with glaucoma. The definitions and terminology used in glaucoma have changed in the recent past and are likely to change again in the next few years. The implication of new definitions is that the rates of glaucoma reported in population studies must be reassessed.

Different populations tend to suffer from different types of glaucoma. Quigley in 1996, reviewed and analyzed a vast compilation of published data to determine a rela-
tionship of POAG and PACG with age in people of European, African and Asian origin, with a comparison estimated for the year 2000. Quigley set forth design features that are required for a proper analysis: random selection, a high rate of examination, and a clear definition of glaucoma, including either optic disc examination or a visual field test. Elevated IOP or low visual acuity alone were not criteria for definitive examination. Evaluation of age-specific POAG and PACG prevalence was performed and a best-fit equation used to generate a model of age specific and ethnic group specific prevalence to estimate global numbers of people with glaucoma. In individuals of European derivation, the best fit of POAG prevalence related to age is exponential (Figure 4.1). There seemed to be no consistent sex difference with regards to POAG where the mean age adjusted prevalence for people above 40 years of age was 2.42% (SD 2.10%). In contrast, that of PACG was 0.20% (SD 0.20%); 11.4 times lower than the POAG prevalence in the same reports. Further analysis of the effect of sex difference could not be carried out as the sample size was too small.

In people of African descent, POAG prevalence/age relation is linear (Figure 4.1). PACG has been shown to be relatively rare, at half the European rate. POAG was the most common form of glaucoma in Ghana, while PACG was the second most common and pseudoexfoliation and pseudoexfoliation-associated glaucoma were not present in the population tested. In the Temba glaucoma study of South Africa, the age and gender adjusted prevalence of glaucoma of all types was 5.3%. POAG was also the most common

![Figure 4.1](image_url)  
*Figure 4.1 Prevalence of POAG in people of African, Asian and European descent by age. (Reproduced with permission from Quigley HA. Number of people with glaucoma worldwide. Br J Ophthalmol 1996; 80:389–393).*
form with an adjusted prevalence of 2.9%; secondary glaucoma occurred with an adjusted prevalence of 2.0% and pseudoexfoliative glaucoma was responsible for 16% of all glaucoma cases. The prevalence of PACG was 0.5% of subjects with POAG; 87% were previously undiagnosed.

There are clear differences in the number of people affected by glaucoma due to variations in age distribution. For example, because of the early onset of disease and the high proportion of young people in the African population, screening would be most effective at 30 years of age, whereas for those of European descent, 50 years of age is the target starting point. In general, people of African heritage and Asians are more inclined to develop glaucoma and to lose their sight than Caucasians. Leske and coworkers measured the incidence of POAG in a black population in Barbados and their results substantiate the high POAG risk in the population of African origin. In Asian people, the age specific data suggest a linear relation of POAG to age. POAG has the lowest rate of severe uniocular visual loss, while the rates for PACG are higher, with secondary glaucoma being the most visually destructive when considering loss of vision in one eye. PACG appears more common among Chinese people than in any other ethnic group (Figure 4.2) Their ratio of PACG to POAG approaches 3:1. PACG is the most common type of glaucoma in the Sino-Mongoloid population. Dandona and others, working in Andhra Pradesh in Southern India, assessed the prevalence and features of PACG and POAG. They showed that the prevalence of POAG is as high as that reported from white populations in developed countries. With both forms, glaucoma was undiagnosed and a large proportion of those with definite glaucoma already had severe glaucomatous damage.

Figure 4.2 Frequency of different types of glaucoma leading to optic neuropathy in Chinese Singaporeans. (Reproduced with permission from Goldberg I. In: Weinreb RN, Kitazawa Y,
Glaucoma prevalence in the Middle East and Latin America is unfortunately speculative\(^2\). PACG is seen to be more common and is estimated at five times the rate of that in the European derived group, whereas POAG appears to show similar rates to the Europeans. A study addressing the leading causes of blindness and visual impairment in a population-based sample of people of Hispanic origin in the United States showed POAG to be the primary cause.\(^{20,21}\)

In all cases, age is a risk factor for the development of both forms of glaucoma, with older individuals more susceptible than younger cohort groups. It would seem that the number of children with glaucoma is quite small as compared to adults,\(^{22}\) but there is also a lack of data to back that assumption. Comparatively few studies describe secondary glaucoma as a separate entity, as it has not yet been properly defined. Quigley considers that people with pigmentary and pseudoexfoliation (or capsular) glaucoma have POAG. The contribution of secondary glaucomas to the world’s glaucoma burden is relatively small, about 20% of that for OAG.\(^4\) In a review of a number of studies including European, African and Asian people, Quigley calculated the mean prevalence for secondary glaucoma to be 0.44% (SD 0.36%) or 18% of the mean OAG prevalence in Europeans. Of concern in glaucoma epidemiology is the lack of an adequate number of studies that consider the incidence in diagnosed versus newly discovered disease. Most data are from studies in people of European origin and it would be likely that the number of known cases versus undiagnosed cases is lower in developing countries.

\textit{To treat or not to treat}

An estimate of the number of people expected to be blind from glaucoma is of great importance. The WHO sets a blindness standard of <20/400 (3/60). Glaucoma blindness rates are probably higher in developing countries than in Europe or the United States, assuming that most people in developed countries are under therapy and that treatment is more effective. Table 4.1 shows an estimate of the number of people affected by OAG.

<table>
<thead>
<tr>
<th>Group</th>
<th>Angle-closure (million)</th>
<th>Open-angle (million)</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>22.3</td>
<td>7.4</td>
</tr>
<tr>
<td>India</td>
<td>5.6</td>
<td>5.6</td>
</tr>
<tr>
<td>South Asia</td>
<td>4.2</td>
<td>4.2</td>
</tr>
<tr>
<td>Europe</td>
<td>0.6</td>
<td>6.9</td>
</tr>
<tr>
<td>Africa</td>
<td>0.05</td>
<td>7.0</td>
</tr>
<tr>
<td>Latin America</td>
<td>0.5</td>
<td>1.3</td>
</tr>
<tr>
<td>Near East</td>
<td>0.3</td>
<td>0.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>-------</td>
<td>-------</td>
</tr>
<tr>
<td>Total</td>
<td>33.55</td>
<td>33.1</td>
</tr>
</tbody>
</table>
and ACG in relation to the total population and suggests that 66.8 million people have OAG and ACG in nearly equal numbers; it is estimated that an additional 6.8 million people have secondary glaucoma and 6.7 million suffer from bilateral blindness. ACG is more prevalent in Asia, whereas OAG is more equally distributed. Table 4.2 shows another estimate from a more recently published source that reports significantly greater number of people affected by primary glaucoma worldwide.

The clear implication of the studies on disease progression is that not every patient with glaucoma, however defined, may require treatment. Quigley demonstrated that most patients may not go blind even at a high rate of progression and that many patients may die before they have visual field loss. However, glaucoma is a progressively debilitating disease, impaired vision having a severe impact on the quality of life. It would seem prudent, therefore, not to overlook this serious consideration when defining treatment criteria. Current standards of care call for the treatment of all patients who have glaucoma. All patients with or who are susceptible to PACG should be treated, given the natural history of those without treatment.

Because OAG is asymptomatic before blindness, patients are unaware of the disease. Acute cases of ACG are more likely to be presented for care, therefore statistics tend to overestimate the proportion of ACG to OAG. Because most people tend to wait for blindness to occur, believing erroneously that it can be reversed, awareness raising and educational efforts in blindness prevention must target high-risk populations with this information and may lead to the desired early detection.

The wisest approach would seem to have to be highly specific in targeting high-risk populations, sensitive enough to find those with moderate to severe glaucoma damage, thereby decreasing the burden of multiple examinations and consequently gaining ready consent for therapy. Mass glaucoma screening is not warranted however, there should be an emphasis on early detection. For example, simple and effective therapy could be administered for the asymptomatic form of PACG, thereby removing the need for more rigorous attention on the advanced stage.

Table 4.2 Estimated number (in millions) of people affected by primary glaucoma worldwide

<table>
<thead>
<tr>
<th>Region</th>
<th>Open-angle glaucoma</th>
<th>Angle-closure glaucoma</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>22.5</td>
<td>22.4</td>
<td>1300</td>
</tr>
<tr>
<td>India</td>
<td>5.6</td>
<td>5.6</td>
<td>1450</td>
</tr>
<tr>
<td>South Asia</td>
<td>4.2</td>
<td>4.2</td>
<td>770</td>
</tr>
<tr>
<td>Europe</td>
<td>6.9</td>
<td>0.6</td>
<td>1150</td>
</tr>
<tr>
<td>Africa</td>
<td>7.0</td>
<td>0.0</td>
<td>524</td>
</tr>
<tr>
<td>Latin</td>
<td>13</td>
<td>0.5</td>
<td>510</td>
</tr>
<tr>
<td>Middle East</td>
<td>0.6</td>
<td>0.3</td>
<td>330</td>
</tr>
<tr>
<td>Total</td>
<td>40.1</td>
<td>33.65</td>
<td>6234</td>
</tr>
</tbody>
</table>
Our limited resources

Glaucoma, as a subspeciality among ophthalmologists, is not novel; nevertheless, the majority of glaucoma specialists reside and practice in developed countries. There is a significant deficiency in glaucoma specialists and well-trained ophthalmologists in glaucoma, even relative to the overall scarcity of ophthalmologists in developing countries. Egypt has about one ophthalmologist per 20,000 people, while the ratio in India is one per 100,000 people. The situation is more dire in many African countries, where the ratio jumps to one ophthalmologist per 1 million people, if not more, and although 80% of Africans live in rural areas, eye care services are almost entirely situated in the capital cities and large provincial towns. This schism exists not only in resources and availability of medical care, but also in thoughts and ideas. The vast majority of research in glaucoma is aimed at either identifying pathophysiological disease pathways or the development of medical therapies. These are of course important fields of research, but unfortunately do not address the immediate needs of the vast majority of glaucoma patients.

We are currently not in possession of any cost-effective and reliable tools for the accurate diagnosis of glaucoma, which complicates the task. Furthermore, glaucoma surgery, which is virtually the only therapy option for the majority of our patients, has not taken the comparable great leaps forward that cataract surgery has taken during the past 30 years. Trabeculectomy remains the golden standard. If ophthalmic nurses and assistants are successfully trained to perform intracapsular cataract extraction in rural areas of Africa, it is quite possible that they can also be trained to perform trabeculectomy. Unfortunately, unlike cataract extraction, trabeculectomy requires exhaustive follow-up, and the postoperative period is a cornerstone of its success.

Non-penetrating surgery, namely deep sclerectomy or viscocanalostomy, is unquestionably a more costly, more complicated surgery compared to trabeculectomy, and has, undeniably, a long learning curve. It is probably not the answer to the prayers of glaucoma patients in the developing world.

Practical approaches

It is of paramount importance to realize that the great schism that separates the developed from the developing world entails clearly different pragmatic approaches. In the developed world the major challenge remains the vast number of undiagnosed cases. Even among highly industrialized societies and among well-educated individuals, the awareness of glaucoma is certainly lacking. Moreover, screening programs are not covered by medical insurance. Most screening programs consist of fundus biomicroscopy examination by an experienced observer and IOP measurement. If glaucoma is suspected, automated perimetry usually follows. More sophisticated technologies have not been demonstrated to be superior to experienced ophthalmologists in terms of sensitivity and
specificity. Arguably, automated methods might have the advantage of speed, but their wide use is still hindered by cost and logistics.

There is certainly a wider spectrum of glaucoma therapy available to both the ophthalmologist and the patient in the developed world. However, much to our dismay, we still lack applicable and proven concepts of therapy beyond decreasing intraocular pressure.32

In recent years, the availability of large multicentric studies has substantiated the protective value of lowering IOP in glaucomatous28,33 and ocular hypotensive individuals,34,33 but at the same time it is probably now clearer than ever before that other therapeutic concepts are needed. Tackling vascular dysregulation36 and neuroprotection37–40 may offer tremendous advantages in glaucoma management, if proven effective.

More efforts aimed at elevating public awareness are under way through multiple non-governmental foundations in the developed world. National and international glaucoma societies as well as glaucoma departments in specialized centers have contributed extensively through the media, especially through internet websites aimed at educating the general population as well as glaucoma patients.

In developing countries approaches should be considerably different, focusing on costeffectiveness and the impact on target populations. In the authors’ personal experience there are two major shortcomings with health-related strategies for many countries in the developing world, with a clear demarcation between those who can afford something and those who can afford nothing. Often, limited resources are misdirected in the pursuit of advanced technologies that are high maintenance and lacking in cost-effectiveness. There are ophthalmology centers in the developing countries that have retinal tomographs and no applanation tonometers. In the more financially distraught countries, a lack of what is considered basic in developed countries, such as slit-lamps and tonometers, is evident. Therefore extensive screening for early stages of glaucoma may not be the soundest approach. Overstretched financial resources can be better used to treat established glaucoma cases.

The main problems of glaucoma management in developing countries are the lack of well-trained ophthalmologists, limitations of medications, poor compliance, and inadequate follow-up of therapy. The use of present day medical glaucoma therapy in developing countries is therefore impractical. In many developing countries ocular hypotensive medications are not constantly available, and if available the means to purchase them are definitely not. It is important to note that many ocular hypotensive medications currently available such as Xalatan (Pharmacia, Kalamazoo, MI), Betoptic (Alcon, Fort Worth, TX) and Trusopt (Merck and Co, West Point, PA) cost about one dollar per day,41 when half the world population, nearly three billion people, live on less than two dollars per day, and 30% of the world population live on less than one dollar per day. In some subSaharan African countries university professors cannot even afford ocular hypotensive medications, as they have to survive on official salaries of as little as 10 dollars per month.

Local small-scale manufacture of ocular hypotensive eye drops, for example, could help considerably, but the magnitude of the problem and the logistical difficulties involved would probably render this an invalid solution. Research should concentrate on produc-
ing longer-acting drugs with a higher degree of IOP lowering. Devices or drugs that would be implantable or injectable to treat glaucoma once per year, such as was attempted with ethacrynic acid into the anterior chamber, would be future prospects.

At the present time, there is general agreement that the surgical approach is the most likely to be implementable and the most efficacious. Methods to both decrease complications and simplify the procedures are needed. Research is also warranted to test whether the rates of expected success and complications that are seen in developed countries can be compared to those of the developing world, with its different patient base, surgical setting and skills. Glaucoma surgery has benefited from the addition of antimetabolites, which can be applied pre-, intra-, or postoperatively to decrease scarring, but safer agents in this class are needed. Simple ‘plug-in’ devices are being studied that could make rapid glaucoma filtering surgery possible. Cyclodestructive surgery has promise, although the optimal energy levels to achieve satisfactory IOP lowering with minimal complications have not yet been sufficiently tested in representative populations.

Where cataract is common and where cataract surgical programs are being conducted, combined cataract/glaucoma surgery represents an initial approach that needs to be tested and evaluated. It is recognized that the success of combined cataract/glaucoma surgery may be lower than that of glaucoma surgery alone with respect to IOP control, but the combined surgery would be expected to eliminate the frequent progression of cataract after glaucoma surgery alone, which would either ruin the value of the procedure or necessitate a second procedure.

Human development will be the cornerstone of any solution. Skill transfer programs between developed and developing countries would, if well organized, have considerable impact. Two examples of these programs are the VISION FOR ALL (www.visionforall.ch) and the Pro Addis Ababa Foundation (proaddisabeba@bluewin.ch). Both foundations concentrate on skill transfer, in the form of surgical training for local ophthalmologists, in India, the Congo, Ethiopia, and Zambia (Figures 4.3 and 4.4). Once again, the schism between developed and developing countries accounts for less than optimal collaboration. It is often the case that developing world surgeons need to learn a skill that has become obsolete in developed countries, therefore a reasonable scenario would be skill transfer between developing countries. Continental, or preferably regional, centers could be set up to provide specific well-focused skill transfer programs. Some centers do exist and should be strengthened. Good examples are the CBM ophthalmic training center for central Africa (kincbm@ic.cd) and the SADC ophthalmic training program, Malawi College of Health Sciences (mchs@malawi.net).

Research attitude changes

The worldwide glaucoma problem is closely associated with the global efforts of preventing blindness. In a world where one person goes blind every 5 seconds, and a child goes
Figures 4.3 and 4.4 VISION FOR ALL skill transfer program in the Democratic Republic of Congo.
blind every minute, the ophthalmological community believes that the case for the prevention of blindness is justified on economic and, more importantly, humanitarian grounds. Blindness is a hundred times more common in rural, underdeveloped areas of the world rather than urban, developed settings. In these locations, it is not a quality of life issue, but a life or death one. In fact, the mortality rate for the blind in Africa is four times that for the sighted. At present, this is poorly appreciated by many ministries of health in the developing world, where preventing blindness has a low priority, competing with major health issues such as malaria, tuberculosis, and AIDS. Of lower priority still, on the almost neglected issue of blindness prevention, is glaucoma. Despite the fact that it is now recognized, without a doubt, as the second leading cause of blindness worldwide, as stated earlier, it has not been included in the first 5-year plan of the 2020 vision initiative of the WHO.

The responsibility of glaucoma specialists is two-fold: first, to continue to lobby for glaucoma, presenting well-researched and reasoned arguments to politicians and policy makers; second, and probably more important, is to realize that the situation demands that we, at least slightly, shift research directions from focusing on pathophysiology, medical therapies, and laser imaging, to possibly cost-effective diagnostic technologies, and simpler, safer and effective surgical modalities.

The plight of millions of glaucoma patients should be well addressed. The solution should come, if it comes, from glaucoma specialists recognizing the global impact of their profession, and striving to put their efforts where they are most likely to make a real difference.

References


5. INDICATIONS FOR INTRAOCULAR PRESSURE REDUCTION AND TARGET INTRAOCULAR PRESSURE

Alain Bron

Introduction

Glaucoma is the second major cause of blindness worldwide. In contrast to cataract, the prevalence and blindness of glaucoma are not ‘economy dependent’ and Western and developing countries share the same sight threatening burden.

Following the revolution of the introduction of topical beta blockers in the 1970s, the treatment of glaucoma has been greatly improved in the last few years by the availability of new classes of topical drugs. Ophthalmologists and their patients can now benefit from carbonic anhydrase inhibitors, α2-adrenergic agonists, prostaglandin analogues and prostamides. Laser procedures and new approaches to glaucoma surgery such as antimetabolites and non-penetrating surgery have been developed to increase the efficacy and safety of our surgical armamentarium.

However, this exponential increase in available antiglaucomatous drugs and surgical improvements contrasts dramatically with areas of uncertainty in our knowledge:

• Is IOP reduction of benefit in glaucoma?
• Does IOP reduction avoid the progression to glaucoma in ocular hypertensive patients?
• If yes, what is the correct magnitude of IOP reduction?
• Can we identify the patients at risk?

The following sentence by Luca Rossetti is a good example of the lack of evidence linking glaucoma and IOP that prevailed a decade ago: ‘Practicing ophthalmologists should be aware that the effectiveness of pressure-lowering agents in the treatment of primary open angle glaucoma is still to be determined and that the vast majority of published trials are not appropriate to guide clinical practice’.

Nowadays ophthalmologists and their patients are fortunate because most of the answers to these questions are solved and constitute the main pieces of the dazzling puzzle of main glaucoma enigmas. These pieces are the great and well-performed clinical trials published over the last few years that constitute our modern knowledge about the
relationship between glaucoma, ocular hypertension (OHT) and the most appropriate way to modulate IOP reduction according to the type of clinical condition. This chapter will summarize the principal clinical trials and emphasize how they could modify our management of OHT and glaucomatous patients in our daily practice.

**General presentation**

The clinical studies are all well designed and performed and they share the following positive characteristics, being:

- Multicentric, randomized, prospective.
- Long term with a large number of patients.
- Reading centers for visual fields and optic disks with masked readers.

However, some weaknesses can be found such as follows:

- Selection bias due to inclusion and exclusion criteria.
- Well-educated, clean patients who do not reflect real practice.
- Each study has its own rating score for visual field progression that is not fully comparable to others; i.e. lack of standardization.

These clinical trials have investigated the full spectrum of glaucoma from the OHT (OHTS), through early glaucoma (EMGTS, CIGTS) to advanced glaucoma (AGIS, NTGS).

**OHTS (Ocular Hypertension Treatment Study)**

**Aim**

- To evaluate the safety and efficacy of topical ocular hypotensive medications in delaying or preventing the development of primary open-angle glaucoma (POAG) in individuals with elevated intraocular pressure (IOP).  
- To identify baseline demographic and clinical factors that predict which participants will develop POAG.

**Design**

From 1994 to 1996, 1836 individuals fulfilling inclusion and exclusion criteria were randomized to medical treatment or to observation and followed for more than 6 years (25% were African American). Briefly, participants were between 40 and 80 years, with untreated IOP between 24 and 32 mm Hg in the qualifying eye, and with normal optic disk appearance and normal standard automated perimetry (SAP).
In the treated group, investigators were asked to reach a 20% reduction of IOP with any available drug on the market.

Endpoints

Progression was judged on CPSD (corrected pattern standard deviation), with a 5% threshold probability and a GHT (glaucoma hemifield test) outside normal limits. Three visual fields (VF) were required to conclude a definitive progression. It is interesting; to note that among all these changes, 85.9% were not observed in subsequent fields. Progression was also estimated on optic disk changes such as pallor, neuro-retinal rim area notching or thinning, and cup/disk ratio.

Results

At 5 years, the cumulative probability of developing POAG was 4.4% in the treated group versus 9.5% in the observation group. It was thus concluded that ocular hypotensive therapy was effective in delaying or preventing the onset of glaucoma in OHT patients with a 20% reduction of baseline IOP.

The global local and systemic safety of medications was acceptable; however, a slight increase in cataract surgery and in psychiatric and genitourinary adverse events among the medication group was noted.

Prognostic factors leading to glaucoma in this population were identified in multi-variate analyses as follows: increasing age, larger cup-to-disk ratios, higher IOPs, greater pattern standard deviation with Humphrey perimetry, and thinner central corneal thickness (CCT). Actually the risk of progression to glaucoma was highly variable (from 2% to 36%) among individuals. For the first time CCT was recognized as a risk factor; however, this term is not appropriate and the wording ‘confounding factor’ is certainly more accurate since a thicker cornea may falsely lead to higher IOP and conversely.

It could be speculated whether a greater magnitude of IOP reduction would have led to a smaller rate of progression, since when combined with other studies there seems to be a dose-response relationship between IOP and the risk of glaucoma progression.

CIGTS (Collaborative Initial Treatment Glaucoma Study)

Aim

- To compare initial treatment with medication versus filtering surgery in patients with newly diagnosed early open-angle glaucoma.
- To assess the quality of life in participants.
Design

Investigators from 14 centers included a total of 607 patients with newly diagnosed early open-angle glaucoma from 1993 to 1997. The main inclusion criteria were age between 25 and 75, POAG, and exfoliative and pigmentary glaucoma with an IOP>20 mm Hg. All patients were naive to previous treatment.

The medical group (n=307) received a β-blocker as initial therapy, followed by adjunctive medical therapies if necessary. In case of failure to reach the target pressure (TIOP), argon laser trabeculoplasty (ALT) was the next procedure, then trabeculectomy. In the surgical group (n=300) a trabeculectomy was performed first with or without antimetabolites. ALT was used as the next strategy in case of failure, then medication was tried.

Endpoints

A target IOP was set for every patient with the following formula:

$$\text{TIOP} = [1-(\text{PIOref} + \text{CVscore})/100]*\text{PIOref}$$

were PIOref was the average of six measurements and CVscore was an especially designed score to assess visual field damage and progression with a scale from 0 to 20. The quality of life was evaluated with a questionnaire designed for the CIGTS.

Results

Baseline IOP was decreased by 38% in the medical group and by 45% in the surgical group. The requirement for ALT at 1 year was 23.6% in the medical group versus 11.8% in the surgery group, and at 4 years the values were 27.9% and 20.8%, respectively. In the medical group, 8.5% went on to ALT and surgery, while 8.3% went on to ALT and medicine in the surgery group.

Visual field and visual acuity losses were greater in the surgery group for the first 3 years, but these differences were not seen at 5 years. After 5 years, the visual field did not deteriorate as a whole in both groups, however visual loss occurred in 10.7% of medical eyes and in 13.5% of surgery eyes, while significant visual acuity loss was noted in 3.9% of medical eyes and in 7.2% of surgery eyes. Cataract surgery was needed in 19% of the surgical group and in 8% of the medical group at 5 years.

The findings of this study showing the equivalent ability of medicine and surgery to maintain a good visual field, although a different magnitude in IOP reduction, were in contrast to the well established superiority of primary surgery in POAG. However, the groups and the methods of evaluation of visual field damage are certainly different, and the IOP-lowering effect of new drugs is greater than observed with medications which were available in the 1990s.
**EMGT (Early Manifest Glaucoma Trial)**

**Aim**

- To evaluate the efficacy and safety of IOP reduction in patients with newly diagnosed early open-angle glaucoma.\(^{13}\)
- To identify risk factors for glaucoma progression.\(^ {14}\)

**Design**

One center in Malmö, Sweden, selected from a population-based glaucoma screening 255 patients presenting with newly diagnosed early open-angle glaucoma. The randomization period took place between 1993 and 1997. The median follow-up was 6 years and patients with POAG, PEX and normal-tension glaucoma (NTG) were included, with IOP ranging from 13 to 30 mm Hg. The age of the patients was between 50 and 80 years and the median mean deviation was \(-4\) dB. One group was assigned to a 25% IOP reduction with betaxolol 0.5% twice a day and ALT \((n=129)\) and the other group was left untreated \((n=126)\).

**Endpoints**

Optic disk changes and visual field progression were evaluated by a special scoring system based on glaucoma change probability, an event analysis available in the Statpac 2 of the Humphrey perimeter.

**Results**

In the treatment group IOP was decreased from 20.6 mm Hg at baseline to 15.5 mm Hg throughout follow-up. In fact, IOP reduction was greater for baseline IOP>21 mm than for IOP<21 mm (29% and 18%, respectively). In the control group, baseline IOP (20.9 mm Hg) was almost unchanged.

As defined in this study, glaucoma progression was greater in the observation group than in treated patients (62% and 45%, respectively); this difference was statistically significant. Treatment delayed glaucoma progression by 18 months (48 months versus 66 months in the observation group). Safety was acceptable in the treated patients in spite of a statistically significant increase in nuclear opacities.

Factors for glaucoma progression were identified as higher baseline IOP, exfoliation, having both eyes eligible in this study, and disk hemorrhages during follow-up. It was estimated that 1 mm Hg IOP reduction leads to a 10% decrease in risk of progression. The magnitude of IOP reduction at the 3 months’ visit and mean IOP during follow-up were related to progression with a relative risk ratio of 1.1.
AGIS (Advanced Glaucoma Intervention Study)

Aim

• To evaluate the safety and the efficacy of two treatment sequences in advanced glaucoma with maximal medical tolerated treatment.

AGIS is a vast and quite complicated trial with a lot of information that has been reported in more than 12 papers.\textsuperscript{15,16}

Design

From 1988 to 1992, 591 patients (789 eyes) with POAG poorly controlled with medical treatment were recruited. Black people were highly represented (\(n=451\) eyes) compared with white people (\(n=325\) eyes) and others (\(n=13\) eyes) and baseline IOP was greater than 22 mm Hg in 75%. The goal of the treatments was to decrease IOP below 18 mm Hg.

Patients were allocated to the following sequences:

• ATT: ALT then trabeculectomy and trabeculectomy if failure.
• TAT: trabeculectomy first then ALT and trabeculectomy if failure.

Endpoints

Progression was based on a sophisticated scoring system ranging from 0 to 20. A difference of 3 then 4 points was required to identify a true change in visual fields. The AGIS VF score was less sensitive than the CIGTS score, which was able to show progression much more frequently, but in a very different population.\textsuperscript{17}

Results

The role of ethnic origin

The sequence ATT worked better than the TAT in black people than in whites, without any satisfying explanation.

IOP reduction and visual field progression

Two different analyses have shown than the larger the IOP reduction, the better the final outcome. Patients with a mean IOP of 12.3 mm Hg, which satisfied the criterion of an IOP below 18 mm Hg at all visits during follow-up, did not have deterioration in their visual field, while those with higher mean IOPs, even below 18 mm Hg, had a less favorable figure. However, progression was relatively slow in most treated patients.

IOP control
Argon laser trabeculoplasty (ALT) controlled IOP in 55% of black patients and in 50% of white patients for 7 years, but it did not reduce medication needs. Trabeculectomy without antimetabolites, as it was done in the AGIS study, achieved IOP control and stable perimetric sensitivities in 75% of black people and 85% of whites. As for ALT, many eyes needed medications again.
Trabeculectomy and cataract

After 7 years, 45% of operated eyes developed cataract; 47% more often than in the ALT group when surgery was uncomplicated, and 104% more often when severe inflammation or a shallow/flat anterior chamber was observed. Cataract extraction improved visual field sensitivity modestly by 2 dB.

CNTGS (Collaborative Normal Tension Glaucoma Study)

Aim

• To determine whether IOP reduction is beneficial in the management of normal tension glaucoma (NTG).18–20

Design

Twenty-four centers enrolled patients with NTG (230 eyes). Patients were between 20 and 90 years old and, after a complete wash-out of their medications, the median of ten IOP readings had to be 20 mmHg or less and no measurement above 24 mm Hg. Patients were included if they showed progression or a threat to fixation; 145 patients (145 eyes) were in this situation, but five withdrew before IOP stabilization. A 30% IOP reduction was obtained in the treatment group (n=61) with medication and/or surgery while 79 eyes were left untreated.

Endpoints

Progression was evaluated on stereo slides of the optic disk and on visual fields (Humphrey 30–2), again with a specific method. Progression was confirmed when four of five consecutive VFs showed progression to baseline fields.

Results

The mean IOP was 16 mm Hg and 10.6 mm Hg during follow-up in the control group and in the treated group, respectively. Treatment delayed further glaucoma progression by approximately 3 years. In the control group 35% of the eyes progressed versus 12% in the treated group (p<0.001). However, when an intent-to-treat analysis (including the 145 eyes) was undertaken this difference was no longer observed.19 Cataract occurrence was statistically seen more often in the treated group (38%) than in the control group (14%), which was due to glaucoma surgery. The deleterious effect of cataract on visual fields was indicated by the fact that after censoring data when cataract affected visual acuity, the difference of glaucoma progression was again statistically significant.

Additional information was retrieved from the observation of patients who were enrolled in the study but not randomized because they did not show glaucoma progression.
They were not treated but followed for 7 years and constituted a good cohort with ‘a natural history’. Actually in this group only half showed localized progression within 5 to 7 years. The VF losses were very variable, ranging from −0.2 to 2 dB per year.

Conclusion

When considering these studies as a whole it seems reasonable to see a sort of dose-response curve to IOP reduction and glaucoma progression. It also appears that, without being the cause but only a risk factor of glaucoma, IOP has to be placed in the first line in our management of glaucoma; Paul Lichter uses a nice definition to illustrate that point; he advocates an ‘intraocular-sensitive optic neuropathy’.

Other short take-home messages can be found in the literature:

• Corneal thickness assessment is mandatory to evaluate the risk of ocular hypertensive patients of developing glaucoma, and then the appropriate decision ‘to treat or not to treat’ must be made.
• In early glaucoma we have to decrease IOP more than previously thought; a 20% IOP reduction, as recommended in most countries, is certainly not sufficient.
• In advanced glaucoma it is desirable to reach low IOPs of around 12 mm Hg. However, this aim does only apply to advanced glaucoma and not to all cases of glaucoma. Moreover, ‘the price to pay’ may be quite high since antimetabolites needed to reach such low pressures may lead to severe complications.
• In NTG, observation is a good approach until progression is documented and IOP reduction seems beneficial.
• An individual target IOP based on personal risk factors has to be estimated for every patient and modified according to VF progression and optic disk changes.

As for the ‘Good Book’ or other holy books, it will take time to extract all information relevant to glaucoma management. Moreover, we have to inform our patients of these new findings and this will be time consuming as well.

References


6. LIPIDS AND GLAUCOMA

Juergen Drewe

Introduction

Elevated intraocular pressure (IOP) is a major risk factor for optic nerve damage and loss of visual field in patients with glaucoma and ocular hypertension. In addition to β-adrenergic antagonists, carbonic anhydrase inhibitors, and cholinergic agonists, prostaglandin derivatives are a proven therapeutic option to reduce IOP.

Prostaglandins (PGs) are built in many tissues, including the eye, from their precursor arachidonic acid (Figure 6.1). PG receptors are G-protein coupled and bind predominantly selected PGs: prostaglandin D$_2$ (PGD$_2$) binds to DP receptors, prostaglandin E$_2$ (PGE$_2$) binds to EP$_1$, EP$_2$, EP$_3$ and EP$_4$ receptors, prostaglandin F$_{2\alpha}$ (PGF$_{2\alpha}$) binds to FP receptors, prostaglandin I$_2$ (PGI$_2$) binds to IP receptors and thromboxane A$_2$ (TXA$_2$) and prostaglandin H$_2$ (PGH$_2$) bind to TP receptors. In the eye, PGs have miotic effects and are involved in inflammatory processes. Although there are a lot of experimental data in animals that PGD$_2$ as well as PGE$_2$ reduces IOP, in humans only contradicting results have
Figure 6.1 Metabolic pathway of arachidonic acid. COX 1/2 = cyclooxygenase isoforms 1 and 2.
been obtained and irritating adverse effects observed. Specific effects have only been shown for PGF$_{2\alpha}$ or its derivative, which showed a consistent decrease in IOP.$^{2,3}$

**Clinically investigated prostaglandin analogs**

The clinical use of naturally occurring PGs has not been successful: although the administration of PGF$_{2\alpha}$ as such, or in esterified form as PGF$_{2\alpha}$-isopropyl ester (PGF$_{2\alpha}$-IE), showed a clear reduction of IOP in humans, it was accompanied by moderate superficial irritation and conjunctival hyperemia, foreign body sensations and ocular pain as well as headache.$^{4,5}$ Only very low doses could be used in order to prevent these adverse events. Therefore, other analogs with better tolerability had to be developed (Figure 6.2), with maintained or even improved activity at the FP receptor. These PGF$_{2\alpha}$ analogs are isopropyl unoprostone (a modified metabolite of PGF$_{2\alpha}$), latanoprost, travoprost, and bimatoprost. Their potency (EC$_{50}$) or that of their active metabolites (bimatoprost) at the FP receptor is bimatoprost=travoprost>PGF$_{2\alpha}$>latanoprost>unoprostone.$^6$ All of these analogs have been shown to be effective in the treatment of glaucoma or ocular hypertension. Travoprost has been equally effective as or superior to latanoprost and superior to timolol in the treatment of patients with open-angle glaucoma or ocular hypertension.$^1$
**Figure 6.2** Prostaglandin $F_{2\alpha}$ analogs. Prostamid bimatoprost is displayed for comparison. PGF$_{2\alpha}$ -IE=PGF$_{2\alpha}$-isopropyl ester.
Although bimatoprost shows some structural similarities with PGF₂α (Figure 6.2), it was reported not to bind to the FP receptor and its mode of action is not fully understood.⁷ It is chemically related to prostamide F, a naturally occurring substance which is derived from the endogenous cannabinoid receptor agonist anandamide (arachidonylethanolamide, AEA; see Figure 6.3) by the contribution of cyclooxygenase-2. The prostamide F receptor has not yet been identified. However, recent reports show that bimatoprost and its free acid replaced [³H]-PGF₂α from the FP receptor and mobilized intracellular calcium via cloned human FP receptors expressed in human embryonic kidney cells.⁸ This effect could be blocked by an FP receptor antagonist. In the same line of evidence, further studies of bimatoprost metabolism in corneal tissue showed that bimatoprost is converted in vitro to 17-phenyl-18, 19, 20-trinor prostaglandin F₂α, which is identical to the free acid of latanoprost with the exception of a double, rather than a single bond at the 13–14 position.⁹ If this occurs in vivo as well this finding may explain the IOP-reducing effect of bimatoprost. The onset of the IOP-reducing effect is about 3 to 4 hours after administration for all of these analogs; the maximum effect, achieved after 8 to 12 hours, is maintained over 24 hours.

The most extensive information on mechanisms of effect and clinical use is available
Figure 6.3 Endogenous and exogenous phytocannabinoids and analogs. FAAH=fatty acid amide hydrolase.
for latanoprost, but may be at least in part representative of the other analogs as well. Latanoprost is a prodrug of PGF$_{2\alpha}$. It is even more selective for the FP receptor than PGF$_{2\alpha}$ itself and has only marginal affinity for the other PG receptors.$^{10}$ This may be an explanation of the improved tolerability of latanoprost. Latanoprost and unoprostone show a strong increase in the uveoscleral outflow of aqueous humor through the ciliary muscle region to the suprachoroidal space and the episcleral veins.$^{10-12}$ Latanoprost has a strong IOP-reducing effect when given alone$^{13-20}$ or in combination with other drugs.$^{21-23}$ The latter adds to the increase in uveoscleral outflow and the inhibition of the humoral inflow by β-adrenergic inhibitors or carbonic anhydrase inhibitors.$^{24}$ This additive effect was also observed in patients resistant to other maximally tolerated pharmacological therapy.$^{25}$

Latanoprost pharmacokinetics after topical administration were investigated in healthy volunteers.$^{24}$ Latanoprost was rapidly hydrolyzed in the cornea and in blood. The maximum concentration of the active metabolite, latanprost free acid, was detected in aqueous humor 1 to 2 hours after topical administration and amounted to 15–30 ng/ml. The half-life in humor was 2 to 3 hours. In the systemic circulation, maximum concentrations were of 53 pg/ml, measured 5 minutes after topical administration, and displayed a half-life of 17 minutes.$^{26}$ The optimal dose of latanoprost is 0.005% given topically in the evening.$^{24}$

Safety of PGF$_{2\alpha}$ analogs analogs

Latanoprost, unoprostone, travoprost, and the prostamide bimatoprost cause increased pigmentation of the iris in some of the patients.$^6$ These changes appear to be permanent or slowly reversible. The incidence was reported to be less than 5% during 2 years of treatment, but it increased in patients with blue-brown heterochromatic eye color (20%) and further increased to 50% in patients with yellow-brown or green-brown eye color at 1 year of treatment.$^{27}$ Other than melanocyte stimulation no pathological changes have been observed in histology. It was demonstrated in vitro that PGF$_{2\alpha}$ analogs have a proliferating effect on corneal tissue.$^{28}$ However, this has not yet been confirmed in clinical studies.

Cannabinoids and intraocular pressure

Prostaglandins have a close structural relationship to endogenous cannabinoids (Figure 6.3), such as arachidonylethanolamide (anandamide) and 2-arachidonylglycerol (2-AG). Both classes are linked by metabolism: anandamide is hydrolyzed to arachidonic acid and ethanolamine by fatty acid amide hydroxylase (FAAH). Both endogenous cannabinoids
AEA and 2-AG have been found in bovine and rat retina.\textsuperscript{29} The expression of CB1 and CB2 cannabinoid receptors was demonstrated in ocular tissue.\textsuperscript{29–32} Both belong to the super-family of G-protein-coupled receptors. In 1971, first reports showed that marijuana smoking reduced IOP.\textsuperscript{33} However, this beneficial effect was accompanied by undesired adverse effects such as psychotropic effects, conjunctival hyperemia, 50% decreased lacrimation, and postural hypotension.\textsuperscript{34,35} In subsequent years, intravenous and oral administration of various cannabinoids, including Δ\textsuperscript{9}-THC and Δ\textsuperscript{8}-THC, was shown to reduce IOP in animals and humans.\textsuperscript{36–39} In order to separate the IOP reduction from psychotropic effects, topical administrations were developed.

Cannabinoids have poor water solubility, which limits their use in topical formulations. To overcome this, a number of galenical preparations including microemulsion (Muchtar 1992), sesame oil,\textsuperscript{40} and mineral oil\textsuperscript{37} have been prepared. The latter worked best but was sometimes locally irritating.\textsuperscript{41} More recently, formulations of polyethylene glycol,\textsuperscript{42} Tween 80\textsuperscript{43} and cyclodextrin\textsuperscript{44} (Jarho 1998) and prodrug approaches using a water-soluble ester of a maleate salt of Δ9-THC have been applied, which has facilitated the preparation of topical dosage forms. In addition, non-classical cannabinoids (such as CP-55, 940\textsuperscript{45}) or aminoalkylindoles (such as WIN-55, 212–2\textsuperscript{46}) have been used successfully to reduce IOP.

Conclusions

Lipid-derived prostaglandins and endogenous or naturally occurring phytocannabinoids and their analogs appear to be useful therapeutic alternatives to the classical pharmacological treatment of glaucoma and ocular hypertension.

References


Introduction

Lowering intraocular pressure (IOP) is the only proven method currently available to reduce the risk for glaucomatous visual field loss. In recent years significant advances have been achieved in the development of topical glaucoma medications. These medications are being used more commonly as there is an increasing trend by ophthalmologists to aggressively lower IOP. Among the currently utilized IOP lowering agents, prostaglandin analogs (that is, latanoprost, bimatoprost, and travoprost) are the most potent.\(^1\) Topical administration of latanoprost 0.005%, bimatoprost 0.03%, and travoprost 0.004% solutions is as or more effective in lowering IOP than the traditional first-line agent and reference standard, timolol 0.5%.\(^2\)–\(^6\)

Latanoprost (Xalatan\textsuperscript{®}) is approved in the United States, Europe, and Japan as a topically applied first-line treatment in patients with open-angle glaucoma or ocular hypertension. Studies have confirmed that a single drop of latanoprost 0.005% solution (approximately 1.5 μg) administered topically once daily effectively reduces diurnal IOP by 20% to 40%. The IOP-lowering effects of a single dose of latanoprost last up to 24 hours thereby allowing for a convenient once-daily dosing regimen. Numerous studies have evaluated the pharmacodynamics, pharmacokinetics, clinical efficacy, tolerability, and safety of latanoprost as monotherapy or adjunctive therapy in patients with open-angle glaucoma or ocular hypertension.

Pharmacodynamics

Mechanism of action

Latanoprost, the ester prodrug analog of prostaglandin F\(_{2α}\), has a high selectivity for the FP subtype of prostanoid receptors found in ciliary muscles.\(^7\)–\(^8\) Although the precise mechanism by which latanoprost and other prostaglandins decrease IOP is unclear, they
are believed to act by increasing aqueous humor outflow through both the trabecular route (via Schlemm’s canal and the episcleral veins) and the uveoscleral (ciliary muscle) pathway.⁹⁻²⁰

**Ocular effects**

A single topical dose of latanoprost 0.005% or 0.006% produces maximal IOP reduction within 8 to 12 hours when administered to healthy volunteers or patients with ocular hypertension or open-angle glaucoma.¹¹⁻²³ IOP remains below pretreatment levels for at least 24 hours following latanoprost administration.¹¹⁻²³ Latanoprost provides a steady reduction of the IOP during both daytime and nighttime hours, with minimal circadian fluctuation observed.¹¹⁻²³⁻²⁶ A single dose of latanoprost 0.005% administered to healthy volunteers results in a significant reduction in IOP that is maintained for 24 hours, with a less pronounced but still present IOP-lowering effect observed after 48 hours.²³ IOP returns to pretreatment levels generally within 2 weeks of latanoprost discontinuation.²⁷ The IOP-reducing effectiveness of latanoprost is greater with once-daily compared to twice-daily administration, an effect possibly attributable to receptor subsensitivity.²⁸⁻³⁰

**Pharmacokinetics**

The pharmacokinetic properties of latanoprost following instillation into the eye have been confirmed in healthy volunteers using³¹³⁻latanoprost and radio-immunoassay, and in patients undergoing cataract surgery using radio-immunoassay.³¹ In both populations, the hydrolysis of latanoprost to its primary metabolite, latanoprost acid, occurs rapidly following topical instillation in the eye.

In a study of four healthy volunteers who received topical administration of latanoprost (30 μl of a 50 (μg/ml solution), the peak plasma concentration of latanoprost acid (C\text{max}) appeared 5 minutes following instillation, reached a level of 53 pg/ml, and exhibited an elimination half-life (t\text{1/2}) of 17 minutes.³¹ The latanoprost area under the plasma concentration time curve was 34 ng.h/l and the volume of distribution was 0.36 17kg.³¹

Among patients undergoing cataract surgery, a single 30 μl drop of latanoprost 50 (μg/ml produced a C\text{max} in the aqueous humor of 32.6 μg/l approximately 2.5 hours following instillation, with a latanoprost acid aqueous humor elimination t\text{1/2} of 2.5 hours: the concentration of latanoprost 24 hours following administration was\text{≤0.2 μg/l.}³¹ Latanoprost undergoes extensive first-pass metabolism in the liver via β-oxidation prior to being eliminated primarily in the urine (88%) and the feces.³¹

Similar to latanoprost, other members of the prostaglandin analog class of agents, bimatoprost and travoprost, are also prodrugs that undergo hydrolysis to their acid form following ocular administration.³²⁻³⁶
Clinical efficacy

Open-angle glaucoma or ocular hypertension

Latanoprost is indicated as first-line treatment in patients with open-angle glaucoma or ocular hypertension. In addition, latanoprost effectively reduces IOP when administered as adjunctive therapy in patients who have not achieved optimal IOP control with their current glaucoma treatment regimen. Selected latanoprost efficacy studies are summarized in Table 7.1.

Monotherapy

Compared with timolol

In well-controlled randomized, comparative, clinical trials of patients with open-angle or ocular hypertension, monotherapy with latanoprost reduced IOP levels by between 20% and 40% during the 1 to 12 months of treatment. The majority of comparator studies were double-blind, including all of those performed with timolol as the comparator.\textsuperscript{2, 3, 4, 37, 38} Latanoprost 0.005% once daily was significantly more effective than timolol 0.5% twice daily for 3 or 6 months in four out of five studies performed in the United States, Scandinavia, and Asia (Table 7.1). Overall, latanoprost reduced mean baseline diurnal IOP by 6.2 to 11.1 mm Hg (27% to 39%) compared to reductions of 4.4 to 9.1 mm Hg with timolol (19% to 33%). In 1- and 2-year extensions of these clinical trials patients did not exhibit any signs of diminishing IOP-lowering efficacy, confirming that the efficacy of latanoprost is sustained with long-term treatment.\textsuperscript{39–42}

The IOP-lowering effects of latanoprost are greater and more consistent between day-time and nighttime hours as compared to timolol. Randomized, 4-week, crossover trials of latanoprost and timolol (solution and gel-forming solution) found significantly greater mean reductions in IOP during the daytime and nighttime hours with latanoprost (\textit{p} \leq 0.05)\textsuperscript{23, 26} as well as at study completion (\textit{p} < 0.001).\textsuperscript{26} Unlike timolol, which reduced IOP to a significantly greater extent during the daytime compared to nighttime (\textit{p} = 0.04), there were no significant differences between daytime and nighttime IOP-lowering efficacy with latanoprost.\textsuperscript{26}

The ability of latanoprost to reduce IOP is consistent in a heterogeneous global population. In a study of 1389 African-American, Asian, Caucasian, and Mexican patients with glaucoma or ocular hypertension, latanoprost 0.005% once daily (\textit{n} = 737) produced a 7.9 mm Hg reduction in mean diurnal IOP compared to a 6.4 mm Hg reduction in those treated with timolol (\textit{n} = 652).\textsuperscript{43}

Compared with dorzolamide

In a non-blinded study, latanoprost 0.005% once daily was significantly more effective than
dorzolamide 2% three times daily (mean IOP reduction from baseline 8.5 mm Hg versus 5.6 mm Hg, respectively; \( p<0.001 \)). The percentage of patients achieving an
Table 7.1 Summary of prospective, randomized clinical trials comparing the intraocular pressure (IOP)-lowering efficacy of topical latanoprost (L) monotherapy with other topical pressure-lowering agents in patients with open-angle glaucoma or ocular hypertension

<table>
<thead>
<tr>
<th>Reference (study design)</th>
<th>No of evaluated patients</th>
<th>Treatment regimes</th>
<th>IOP (mm Hg; mean)</th>
<th>Baseline Reduction from baseline (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Compared with timolol (T)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alm et al,2 db</td>
<td>89</td>
<td>L 0.005% od am×3 mo then pm×3 mo</td>
<td>24.8 8.6 (35)*††</td>
<td></td>
</tr>
<tr>
<td></td>
<td>94</td>
<td>L 0.005% od pm×3 mo then am×3 mg</td>
<td>25.5 7.8 (31)*</td>
<td></td>
</tr>
<tr>
<td>Aquino and Lat-Luna,37 db</td>
<td>28</td>
<td>L 0.005% od×3 mo</td>
<td>29.3 11.1 (39)**†</td>
<td></td>
</tr>
<tr>
<td></td>
<td>29</td>
<td>T 0.05% bid×6 mo</td>
<td>29.3 9.1 (32)**</td>
<td></td>
</tr>
<tr>
<td>Camras et al,3 db</td>
<td>118</td>
<td>L 0.005% od×6 mo</td>
<td>25 6.7 (27)††</td>
<td></td>
</tr>
<tr>
<td></td>
<td>130</td>
<td>T 0.5% bid×6 mo</td>
<td>25 4.9 (20)</td>
<td></td>
</tr>
<tr>
<td>Mishima et al,38 db</td>
<td>80e</td>
<td>L 0.005% od am×3 mo</td>
<td>23.1f 6.2 (27)††</td>
<td></td>
</tr>
<tr>
<td></td>
<td>83e</td>
<td>T 0.5% bid am×3 mo</td>
<td>23.1f 4.4 (19)</td>
<td></td>
</tr>
<tr>
<td>Watson et al,4 db</td>
<td>86</td>
<td>L 0.005% od×6 mo</td>
<td>25.2 8.5 (34)**</td>
<td></td>
</tr>
<tr>
<td></td>
<td>79</td>
<td>T 0.5% bid×6 mo</td>
<td>25.4 8.3 (33)**</td>
<td></td>
</tr>
<tr>
<td><strong>Compared with dorzolamide (D)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O’Donoghue,44 nb, me</td>
<td>109</td>
<td>L 0.005% od×3 mo</td>
<td>27.2 8.5 (31)††</td>
<td></td>
</tr>
<tr>
<td></td>
<td>107</td>
<td>D 2% tid×3 mo</td>
<td>27.2 5.6 (21)</td>
<td></td>
</tr>
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</table>
Compared with brimonidine (BR)

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Duration</th>
<th>Treatment</th>
<th>IOP</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Camras, 48 nb, me</td>
<td>152 (total)</td>
<td>6 mo</td>
<td>L 0.005% od×6</td>
<td>24.5</td>
<td>5.7 (23)††</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BR 0.2% bid×6</td>
<td>24.8</td>
<td>3.3 (13)</td>
</tr>
<tr>
<td>DuBiner et al, 49 db, me</td>
<td>61c</td>
<td>3 mo</td>
<td>L 0.005% od×3</td>
<td>24.1f</td>
<td>6.5 (27)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BR 0.2% bid×3</td>
<td>24.5f</td>
<td>6.8 (28)</td>
</tr>
<tr>
<td>Study</td>
<td>Dose</td>
<td>Treatment</td>
<td>Duration</td>
<td>IOP Reduction</td>
<td>Comparison</td>
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</tr>
<tr>
<td>Kampik et al,47 nb, mc</td>
<td>L</td>
<td>0.005% od×6 mo</td>
<td>25.1</td>
<td>7.1 (28)**††</td>
<td>Compared with bimatoprost (B)</td>
</tr>
<tr>
<td></td>
<td>BR</td>
<td>0.2% bid×6 mo</td>
<td>24.9</td>
<td>5.2 (21)**</td>
<td></td>
</tr>
<tr>
<td>Stewart et al,46 db, co, mc</td>
<td>L</td>
<td>0.005% od×6 wk</td>
<td>19.8</td>
<td>4.4 (22)**††</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BR</td>
<td>0.2% bid×6 wk</td>
<td>19.8</td>
<td>2.2 (11)**††</td>
<td></td>
</tr>
<tr>
<td>Computed with bimatoprost (B)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DuBiner et al,50 db, mc</td>
<td>L</td>
<td>0.005% od×1 mo</td>
<td>25.2f</td>
<td>7.6 (30)**</td>
<td>Compared with travoprost (TR)</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>0.3% od×1 mo</td>
<td>25.6f</td>
<td>8 (31)**</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PL</td>
<td>od×1 mo</td>
<td>25.8f</td>
<td>1.7 (7)</td>
<td></td>
</tr>
<tr>
<td>Gandolfi et al,51 sb, mc</td>
<td>L</td>
<td>0.005% od×3 mo</td>
<td>25.7f</td>
<td>7.8 (30)**</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>0.3% od×3 mo</td>
<td>25.7f</td>
<td>8.2 (32)**</td>
<td></td>
</tr>
<tr>
<td>Walters et al,52 sb, mc</td>
<td>L</td>
<td>0.005% od×1 mo</td>
<td>23.6f</td>
<td>7.5 (32)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>0.3% od×1 mo</td>
<td>24.1f</td>
<td>8.2 (34)</td>
<td></td>
</tr>
<tr>
<td>Noecker et al,55 sb, mc</td>
<td>L</td>
<td>0.005% od×6 mo</td>
<td>25.7f</td>
<td>6.0 (24)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>0.03% od×6 mo</td>
<td>25.0f</td>
<td>7.5 (30)</td>
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<tr>
<td>Parrish et al,53 sb, mc</td>
<td>L</td>
<td>0.005% od×12 wk</td>
<td>25.7f</td>
<td>8.6 (33)</td>
<td>Compared with unoprostone (U)</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>0.03% od×12 wk</td>
<td>25.7f</td>
<td>8.7 (34)</td>
<td></td>
</tr>
<tr>
<td>Computed with unoprostone (U)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aung et al,56 db, co</td>
<td>L</td>
<td>0.005% od×1 mo</td>
<td>22.3</td>
<td>6.1 (27)**†</td>
<td></td>
</tr>
<tr>
<td></td>
<td>U</td>
<td>0.12% bid×1 mo</td>
<td>23.2</td>
<td>4.2 (18)**</td>
<td></td>
</tr>
<tr>
<td>Jampe et al,57 nb, mc</td>
<td>L</td>
<td>0.005% od×8 wk</td>
<td>25.3</td>
<td>7.2 (28)**††</td>
<td></td>
</tr>
<tr>
<td></td>
<td>U</td>
<td>0.15% bid×8 wk</td>
<td>25.5</td>
<td>3.9 (15)</td>
<td></td>
</tr>
<tr>
<td>Reference (study design)a</td>
<td>No of evaluated patientsb</td>
<td>Treatment regimenc</td>
<td>IOP (mm Hg; mean)d</td>
<td>Baseline Reduction from baseline (%)</td>
<td></td>
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<tr>
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<tr>
<td>Saito et al,58 nb</td>
<td>26</td>
<td>U 0.12% bid od×6 wk</td>
<td>22.9</td>
<td>6 (26)*†</td>
<td></td>
</tr>
<tr>
<td>Susanna et al,59 db</td>
<td>52e</td>
<td>L 0.005% od×2 mo</td>
<td>24.1</td>
<td>6.7 (28)**††</td>
<td></td>
</tr>
<tr>
<td></td>
<td>53e</td>
<td>U 0.12% bid×2 mo</td>
<td>24.1</td>
<td>3.4 (14)**</td>
<td></td>
</tr>
<tr>
<td>Compared with timolol (T)+dorzolamide (D)g</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Anon,60 nb</td>
<td>80</td>
<td>L 0.005% od×3 mo</td>
<td>23.5</td>
<td>6.1 (26)**††</td>
<td></td>
</tr>
<tr>
<td></td>
<td>75</td>
<td>T 0.5% bid+D 2% bid×3 mo</td>
<td>23.0</td>
<td>4.7 (21)**</td>
<td></td>
</tr>
<tr>
<td>Emmerich,61 nb, mc</td>
<td>85</td>
<td>L 0.005% od×3 mo</td>
<td>22.2</td>
<td>4.5 (20)**</td>
<td></td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>T 0.5% bid+D 2% bid×3 mo</td>
<td>22.2</td>
<td>4.4 (20)**</td>
<td></td>
</tr>
<tr>
<td>Garcia Sánchez,62 nb, mc</td>
<td>77</td>
<td>L 0.005% od×3 mo</td>
<td>23.0</td>
<td>5.2 (23)**††</td>
<td></td>
</tr>
<tr>
<td></td>
<td>79</td>
<td>T 0.5% bid+D 2% bid×3 mo</td>
<td>23.7</td>
<td>4.0 (17)**</td>
<td></td>
</tr>
<tr>
<td>Honrubia et al,63 nb, mc</td>
<td>113</td>
<td>L 0.005% od×3 mo</td>
<td>23.2</td>
<td>4.3 (19)**</td>
<td></td>
</tr>
<tr>
<td></td>
<td>113</td>
<td>T 0.05% bid+D 2% bid×3 mo</td>
<td>23.1</td>
<td>4.0 (17)**</td>
<td></td>
</tr>
<tr>
<td>Polo et al,64 me, nb</td>
<td>18</td>
<td>L 0.005% od×3 mo</td>
<td>22.1</td>
<td>5.0 (23)**</td>
<td></td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>T 0.05% bid+D 2% bid×3 mo</td>
<td>22.4</td>
<td>3.4 (18)**</td>
<td></td>
</tr>
</tbody>
</table>
Compared with timolol (T) 1 pilocarpine (P) 2

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration</th>
<th>Mean Decrease (h)</th>
<th>Standard Deviation (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bucci, 65 sb, me</td>
<td>46</td>
<td>21.5</td>
<td>5.5</td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>22.3</td>
<td>4.2</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>21.5</td>
<td>6.1</td>
</tr>
<tr>
<td>Nordman et al, 66 sb, me</td>
<td>102</td>
<td>24.3</td>
<td>5.4</td>
</tr>
<tr>
<td></td>
<td>95</td>
<td>24.2</td>
<td>4.9</td>
</tr>
</tbody>
</table>
Compared with β-blocker+other agents

Pullunat et al, 67

<p>| | | | | |</p>
<table>
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<tbody>
<tr>
<td></td>
<td>β-blocker+</td>
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<tr>
<td></td>
<td>all other</td>
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</table>

a. In general, patients were 218 years of age or older with a baseline IOP of 2.22 mm Hg with or without pre-existing glaucoma therapy, unless otherwise specified. Exclusion criteria included angle-closure glaucoma, previous ocular surgery (including laser treatment within prior 6 months) or ocular trauma, contact lens use, severe dry eye syndrome, ocular inflammation within the prior 3 months, use of concomitant medications known to affect IOP, and any condition that prevented reliable applanation tonometry. The primary efficacy endpoint was the mean reduction in IOP from baseline. Comparative trials involving glaucoma medications requiring twice-daily administration were double-dummy in design.

b. Patients were either treatment-naïve or had withdrawn from other pressure-lowering therapy (with no more than two other agents) prior to the trial; the percentage of treatment-naïve versus previously treated patients was not provided except where indicated.

c. L was administered as a single drop to the eye in the evening unless otherwise specified.

d. Assessment of changes in diurnal IOP was calculated from the mean of two or three measurements taken between 8:00 am and 6:00 pm (unless otherwise indicated).

e. Percentage of treatment-naïve patients was 47% and 46% of L and T groups, 38 77% of all patients, 56 14% and 15% of L and U recipients, 59 and 48% and 39% of L and BR recipients. 50

f. Measured in the morning before drug application (trough), 38 between 9:00 am and 11:00 am, 50 and at 8:00 am, the time of peak effect for patients administered drug in the evening. 5, 50, 51, 53, 55

g. All patients underwent a 2- to 4-week run-in period with T before switching to L or continuing with T and adding D or P.

h. Baseline values estimated from graph.

i. Compared with timolol plus pilocarpine only.

j. Fixed combination.

k. At baseline, patients with well-controlled glaucoma were receiving dual therapy of β-blocker plus one other medication and had IOP ≤21 mm Hg.

l. Adjunctive treatment to β-blocker therapy included dorzolamide, pilocarpine, brimonidine, clonidine, and dipivefrine.

bid = twice daily; co = crossover; db = double-blind; me = multicenter; nb = non-blind; od = once daily;
PL = placebo; sb = single-blind (investigator masked).
0.05; ** p < 0.001 vs baseline; † p < 0.005; †† p < 0.001 vs comparator drug.
IOP reduction of $\geq 30\%$ was nearly 4-fold higher in those treated with latanoprost compared to those treated with dorzolamide (52% versus 14%).

**Compared with brimonidine**

A meta-analysis of nine comparative studies found that treatment with latanoprost produced significantly greater reductions in IOP from baseline compared with brimonidine after 3 months ($-8.4$ versus $-6.5$ mm Hg; $p=0.004$) and 6 months ($-8.0$ versus $-6.2$ mm Hg; $p=0.0045$).\(^{45}\) In three more recently published trials (one masked and two unmasked), once-daily latanoprost produced significantly greater reductions in diurnal IOP compared with twice-daily brimonidine 0.2% when administered for 6 weeks\(^{46}\) or 6 months.\(^{47,48}\) The mean IOP reductions from baseline with latanoprost ranged from 4.4 to 7.1 mm Hg (22% to 28%) compared to a range of 2.2 to 5.2 mm Hg (11% to 21%) in those treated with brimonidine. One 3-month trial found a comparable IOP-lowering efficacy of latanoprost and brimonidine (mean IOP reduction from baseline 6.5 mm Hg versus 6.8 mm Hg measured at 8:00 am, the time of peak drug effect following evening administration).\(^{49}\)

**Compared with other prostanglandins**

Trials comparing latanoprost 0.005% with bimatoprost 0.03%\(^{50-53}\) 0.03%\(^{53-55}\) or travoprost 0.0015% and 0.004%\(^{54}\) have, in general, found no clinically significant difference in IOP-lowering ability of these agents at 8:00 am, the time of peak effect (Table 7.1).

In the first trial to simultaneously compare the IOP-lowering efficacy of latanoprost, bimatoprost, and travoprost, Parrish and colleagues\(^{53}\) reported comparable efficacy among the agents. The study was designed as a 12-week, masked-evaluator, multi-center US study in which patients with open-angle glaucoma or ocular hypertension were randomized to once-daily treatment with latanoprost 0.005%, bimatoprost 0.03%, or travoprost 0.004% ophthalmic solutions.\(^{53}\) Baseline mean 8:00 am IOP values were similar among the treatment groups with significant ($p<0.001$) reductions from baseline IOP observed with each treatment at week 12. The reductions in mean IOP at 8:00 am, 12 noon, 4:00 pm, and 8:00 pm after 12 weeks of treatment were similar among the treatment groups. However, fewer latanoprost-treated patients reported ocular adverse events and hyperemia as well as lower average hyperemia scores compared to bimatoprost-treated patients ($p\leq0.001$).

In earlier studies, the IOP-lowering efficacy of latanoprost 0.005% was comparable to that of bimatoprost 0.03% and consistent with the findings of Parrish,\(^{53}\) with few exceptions.\(^{49,51,52}\) These studies found latanoprost and bimatoprost to have similar effects on mean IOP reduction at 8:00 am and throughout the diurnal cycle.\(^{49,51,52}\) However, the IOP-lowering efficacy tended to be more consistent during the day with bimatoprost, although statistically significant differences at all time points were not observed.\(^{49,51}\) Gandolfi and colleagues,\(^{51}\) in a post hoc analysis that did not take into account confounding differences in baseline IOP between the two treatment groups at 12 noon and 4:00 pm, found
significantly ($p<0.05$) lower mean IOPs in those treated with bimatoprost (≈17.1 and ≈17.2 mm Hg) compared to those treated with latanoprost (≈18.1 and
17.9 mm Hg) at these two time points. Walters et al\textsuperscript{52} found that a greater proportion of bimatoprost compared to latanoprost-treated patients achieved an IOP ≤ 15 mm Hg.

One exception to the generally consistent and comparable IOP-lowering efficacy results found in studies of latanoprost and bimatoprost was reported by Noecker et al\textsuperscript{55} who in a 6-month study reported a significantly greater mean IOP reduction in patients treated with bimatoprost compared to latanoprost. Unfortunately, the investigators did not adjust for significant differences between the groups in 12 noon baseline IOP, nor did they report standard deviations or 95% confidence intervals for estimates of differences in IOP reduction after baseline, thus limiting the ability to compare and contrast their findings with those of other investigations.

In one large 12-month study, the IOP-lowering efficacy of latanoprost was generally similar to travoprost administered as a single daily dose of 0.001 5% or 0.004%.\textsuperscript{6} At study completion, the mean IOP at 8:00 am, 10:00 am, or 4:00 pm was similar in patients receiving latanoprost or either dose of travoprost. The percentage of patients considered responders (≥30% reduction in IOP or a final IOP of ≤ 17 mm Hg) was comparable in the latanoprost, travoprost 0.0015%, and travoprost 0.004% treatment groups (49.6%, 49.3%, and 54.7%, respectively; \( p = 0.043 \) latanoprost versus travoprost 0.004%).

In contrast, several trials comparing latanoprost with unoprostone 0.15% twice daily for 1 to 2 months have demonstrated superiority with latanoprost.\textsuperscript{56–59}

\textit{Compared with \( \beta \)-blocker combination therapy}

Latanoprost monotherapy is at least as effective as and often more effective than dual therapy with timolol and dorzolamide or timolol and pilocarpine\textsuperscript{60–67} (Table 7.1). Overall, mean diurnal IOP was reduced by 19% to 26% in those treated with latanoprost,\textsuperscript{60–64} by 17% to 21% in those treated with timolol and dorzolamide for 3 months,\textsuperscript{60,62} and by 19% to 20% in those treated with timolol and pilocarpine for 6 weeks or 6 months.\textsuperscript{65,66}

\textit{Adjunctive therapy}

\textit{Latanoprost and timolol fixed combination}

The fixed combination of latanoprost 0.005% plus timolol 0.5% is significantly more effective at lowering IOP than monotherapy with either component or as compared to the combination of timolol and dorzolamide, and is sustained with long-term treatment\textsuperscript{68–70} In the US study performed by Higginbotham and colleagues,\textsuperscript{68} diurnal IOP levels after 26 and 52 weeks of treatment were 19.4 mm Hg and 18.9 mm Hg, respectively, in those treated with the latanoprost plus timolol combination, compared with 20.1 mm Hg and 20.1 mm Hg in those treated with latanoprost monotherapy, and 21.6 mm Hg and 19.3 mm Hg in those treated with timolol. In the European study by Pfeiffer\textsuperscript{69} the mean diurnal IOP levels observed after 26 weeks of latanoprost plus timolol treatment (18.5 mm Hg) were sustained
after an additional 26 weeks of non-blinded treatment (18.2 mm Hg).

*Adjunct to timolol or other β-blocker therapy*

Latanoprost is an effective IOP-lowering adjunct to timolol therapy, with studies demonstrating further reductions in IOP as compared to continued timolol treatment\(^2,71\) *(Table 7.2).* The
effectiveness of the latanoprost plus timolol combination is comparable regardless of which agent is initially used as monotherapy. The addition of once-daily latanoprost 0.005% to the patient’s current timolol 0.5% twice-daily regimen produced significantly greater reductions in IOP compared with the addition of pilocarpine 2% three times daily or dorzolamide 2% twice daily. When added to existing topical β-blocker monotherapy other than timolol, latanoprost 0.005% once daily and brimonidine 0.2% twice daily were comparable in lowering IOP at peak effect (Table 7.2).

Latanoprost has significant additive IOP-lowering effects when given as an adjunct to orally administered acetazolamide or topically administered dorzolamide, dipivefrine combination, or pilocarpine therapy. The addition of latanoprost to unoprostone therapy resulted in a significant reduction in IOP, but not vice versa, suggestive of a greater IOP lowering potency with latanoprost.

**Adjunct therapy with at least two other glaucoma agents**

Latanoprost 0.005% once daily for 1 month or 1 year produces an additional 16% to 18% reduction in IOP when administered as adjunct therapy to patients with persistently elevated IOP despite treatment with two or more IOP-lowering medications (Table 7.3). The effects of latanoprost add-on therapy were observed after only 1 week of treatment in a non-comparative trial. In a comparative randomized trial of patients with an uncontrolled IOP despite non-selective β-blocker and dorzolamide or pilocarpine treatment, adjunctive therapy with either latanoprost 0.005% once daily or brimonidine 0.2% twice daily produced a similar overall mean reduction in IOP.

**Angle-closure and other types of glaucoma**

In two double-blind clinical trials of patients with persistently elevated IOP despite iridotomy and/or iridectomy, latanoprost 0.005% once daily produced significantly greater reductions in IOP compared with timolol after 2 weeks (−8.8 mm Hg and −5.7 mm Hg, p=0.04) and after 12 weeks (−8.2 mm Hg and −5.2 mm Hg, p=0.04). When administered as adjunct therapy to patients following iridectomy and receiving treatment with β-blockers and pilocarpine with or without oral carbonic anhydrase inhibitors, latanoprost produced a rapid (within one week) and significant decrease in mean IOP (21% reduction from baseline, p<0.005) that was sustained after 3 months (25%) and 1 year (36%).

In randomized studies of patients with normal-tension or steroid-induced glaucoma, the IOP-lowering efficacy of latanoprost 0.005% once daily was similar to that of timolol 0.5% twice daily. In a 12-month study of patients with pigmentary glaucoma, treatment with latanoprost 0.005% once daily produced a significantly greater reduction in IOP (−5.9 mm Hg) compared to timolol 0.5% bid (4.6 mm Hg).
Table 7.2 Summary of results ofn prospective, randomised clinical trials evaluating the IPO-lowering efficacy of latanoprost in combination with timololor other β-blockers

| Reference (study design) | No of evaluated patients | Monotherapy | Adjunct therapy | IOP (mm Hg; mean)
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Baseline</td>
<td>On monotherapy</td>
<td>On combination therapy</td>
</tr>
<tr>
<td>Alm et al,2 db, mc</td>
<td>25</td>
<td>T 0.5% bid (ongoing)</td>
<td>L 0.006% od×2 wk</td>
<td>24.8 – 15.7</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>T 0.5% bid (ongoing)</td>
<td>L 0.006% bid×12 wk</td>
<td>24.9 – 18</td>
</tr>
<tr>
<td>Bron et al,71 db, mc</td>
<td>17</td>
<td>T 0.5% od×2 wk</td>
<td>L 0.005% od×6 Wk</td>
<td>NR 23.2c 17.5c</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>T 0.5% od×2 wk</td>
<td>T monotherapy continued ×6 wk</td>
<td>NR 24.2c 23.8c</td>
</tr>
<tr>
<td>Rulo et al,72 sb</td>
<td>10</td>
<td>L 0.006% bid×1 wk</td>
<td>T 0.5% bid×1 wk</td>
<td>28.5 19.6 17</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>T 0.05% bid×1 wk</td>
<td>L 0.006% bid×1 wk</td>
<td>24.2 18.3 15.7</td>
</tr>
<tr>
<td>Adjunct therapy with timolol-comparator trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bucci,65 sb, mc</td>
<td>45</td>
<td>T 0.5% bid 2–4 wk</td>
<td>L 0.005% od×6 mo</td>
<td>21.5c</td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>T 0.5% bid 2–4 wk</td>
<td>P 2% tid×6 mo</td>
<td>23.3c</td>
</tr>
<tr>
<td>Diestelhorst,73 nb, mc</td>
<td>120†</td>
<td>T 0.5% bid 2–4 wk</td>
<td>L 0.005% od×6 mo</td>
<td>23.3</td>
</tr>
<tr>
<td>5.6 (24)***</td>
<td>120‡</td>
<td>T 0.5% bid 2–4 wk</td>
<td>P 2% tid×6 mo</td>
<td>23.0</td>
</tr>
<tr>
<td>Petounis et al,74 nb, mc</td>
<td>75</td>
<td>T 0.5% bid 2–4 wk</td>
<td>L 0.005% od×3 mo</td>
<td>22.2</td>
</tr>
<tr>
<td></td>
<td>75</td>
<td>T 0.5% bid 2–4 wk</td>
<td>D 2% bid×3 mo</td>
<td>22.5</td>
</tr>
<tr>
<td>Simmons and Earl,75 db mc</td>
<td>53§</td>
<td>β-Blocker (ongoing)</td>
<td>L 0.005% od×3 mo</td>
<td>21.3h</td>
</tr>
<tr>
<td></td>
<td>54</td>
<td>β-blocker (ongoing)</td>
<td>BR 0.2% bid×3 mo</td>
<td>21.4h</td>
</tr>
</tbody>
</table>
a. L was administered as a single drop to the eye in the evening.
b. Mean of two or three recordings taken at different times of day between 8:00 am and 5:00 pm (unless otherwise indicated).
c. Recorded at 9:00 am.
d. Compared to monotherapy value.
e. Baseline estimated from graph.
f. Intent-to-treat analysis: four patients receiving Land 35 receiving P did not complete the study (p < 0.001).
g. Only patients who achieved a ≥ 15% reduction in IOP after 1 month of treatment were included in the 3-month IOP analysis (43 of 53 patients receiving Land 44 of 54 patients receiving BR).
h. Measured at 10:00 am (peak drug effect for both Land BR).

*p<0.05; **p<0.001 versus baseline; †<p<0.005; ††<p<0.001 versus comparator drug
Table 7.3 Efficacy of latanoprost as adjunct in patients receiving at least two other glaucoma medications

<table>
<thead>
<tr>
<th>Reference, study design</th>
<th>No of patients evaluated</th>
<th>Baseline therapy</th>
<th>Added treatment</th>
<th>IOP at baseline (mm Hg)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>IOP reduction (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patelska, et al&lt;sup&gt;83&lt;/sup&gt;</td>
<td>160</td>
<td>Various</td>
<td>L 0.005% od×1 mo</td>
<td>23.3</td>
<td>4.1 (18)*</td>
</tr>
<tr>
<td>Shin et al&lt;sup&gt;84&lt;/sup&gt;</td>
<td>61</td>
<td>Various</td>
<td>L 0.005% od×12 mo</td>
<td>23.5</td>
<td>3.9 (17)***</td>
</tr>
<tr>
<td>Simmons and 20&lt;sup&gt;β&lt;/sup&gt;-blocker+D or P</td>
<td>20</td>
<td>β-blocker+D or P</td>
<td>L 0.005% od×1 mo</td>
<td>NR</td>
<td>3.43 (17)**</td>
</tr>
<tr>
<td>Samuelson,81&lt;sup&gt;r&lt;/sup&gt;, sb, mc</td>
<td>20</td>
<td>β-blocker+D or P</td>
<td>B 0.25% bid×1 mo</td>
<td>NR</td>
<td>4.6 (23)**</td>
</tr>
<tr>
<td>Susanna et al&lt;sup&gt;82&lt;/sup&gt;</td>
<td>47</td>
<td>T 0.05%+D 2%</td>
<td>L 0.005% od×1 mo</td>
<td>19.3</td>
<td>3.1 (16)***</td>
</tr>
</tbody>
</table>

a. Where stated, this was measured at peak effect,
b. Percentage of patients achieving a >15%<sup>81</sup> or ≥20%<sup>82</sup> reduction in IOP.
B=brimonidine; bid=twice daily; D=dorzolamide; IOP= intraocular pressure; mc=multicenter; nc=non-comparative; od=once daily; P=pilocarpine; r=randomized; sb=single-blind (investigator masked); *<sup>p</sup><0.01, **<sup>p</sup><0.001, ***<sup>p</sup><0.0002 versus baseline.
Tolerability/safety

Data from numerous clinical trials confirm the tolerability as well as the ocular and systemic safety of latanoprost when used as first-line monotherapy or adjunctive therapy with other IOP-lowering agents in patients with open-angle glaucoma or ocular hypertension.\textsuperscript{6,44,46,47,49,56,57,59,71,72,76,78,91}

Overall, adverse events reported with latanoprost therapy are mild and reversible upon treatment discontinuation. In comparative studies with timolol, the ocular tolerability profiles were comparable, with 90% or more of patients having no or a minimal detectable increase in conjunctival hyperemia.\textsuperscript{92,93} The incidence of ocular adverse events was similar in short-term trials comparing latanoprost with bimatoprost\textsuperscript{50} or unoprostone.\textsuperscript{56,59} Both bimatoprost and travoprost produced substantially higher rates of ocular adverse events (for example conjunctival hyperemia) compared to latanoprost.\textsuperscript{5,51} In the study by Parrish and colleagues,\textsuperscript{53} latanoprost exhibited greater ocular tolerability compared to bimatoprost, including significantly fewer reported ocular adverse events ($p<0.001$), fewer reported cases of hyperemia ($p=0.001$), and lower average hyperemia scores after 12 weeks of treatment ($p=0.001$). Iridial darkening has been reported in 5% to 25% of those treated with latanoprost, particularly in those with hazel eyes, with no marked pathological changes observed in iris specimens.\textsuperscript{94,95}

Systemic adverse events are infrequent with latanoprost therapy, an effect much different to that of timolol.\textsuperscript{92} Gandolfi\textsuperscript{51} found significantly more increased eyelash growth in those who received bimatoprost compared to latanoprost, although headache was reported more frequently in latanoprost- compared with bimatoprost-treated patients. Respiratory disorders, which may be aggravated by $\beta$-blocker therapy,\textsuperscript{96} are unlikely with selective prostaglandin F\textsubscript{2}$\alpha$ therapies such as latanoprost. Clinical studies of latanoprost found no significant effects on peak expiratory flow, forced expiratory volume in 1 second, forced ventilatory capacity, asthma symptoms, or asthma medication requirements.\textsuperscript{96,97} In clinical trials of latanoprost, upper respiratory tract infection/cold/flu was the most common systemic adverse event, occurring at a rate of approximately 4%. Other systemic events, each with an incidence of less than 2%, included chest pain/angina, muscle/joint/back pain and rash/allergic skin reaction.\textsuperscript{98}

Supportive evidence for the tolerability of latanoprost comes from three retrospective studies of US managed care or pharmacy claims data that assessed medication persistency in treatment-naïve patients with glaucoma receiving monotherapy.\textsuperscript{99–101} Patients receiving latanoprost were significantly less likely to discontinue treatment compared to those given timolol (risk ratio 1.36) or brimonidine (risk ratio 1.54)\textsuperscript{101} and, of those who did discontinue treatment, the length of therapy was significantly longer with latanoprost (216 days) compared to timolol or brimonidine (183 days and 184 days, respectively, $p<0.001$ for each comparison).\textsuperscript{99} Patients treated with $\beta$-blockers, carbonic anhydrase inhibitors, or
brimonidine, were 24%, 122%, and 141% more likely to discontinue or change their
treatment as compared to those treated with latanoprost.\textsuperscript{100} Alm\textsuperscript{102} found that 380 of 519
(73%) patients with open-angle glaucoma enrolled in a 3-year study of latanoprost
0.005% once daily as adjunct therapy continued in a 2-year extension trial. During the 5-year period, IOP in approximately 72% of these patients was well controlled without treatment modification or surgery.

Conclusion

Elevated IOP is the most important risk factor for irreversible blindness in patients with glaucoma; therefore, the aggressive treatment of IOP is warranted. The prostaglandin analogues such as latanoprost are a highly effective and safe mode of first-line monotherapy as well as adjunctive therapy in patients who fail to achieve optimal IOP control with other classes of glaucoma agents. This offers clinicians the opportunity to tailor treatment strategies that optimize IOP lowering. Studies confirm that once-daily topical instillation of latanoprost 0.005% solution produces a robust and sustained IOP reduction of between 20% and 40% in adults with open-angle glaucoma or ocular hypertension. Latanoprost is well tolerated with minimal to no adverse ocular or systemic effects.

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8. BIMATOPROST

Stefano A Gandolfi

Introduction

According to the European Agency for Evaluation of Medicinal Products (EMEA),

‘Bimatoprost is a potent ocular hypotensive agent. It is a synthetic prostamide, structurally related to prostaglandin \( \text{F}_2\alpha \) (PGF\(_{2\alpha}\)). That does not act through any known prostaglandin receptors. Bimatoprost selectively mimics the effects of newly discovered biosynthesised substances called prostamides. The prostamide receptor, however, has not yet been structurally identified. The mechanism of action by which bimatoprost reduces intraocular pressure (IOP) in man is by increasing aqueous humour outflow through the trabecular meshwork and enhancing uveoscleral outflow. Reduction of the intraocular pressure starts approximately 4 hours after the first administration and maximum effect is reached within approximately 8 to 12 hours. The duration of effect is maintained for at least 24 hours.’

On the basis of the results of the phase III and IV studies so far available, we will ascertain how bimatoprost can address the most commonly encountered glaucoma and glaucoma-like situations in everyday life. For a more comprehensive review on the pharmacology and the safety profile of bimatoprost, the reader is referred to previous reviews.

Bimatoprost and ocular hypertension

The Ocular Hypertension Treatment Study (OHTS) has shown that, in eyes affected by ocular hypertension, a planned 20% IOP reduction can reduce by up to 50% the 5-year incidence of conversion to open-angle glaucoma. The baseline IOP of the OHTS population was in the mid twenties range (approximately 25–26 mm Hg). If we try to estimate the IOP in the OHTS-treated group (that is, 20% less than 25–26 mm Hg), we end with a ‘target IOP’ of 20 mm Hg. However, after a proper analysis, the actual incidence of conversion in the untreated group ranged from 2–17% (mean baseline IOP=22.2 mm Hg) to 6–36% (mean baseline IOP=27.9 mm Hg). Therefore, we may assume that a target IOP of 18 mm Hg (that is, 20% less than the lowest baseline IOP upon enrolment) could be considered to be a more reasonable target.
One drop of bimatoprost 0.03%, given once daily in eyes with high IOP, facilitated a target IOP $\leq 18$ mm Hg in 69.2–78% of the treated population.\textsuperscript{7–10} Therefore, a monotherapy with bimatoprost is likely to be an effective schedule in the majority of eyes affected by ocular hypertension.

**Early glaucoma treatment**

The 5-year interim analysis of the Collaborative Initial Glaucoma Treatment Study (CIGTS) has shown that, by dissecting a proper target IOP in each individual glaucomatous patient, either early surgery or a proper treatment with medication is effective in slowing progression of glaucomatous visual field damage.\textsuperscript{11} Treatment with medication seemed to be associated with an overall better outcome in terms of quality of life. Interestingly, the drop in IOP, observed upon medical treatment, ranged between 8 and 9 mm Hg.

One drop of bimatoprost 0.03%, given once daily in eyes with high IOP, could lead to a mean IOP drop of 9.2 mm Hg after 3 months.\textsuperscript{12} Therefore, a monotherapy with bimatoprost is likely to be an effective first-line option in newly diagnosed glaucomatous eyes.

**Advanced glaucoma**

The Advanced Glaucoma Intervention Study (AGIS) was designed to compare the risk-benefit profile of argon laser trabeculoplasty and trabeculectomy as a further option in advanced stage glaucoma. The report number 7 of AGIS offers an interesting post-hoc analysis of the data collected in the study. According to this analysis, a possible correlation between the rate of progression of the glaucomatous damage and the IOP measured through the long-term follow-up has been traced.\textsuperscript{13} In particular, a relative stability of the visual field defect(s) has been observed in those eyes showing an IOP $< 18$ mm Hg at every scheduled visit. Interestingly, the mean IOP observed in this study subgroup proved to lie between 12 and 13 mm Hg. Moreover, the mean IOP, measured during the first 18 months of the study, seemed associated with preservation of the visual field; in fact, the best outcome was observed in those eyes showing a mean IOP $\leq 14$ mm Hg during the first three 6-month visits.

One drop of bimatoprost 0.03%, given once daily in eyes with high IOP, facilitated an IOP $\leq 14$ mm Hg in 20.7–30% of the studied population.\textsuperscript{7–10} Therefore, a monotherapy with bimatoprost is likely to be an effective schedule even in severe glaucoma.
Normal-tension glaucoma

The Collaborative Normal Tension Glaucoma Study (CNTGS), after censoring for cataract, has shown that a 30% IOP reduction can offer some protection from further visual field deterioration in normal-tension glaucoma. These data are consistent with a previous report by Bandhari and coworkers, who showed that surgery was associated with a better outcome than no treatment in those NTG eyes showing at least a 25% IOP reduction over baseline. Thus far, prostaglandin derivatives are the only drugs with a reported efficacy in lowering IOP in eyes affected by normal-tension glaucoma.

Bimatoprost ‘face-to-face’ in comparison with PGF2α isopropyl ester raised fierce debate. Four randomized multicenter prospective clinical trials are so far available. In no case was bimatoprost reported as less effective than PGF2α isopropyl ester. One trial showed comparable efficacy of both drugs on IOP. Two trials showed some improved efficacy of bimatoprost at selected time points on the daily curve. The fourth, among those trials directly comparing bimatoprost with PGF2α isopropyl ester, showed bimatoprost to be more effective at every time point on the daily curve. Interestingly, a short course of bimatoprost 0.03% once daily can significantly decrease IOP in normal subjects. Taken together, the results of these trials show that bimatoprost is likely to offer ‘at least’ the same efficacy profile, if not better, than PGF2α isopropyl ester; therefore, bimatoprost can be offered as a potentially successful option in normal-tension glaucoma.

Eyes non-responders to prostaglandins

Prostaglandin derivatives are potent IOP-reducing agents. However, a significant number of patients can show poor response upon treatment with PGF2α isopropyl ester eye drops. The actual prevalence of non-responders to prostaglandins among the glaucoma population is still a matter of debate. The reported numbers can greatly vary according to (a) the treatment schedule (i.e. monotherapy or multitherapy), and to (b) the more-or-less conservative definition of non-responder. Therefore, the measured prevalence of non-responders can range from 4 to 50% of the studied patients. Dealing with patients who show a poor response to PGF2α isopropyl ester may then be rather difficult.

Due to its supposed mechanism of action, bimatoprost has been repeatedly tested in eyes showing poor response to PGF2α isopropyl ester. In a randomized controlled prospective crossover clinical trial, non-responders to PGF2α isopropyl ester have been exposed to bimatoprost and the vast majority of them showed a clinically relevant IOP drop. Therefore, bimatoprost can be effective in eyes where the PGF2α isopropyl ester is not at all effective.
Conclusions

In summary, a monotherapy with 0.03% bimatoprost can be offered as an effective option in:

- Ocular hypertension
- Early treatment in open-angle glaucoma
- Advanced glaucoma
- Normal-tension glaucoma
- Non-responders to PGF$_2_\alpha$ isopropyl ester.

Considering the unquestionable advantage of therapy with just a single agent, bimatoprost is likely to represent a promising option in terms of (a) cost-efficacy profile and (b) quality of life.

References


9.

TRAVOPROST (TRAVATAN®)

John Thygesen

Introduction

Glaucoma therapy

The goals of glaucoma treatment are to halt the progress of the disease and to preserve vision. According to a number of published randomized clinical trials,\textsuperscript{1–7} mean IOP should be reduced by at least 30\% or to less than 18 mm Hg at all visits, and diurnal IOP fluctuation should be minimized throughout the day.\textsuperscript{8}

First medical glaucoma treatment

For most patients, single drug therapy is adequate to reach a desirable IOP. In many patients β-blockers have been used as the first line of therapy since they are effective and usually topically well tolerated. Caution must be exercised if the patient suffers from a systemic condition such as bronchopulmonary disease or cardiac arrhythmia, since the systemic absorption of these drugs may cause relevant adverse systemic effects.

Over the past few years there has been a gradual shift in the choice of first line medical therapy. Prostaglandin analogues (such as latanoprost, travoprost) and prostamides (bimatoprost) have, in the hands of many ophthalmologists, superceded β-blockers as the first choice. Latanoprost has already received approval by the European health authorities (EMEA) as first-line treatment, but applications were also made for travoprost and bimatoprost. There is an ongoing debate regarding the different prostaglandins and prostamides which has not yet been settled in the scientific community.

<table>
<thead>
<tr>
<th>First treatment</th>
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<td>First line treatment</td>
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<td>First choice treatment</td>
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</table>

EGS Guidelines
Glaucoma medications

Topical ocular medical treatment is currently the method of choice for glaucoma. Medications that are available in topical preparations include α₂-adrenergics, β-adrenergic blockers, carbonic anhydrase inhibitors, parasympathomimetics and prostaglandin analogues/prostamides. Prior to 1978, only three classes of medications were available for the treatment of chronic glaucoma. These were topical miotics, topical non-selective sympathomimetics and oral carbonic anhydrase inhibitors. Topical miotics were generally effective but often poorly tolerated because of induced myopia, poor night vision, fluctuating vision or headache. Topical epinephrine or its analogues was useful, but frequently associated with tachycardia, nervousness and unsightly rebound hyperaemia. Oral carbonic anhydrase inhibitors were also quite effective but often exacted a major price in systemic side-effects such as lethargy, depression, gastrointestinal disturbances and renal lithiasis. Stevens—Johnson syndrome and aplastic anaemia were rare but devastating problems.

We are fortunate today in having many new alternative medications with which to treat chronic glaucoma. We may now individualize initial therapy to suit the medical, social and psychological status of each patient.

From 1978 topical β-blocking agents revolutionized the medical therapy of glaucoma. For the first time, a topical medication was available that had few visual or ocular side-effects. Systemic side-effects also seemed few and mild, at least in the healthier volunteers reported on in the initial studies. Beta-blockers are still among the most popular antiglaucoma agents and they have far surpassed any of their predecessors as the first therapy of choice in open-angle glaucoma. However, the initial hope of a side-effect-free class of drugs has proven illusory. Although the topical side-effects were few, the long-term systemic side-effects of the β-blocking agents have been shown to be many, often profound and, yet, frequently subtle. Exacerbation of asthma and chronic obstructive pulmonary disease due to induced bronchospasm are well known side-effects; therefore, these agents are usually avoided in those patients with a history of bronchospastic disorders. The potential for bradycardia, hypotension and bronchoconstriction restricts the use of β-blocking agents in a large number of patients. In addition, tachyphylaxis is common with timolol and up to 50% of patients require additional drugs within 2 years.

Selective α₂-adrenergic agonists both decrease aqueous humour production and enhance outflow. Examples of this class include apraclonidine and brimonidine. Brimonidine is used both alone and as adjunctive therapy. Apraclonidine is less often used because of frequent occurrence of tachyphylaxis and follicular conjunctivitis.

Topical carbonic anhydrase inhibitors, such as dorzolamide and brinzolamide, decrease the production of aqueous humour. Because they are not as effective as timolol, they are less frequently used as monotherapy.

Prostaglandin analogues and prostamides

Since 1994 a new class of topical agents for the medical treatment of glaucoma has appeared: the prostaglandin analogues/prostamides. The prostaglandin analogues include
latanoprost, travoprost and unoprostone. The prostamides include bimatoprost. This new class has added significantly to our ability to manage glaucoma and has widened the choice of initial and continuing therapy. Latanoprost (Xalatan [Pfizer]) and its chemical cousins, unoprostone isopropyl (Rescula [Novartis]), travoprost (Travatan [Alcon]) and bimatoprost (Lumigan [Allergan]) are prostaglandin-related, prostaglandin-like or, as may be the case with bimatoprost, prostamide medications (Figure 9.1). These drugs appear to lower intraocular pressure by stimulating the release of metalloproteases that degrade the extra-cellular matrix of the cells along the uveoscleral outflow pathways. This in turn promotes the outflow of aqueous humour and the reduction of IOP, although not all of these drugs may work via the same receptor systems.

Latanoprost 0.005% was the first available prostaglandin analogue introduced for glaucoma therapy in 1996. The reduction of IOP by PGF$_2$α is largely caused by increased uveoscleral outflow of aqueous.\textsuperscript{16–18} When used once daily, this medication has been demonstrated to have equivalent or, in some patients, superior efficacy when compared to timolol. Generally, IOP reductions of 25% to 35% may be expected.

The prostaglandin-related analogue unoprostone has low affinity for prostaglandin receptors and may be considered a docosonoid derivative. In addition to lowering the IOP, this agent may inhibit the activity of endothelin-1 and may improve ocular blood flow. However, a beneficial effect on human ocular blood flow remains unproven. Unoprostone has been in use in Japan since 1994. It appears to be safe but not as effective in lowering intraocular pressure as latanoprost or the other agents in this class. Unoprostone may even be additive to latanoprost. Unoprostone is less likely to change iris colour. This medication requires twice daily therapy and appears to have more modest efficacy related to latanoprost and timolol. As best as can be determined, it is useful as a first-line drug only in those cases that do not need large pressure reduction.
Figure 9.1 Chemical structure of prostaglandin derivatives and PGF$_{2\alpha}$ isopropyl ester.
Travoprost is a new prostaglandin F$_{2\alpha}$ analogue introduced in 2001. The efficacy and side-effects will be described in this chapter.

Bimatoprost was also introduced in 2001 and derived from cell-membrane-bound lipids. However, this agent has no demonstrable binding to any of the known prostaglandin receptors and is derived from anandamide rather than arachidonic acid, from which typical prostaglandins such as latanoprost are derived. This agent may, therefore, represent a new class of compounds that have been termed prostamides. Bimatoprost does not seem to activate the same receptors as latanoprost but does act to improve both pressure-sensitive and pressure-insensitive outflow and is at least as potent as latanoprost. Bimatoprost once a day is more potent than timolol twice a day and seems to maintain a flatter diurnal curve.

Latanoprost, bimatoprost and travoprost have all been shown to be at least as effective as timolol when used as monotherapy. In addition, because they work by a different mechanism to the β-adrenergic blocking agents, prostaglandin analogues would seem to be ideal agents to use as adjunctive therapy (Table 9.1).

**Travoprost**

Travoprost (Figure 9.2) is a member of a relatively new family of drugs, the prostaglandin analogues and the prostamides. These drugs, that include latanoprost, travoprost, unoprostone and bimatoprost, have been proven effective for the treatment of glaucoma. Prostaglandin analogues reduce intraocular pressure by increasing uveoscleral aqueous humour outflow. Prostaglandin analogues have fewer cardiovascular and respiratory side-effects than β-blockers. For these reasons, great interest has evolved for developing new prostaglandin analogues for the primary or adjunctive therapy of glaucoma.

**Indication for travoprost**

Travatan® ophthalmic solution is indicated for the reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension who are intolerant of other intraocular pressure lowering medications or insufficiently responsive (failed to achieve target IOP determined after multiple measurements over time) to another intraocular pressure.

**Table 9.1 Prostaglandin derivatives and prostamides**

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Latanoprost</th>
<th>Travoprost</th>
<th>Bimatoprost</th>
<th>Unoprostone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brand name</td>
<td>Xalatan®</td>
<td>Travatan®</td>
<td>Lumigan®</td>
<td>Rescula®</td>
</tr>
<tr>
<td>Drug family</td>
<td>Prostaglandin</td>
<td>Prostaglandin</td>
<td>Prostamide</td>
<td>Docosanoid</td>
</tr>
<tr>
<td>Formulation</td>
<td>0.005%</td>
<td>0.004%</td>
<td>0.03%</td>
<td>0.15%</td>
</tr>
<tr>
<td>Preservative</td>
<td>BAC 0.2 mg/ml</td>
<td>BAC 0.15 mg/ml</td>
<td>BAC 0.05 mg/ml</td>
<td>BAC 0.1 mg/ml</td>
</tr>
<tr>
<td>Dosage</td>
<td>Once daily</td>
<td>Once daily</td>
<td>Once daily</td>
<td>Twice daily</td>
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</table>
lowering medication. Travoprost may be used alone, or as adjunctive therapy. Application for
travoprost as first-line treatment has been made to the European health authorities (EMEA).

**Travoprost pharmacokinetics and pharmacodynamics**

Travoprost (Travatan, Alcon Research, Fort Worth, Texas) is a synthetic prostaglandin F
(PGF)$_{2\alpha}$ analogue that is highly selective for the prostaglandin F (FP) receptor. This
highly-selective characteristic of travoprost makes it less likely to produce side-effects (such
as pain, itching and hyperaemia) that are mediated by other prostanoid and non-prostanoid
receptors. Travoprost is a potent, full agonist at the FP receptor and has a higher affinity for
the FP receptor than do the other prostaglandin analogues$^{23\text{–}25}$ (Figures 9.3–9.5).

Travoprost is a lipophilic prodrug that readily penetrates the cornea. Esterases in the
cornea metabolize the prodrug to the active free acid, whereupon it is absorbed into the eye.
The travoprost free acid then binds to FP receptors on the ciliary muscle and trabecular
meshwork cells. This binding stimulates the release of matrix metalloproteinases (MMPs)
that degrade the extracellular matrix material of the uveoscleral outflow pathway. Aqueous
humour outflow increases, thereby decreasing IOP.$^{26}$

Topical ocular travoprost has been studied in animals and humans in concentrations
ranging from 0.0001% to 0.006%. Ocular pharmacokinetic data are lacking from humans, but
data from rabbits suggest that travoprost reaches maximum concentration in the aqueous
humour within 1 to 2 hours after topical application.$^{24}$ The aqueous humour concentrations
decreased with a half-life of 1.5 hours.$^{24}$ In humans, topical ocular administration of one
drop in each eye of 0.0015% or 0.004% travoprost showed that peak plasma concentrations
were reached within 30 minutes after dosing. By 1 hour post-dose, plasma levels were not
measurable. As expected from these results, travoprost did not accumulate after 1 week of
daily dosing.$^{26}$

In humans, travoprost probably disappears rapidly from the aqueous humour, as it does in
rabbits. However, its effect is prolonged. Trials in human populations show that IOP begins
to fall about 2 hours after corneal administration. The maximum decrease in IOP occurs after
12 hours and reduction is maintained for at least 24 hours.$^{27}$

The high selectivity and affinity for the FP receptor explain travoprost’s effectiveness.
Conversely, the low affinity for other prostaglandin receptors explains its profile of few
ocular and systemic side-effects. The absence of systemic side-effects may also be a result of
the low plasma concentrations and short plasma half-life that occur after topical ocular
Figure 9.3 Functional activity of travoprost and other FP agonists. Travoprost was found to achieve greater FP receptor efficacy and higher potency at lower molar concentrations, compared with bimatoprost and latanoprost free acids.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Receptor Binding Affinity (Ki, nM)</th>
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<tbody>
<tr>
<td></td>
<td>FP</td>
<td>EP&lt;sub&gt;1&lt;/sub&gt;</td>
<td></td>
</tr>
<tr>
<td>Travoprost (acid)</td>
<td>52±2</td>
<td>9,540</td>
<td></td>
</tr>
<tr>
<td>Bimatoprost (acid)</td>
<td>83±2</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>Latanprost (acid)</td>
<td>92±14</td>
<td>2000</td>
<td></td>
</tr>
<tr>
<td>PGF&lt;sub&gt;2&lt;/sub&gt;a</td>
<td>129±12</td>
<td>600</td>
<td></td>
</tr>
<tr>
<td>Unoprostone (acid)</td>
<td>5,649±893</td>
<td>12,000</td>
<td></td>
</tr>
</tbody>
</table>

Note: Lower number implies higher affinity

Figure 9.5 The chemical structure functional activity of travoprost and other FP agonists. The level of FP receptor response was measured in vitro as a percentage of maximum potential response. Due to its unique full-agonist property, travoprost was found to achieve greater FP receptor efficacy and higher potency at lower molar concentrations, compared with bimatoprost and latanoprost free acids. (Adapted from Hellberg M, Sallee V, McLaughlin M et al. Preclinical efficacy of travoprost, a potent and selective FP prostaglandin receptor agonist. J Ocul Pharmacol Ther 2001; 17: 421–432; Sharif NA et al. Eur J Pharmacol 2001; 432: 211–213; Griffin BW et al. J Pharmacol Exp Ther 1997; 281: 845–854.)

dosing. Finally, travoprost’s lasting effect on IOP may be a product of its mechanism of action, namely the release of MMPs. Proteolytic degradation of the extracellular matrix in the trabecular pathway may persist, enhancing aqueous humour outflow for up to a full day.

Clinical efficacy of travoprost

Two randomized, double-masked, placebo-controlled dose-ranging studies were conducted early in development. In one trial, a single dose of travoprost 0.0001%, 0.001%, or 0.002% was given at 8:00 am.28 In the other, a single dose of 0.001%, 0.002%, 0.004%, or 0.006%
was given at 8:00 pm. The reduction in IOP was dose-dependent at the lower concentrations, with the 0.004% concentration producing the maximum effect. IOP decreased by 28.1% to 30.7% (6.8 to 8.3 mm Hg.) Whether travoprost was
given in the morning or evening was immaterial, with both dosing times producing comparable reductions.

**Clinical trials**

Travoprost concentrations of 0.0015% and 0.004% were used for further investigation. More than 2400 patients were involved in four large studies which will be discussed.

1. In a 6-month, masked, multicentre trial a comparison of travoprost 0.0015% and 0.004% with timolol 0.5% in patients with elevated IOP travoprost once daily produced a lower mean IOP than timolol 0.5% twice daily. The difference in mean IOP reduction ranged from 0.9 to 1.8 mm Hg for the 0.0015% dose and from 0.9 to 2.4 mm Hg for the 0.004% dose. The maximum IOP reduction for both concentrations occurred in the second week and the effect was maintained for the entire 6 months of the study.

2. In a 9-month international multicentre pivotal study, with a similar design and using the same drug concentrations, a comparison of topical travoprost eyedrops given once daily and timolol 0.5% given twice daily in patients with open-angle glaucoma or ocular hypertension was performed. The study showed that travoprost produced a greater mean reduction from baseline IOP than did timolol (range −8 to −8.9 mm Hg and −6.3 to −7.9 mm Hg, respectively.)

3. In a 12-month US multicentre pivotal study, travoprost 0.0015% and 0.004% were compared to latanoprost 0.005%, another prostaglandin analogue, and to timolol 0.5%. Both travoprost and latanoprost were given once daily in the evening and timolol 0.5% was given morning and evening. Travoprost was superior to or equal to latanoprost and superior to timolol throughout the 1-year study period (Figures 9.6–9.8). The mean IOP values in the four groups were: travoprost 0.004%, 17.7 to 19.1 mm Hg; travoprost 0.0015%, 17.9 to 19.1 mm Hg; latanoprost 0.005%, 18.5 to 19.2 mm Hg; and timolol 0.5%, 19.4 to 20.3 mm Hg. This study produced two other interesting results. First, travoprost controlled IOP throughout the day, producing a flat diurnal IOP curve. Second, a subgroup analysis suggested that travoprost lowered IOP more effectively in African-Americans than either latanoprost or timolol. African-Americans are affected more severely by glaucoma than the rest of the population.

4. In a 6-month study travoprost was used as adjunctive therapy. Patients who did not respond adequately to 3 weeks of therapy with timolol 0.5% twice daily were started on either travoprost 0.0015%, travoprost 0.004% or placebo. Compared with placebo, both concentrations of travoprost produced additional IOP reductions of approximately 5 to 7 mm Hg more than the reduction obtained with timolol alone. These findings suggest that travoprost is useful as adjunctive therapy, at least in patients who do not respond to monotherapy with timolol (Figure 9.9).

In a new three-way study, latanoprost, bimatoprost and travoprost were compared. The 12-week, randomized, parallel-group study was intended to compare the IOP-lowering effect and safety of latanoprost, bimatoprost and travoprost in patients with open-angle glaucoma or ocular hypertension. The study was conducted at 45 sites in the US. Between 130 and 140 subjects were randomly assigned to each of these prostaglandin
Figure 9.6 Responder analyses for travoprost, latanoprost and timolol. The responder analyses were based on percentage IOP reduction (30% or greater) or mean IOP (17 mm Hg or less). The differences between travoprost 0.004% compared with latanoprost 0.005% and timolol 0.5% were statistically significant \( p = 0.0430 \) and \( p = 0.0001 \) or less, respectively. (Reprinted with permission from Elsevier Science Inc, from Netland PA, Landry T, Sullivan EK et al and The Travoprost Study Group. Travoprost compared with latanoprost and timolol in patients with open-angle glaucoma or ocular hypertension. Am J Ophthalmol 2001; 132:472–484.)

analogues. At 3 months, the change in pressure achieved with each drug was virtually the same within 0.3 mm Hg, so that they were statistically indistinguishable.

Clinical safety of travoprost

Clinical safety in prostaglandin derivatives

The most common side-effects associated with PG analogues are ocular hyperaemia, increased eyelash growth, eyelid skin darkening, and change in iris pigmentation.\textsuperscript{35–37} Of some concern is the ability of these agents to cause an increase in the melanin granule population of melanocytes in the iris stroma, resulting in permanent iris colour changes. Although no cellular proliferation or other dangerous sequelae of this effect have been seen, long-term consequences of prostaglandin use, especially in young patients, are of concern. Certainly, these agents should be avoided if possible in young patients who need unilateral treatment because of the risk of increased iris pigmentation and its increased recognizability when used in only one eye. Prostaglandin derivatives should also be avoided in pregnant
women because prostaglandins are known to induce labour; although there are no reports of premature labour associated with the use of prostaglandin derivatives, it seems prudent at this time to refrain from its use during pregnancy.

The use of prostaglandin derivatives has been reported to be associated with exacerbation of uveitis and cystoid macular oedema, but these associations have not been proven.
Figure 9.7 Mean intraocular pressure following travoprost 0.0015%, travoprost 0.004% and latanoprost 0.005% at different time points (8:00 am, 10:00 am and 4:00 pm), pooled from all visits. The baseline values were not significantly different for the travoprost 0.004% and the latanoprost 0.005% groups. The asterisk indicates that the mean IOP was significantly lower at the 4:00 pm time point for travoprost 0.004% compared with latanoprost 0.005% (p=0.0191). IOP = intraocular pressure. (Reprinted with permission from Elsevier Science Inc, from Netland PA, Landry T, Sullivan EK et al and The Travoprost Study Group. Travoprost compared with latanoprost and timolol in patients with open-angle glaucoma or ocular hypertension. Am J Ophthalmol 2001; 132:472–484.)

to be causal, thus their use may be contraindicated in those patients with a history of uveitis or recent complicated ocular surgery. More significant but uncommon side-effects include herpes simplex or herpes simplex-like keratopathy, muscle aches and flu-like symptoms.

Clinical safety in travoprost

At any of the concentrations studied, travoprost was safe and well tolerated. Fewer than 5% of patients withdrew from a study because of an adverse event. Perhaps most importantly for practitioners, the undesirable effects of β-blockers (for example, changes in pulse or blood pressure) did not occur with travoprost. Hyperaemia, the most common side-effect, occurred in all the studies. However, the hyperaemia was generally mild to moderate (less than 1 on a 3-point scale), and resolved without treatment. The frequency of hyperaemia appeared to be dose-dependent, occurring more often in patients receiving the 0.004% concentration than in those receiving 0.0015%. Hyperaemia was reported in up to 42% of patients receiving travoprost. By comparison, in one study, hyperaemia occurred in 1.6% of timolol patients, and in another study, hyperaemia occurred in 28% of latanoprost patients.
Figure 9.8 Travoprost vs latanoprost, US 12-month study, all patients, mean IOP at 4 pm. (Adapted from Netland PA, Landry T, Sullivan EK et al and The Travoprost Study Group. Travoprost compared with latanoprost and timolol in patients with open-angle glaucoma or ocular hypertension. Am J Ophthalmol 2001; 132:472–484.)

Figure 9.9 The efficacy of travoprost as adjunctive therapy to a β-blocker was demonstrated in the US 6-month adjunctive study involving more than 400 patients. In this study, the addition of travoprost 0.004% dosed once daily in patients whose open-angle glaucoma or ocular hypertension was insufficiently controlled with timolol 0.5% dosed twice daily further reduced IOP by up to 7 mm Hg. (Adapted from Orengo-Nania S, Landry T, Von Tress M et
Changes to eyelashes (colour, length, density and thickness) occurred in the longer studies. Eyelash growth occurred in more than 50% of patients. However, fewer than 1% of patients complained about eyelash changes. Iris hyperpigmentation occurred in 1% of patients who were treated with the 0.004% concentration. The incidence of iris hyper-pigmentation increased with length of exposure to travoprost 0.004%, occurring in 3.6% of patients treated for 1 year.

**Patient acceptance and compliance**

Travoprost has some compliance advantages. Unlike timolol, which is usually given twice a day, travoprost may be given once daily in the evening. This should be more convenient for patients, and should increase compliance. Unlike latanoprost, which has to be stored in a dark, cool location, travoprost is stable in light and can be stored at room temperature.

Travoprost has a higher frequency of hyperaemia that timolol or latanoprost. However, the hyperaemia is usually mild and resolves without treatment. It is unlikely that hyperaemia alone would preclude the use of travoprost.

Travatan®, the marketed formulation of travoprost, comes in a polypropylene bottle that dispenses a uniform drop size, ensuring proper dosing. This bottle is sealed in a pouch that inhibits evaporation of water, thereby increasing product shelf life.

**Conclusions**

Travoprost is a highly selective prostaglandin analogue that reduces IOP more effectively than timolol, and at least as well as latanoprost. Like latanoprost, travoprost can be given once daily and produces a flat diurnal IOP curve. Travoprost also provides additional IOP decreases when used as an adjunct to timolol. Interestingly, travoprost may provide greater IOP reduction than other drugs in African-American patients. Unlike timolol and other β-blocking agents, it has no cardiovascular or respiratory side-effects, and tachyphylaxis apparently does not occur. Other than mild hyperaemia, travoprost has few side-effects. Travoprost’s stability and packaging provide for accurate dosing and convenience. Travoprost is a valuable addition to the modern medical treatment of glaucoma.

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10.
PROS AND CONS OF OCULAR HYPOTENSIVE LIPIDS

Norbert Pfeiffer and Jochen Wahl

Introduction

For various reasons, medical treatment of glaucoma has become more complicated lately; until 1995, only three large groups of topical glaucoma medications were available, namely cholinergic drugs, sympathomimetic drugs and β-blockers. In a very few countries, only α2-agonists such as clonidine were also available. With the advent of the topical carbonic anhydrase inhibitors in 1995, the armamentarium of the glaucoma specialist grew richer, soon followed by brimonidine, another α2-agonist, and a whole new class of substances, heralded by latanoprost. Until 1995, the ophthalmologist faced simple choices: if the patient did not like the narrow pupil, he avoided pilocarpin; and if he suffered from asthma or second degree atrioventricular block, he avoided β-blockers. Now, we can treat such a patient successfully, even if he has both or even more contraindications, but we also face the agony of choice. This is particularly true for the group of drugs often referred to as the prostaglandins. At first glance they appear to have fairly similar properties, but this is heavily disputed by their manufacturers and distributors. Thus, this chapter is divided into three parts. The first part will explain some of the similarities and differences of the various prostaglandins. The second part will look into advantages and disadvantages of this group, and in the third part, the chapter will try to give recommendations for the selection of a specific drug for a specific patient.

Description of ocular hypotensive lipids

Prostaglandins are naturally occurring substances which are abundant in the eye. They were first extracted from the iris, a process that coined the German term ‘irine’ as a description for this group of substances. Later, it was discovered that these irines, then according to their structure called prostaglandins, occur virtually everywhere in the body. They are produced topically, trigger one or several of now well-described prostaglandin receptors and are degraded locally, before they can be distributed systemically to the rest of the body. Five different types of prostaglandin receptors have been described, namely
the FP, EP₁, EP₂, EP₃, and EP₄, IP, TP and DP receptors. The number of natural occurring prostaglandins is very high. The substances are degraded rapidly, but their metabolites may also have prostaglandin activity at the same receptors, or often at other receptors.

Almost as soon as prostaglandins were detected in the eye and their role as mediators of inflammation became clear, it was also apparent that they might serve as IOP-lowering agents: for a long time, it had been observed that in an acutely inflamed uveitic eye, the intraocular pressure was often lower and not higher than in the other, not inflamed eye. Thus, there was a keen search for prostaglandins which lowered intraocular pressure. However, most substances were not appropriate, because they carried with them a rather strong inflammatory reaction.

Latanoprost (trade name Xalatan, Pharmacia/Pfizer) was the first substance to exhibit a very high IOP-lowering activity while being almost devoid of inflammatory activity. Its clinical profile has been well described in many previous papers. At about the same time, Ueno synthesized unoprostone (trade name Rescula, Novartis), which still bears the name of its inventor. It also has a prostaglandin structure, but has two carbon atoms fewer than prostaglandin.¹ It shows a weaker IOP-lowering activity than latanoprost and must be given twice daily rather than once. It also has a much lower activity at the FP receptor when compared to latanoprost, and its mechanism of action may be an increase of trabecular outflow as opposed to latanoprost, which increases the uveoscleral outflow. Thus, it was concluded that it might not be a prostaglandin and the term docosanoid was coined for unoprostone.

The case was more straightforward for travoprost (trade name Travatan, Allergan). This substance is structurally very similar to latanoprost and it is also clinically similar in terms of mechanism of action, strength, duration and side-effects.² Thus, both manufacturers and users were happy to call it a prostaglandin.

The case became more complicated with the advent of bimatoprost (trade name Lumigan, Allergan). Again, this substance has a typical prostaglandin-like chemical structure. However, it was proposed that activity at the FP receptor was almost absent. However, in a human ciliary body cloned cell, agonist activity was shown for bimatoprost, travoprost, latanoprost, unoprostone isopropyl ester and other prostaglandin analogues at the cloned human body FP prostaglandin receptor.³ Bimatroprost lowers intraocular pressure to about the same extent as latanoprost and travoprost when given once daily, yet it was discovered that the mechanism of action is an increase of trabecular outflow and uveal outflow,⁴ rather than an increase of uveoscleral outflow, only. Thus, it was concluded that, since it behaved differently from the well-known prostaglandin latanoprost, it was not a prostaglandin, and the term prostanoid was invented. Given the variety of naturally occurring prostaglandins, there would not necessarily be a need to find new terms for the relatively slight variation in chemical structure or clinical behaviour of substances. However, the argument was also overshadowed by a lawsuit between the manufacturers of latanoprost and bimatoprost, Pharmacia and Allergan, respectively. Pharmacia claimed that Allergan had infringed a number of their patents referring to IOP-lowering prostaglandins. Eventually, the companies agreed that Allergan would dismiss challenges
to the validity of Pharmacia’s patents for latanoprost, while Pharmacia agreed to withdraw a challenge to Allergan’s patent for Lumigan. However, this history should be kept in mind when referring to the four prostaglandin-like substances. More hypotensive lipids are currently under evaluation.\textsuperscript{5}

The common denominator of all these substances is that they are lipids. While this term cannot be used to infringe on anybody’s rights or beliefs about the specificity of a specific substance, it is an extremely broad term which can be appreciated by everybody. A more specific description would call these substances phospholipids. Both terms are now used to avoid dispute. However, from a scientific point of view, it is exactly this dispute which should help us to understand more clearly whether these substances lower intraocular pressure because they are prostaglandins or despite the fact that they are prostaglandins, or, perhaps, for some other, still unknown reason.

**Pros and cons of hypotensive lipids**

There is no doubt that hypotensive lipids have enriched the armamentarium of modern glaucoma therapy. Many patients, who up until recently have not been treated adequately with medical therapy, can now be kept satisfactorily on topical agents. Also, the latest studies such as CNTGS,\textsuperscript{6} AGIS\textsuperscript{7} or EMGS have suggested that low intraocular pressures are necessary to stop the progression of glaucomatous diseases. Thus, agents with stronger IOP-lowering activity than previously available are warranted as much as agents that can be combined with previously available substances for even stronger combination therapy. In ocular hypertension lowering of IOP may prevent conversion to glaucoma as indicated by data from several groups.\textsuperscript{8–10}

**IOP-lowering activity**

In all studies latanoprost,\textsuperscript{11–13} travoprost\textsuperscript{13} and bimatoprost\textsuperscript{14,15} showed at least equal and usually higher IOP-lowering activity than timolol, which has been the gold standard of glaucoma therapy so far. While timolol rendered about 25% IOP-lowering activity, the three hypotensive lipids showed higher activity which was mostly statistically and often clinically significantly different from timolol. That is not true for unoprostone, which in most studies showed lower IOP reducing activity than timolol.\textsuperscript{16,17} Unoprostone also has weaker IOP-lowering activity than latanoprost.\textsuperscript{16} As mentioned above, target pressures are set towards lower values; thus, any drug with a high IOP-lowering activity has an inherent advantage.

**Administration once daily**

Latanoprost, travoprost and bimatoprost need only be administered once daily. Administration both at night and in the evening has been tested and has led to different IOP control over daytime of the following day. Yet application once daily is sufficient with
both regimes. Once daily administration is acceptable by patients and doctors alike; it interferes minimally with daily routine and must be perceived as a great advantage over twice, thrice or even four times a day application of other drugs.

All ocular hypotensive lipids show very good IOP control over 24 hours, including unoprostone when given twice daily. Thus, the IOP curve is flattened out. This can be seen as an advantage over other drugs.\textsuperscript{18}

**Combination therapy**

Prostaglandins have a mechanism of action which is unique, since it increases uveoscleral outflow. This seems to be less true for bimatoprost and unoprostone. Latanoprost and travoprost can be regarded as an additive to other IOP lowering drugs. There are, however, restrictions: the contractive force of pilocarpin and other parasympathomimetics reduces uveoscleral outflow, therefore they reduce the maximum effect of, for example, latanoprost.\textsuperscript{19}

The additive effect of outflow-increasing drugs (both conventional or uveoscleral outflow) can be combined with inflow-reducing drugs such as β-blockers or carbonic anhydrase inhibitors. Additive effects were shown for all four drugs, although the effect in some of the studies was less pronounced than expected. For this reason, Xalacom—a combination of latanoprost and timolol—has been released in Europe but not yet in the United States, since the combined effect of both drugs showed not enough advantage over the single drug to convince the FDA of its superiority over the administration of the respective single drugs or concomitant administration of latanoprost and timolol.\textsuperscript{20,21}

**Arguments against the use of ocular hypotensive lipids**

As is always the case with a new drug, in the beginning there is relatively little experience with the new drug or, in this case, new class of drugs. The lack of experience is usually linked to the occurrence of systemic or topical side-effects.

**Systemic side-effects**

Within the clinical evaluation of the four ocular hypotensive lipids, a number of systemic side-effects have been described.\textsuperscript{22} However, none of them could be definitely linked to the administration of the topical hypotensive lipid. The most likely reason for this is that, as for all prostaglandins, these substances are degraded very quickly. Prostaglandins, exogenous as much as endogenous forms, are degraded quickly because there is a rich choir of enzymes which degrade naturally occurring prostaglandins not far from the place where they are produced and released or, in the case of eye drops, applied to the conjunctival sac. Although there is a number of systemic contraindications, it appears that hypotensive lipids show an extremely good systemic risk profile. Consideration of side-effects is particularly important in the application of products.
Topical side-effects

Red eye
Prostaglandins are mediators of topical inflammation in the eye. Thus, it is not surprising that synthetic prostaglandins or hypotensive lipids can also induce inflammatory reactions. In addition to the intrinsic properties of substances in relation to their prostaglandin nature, these substances can be irritating by themselves. The topical preservatives may also cause irritating reactions. All hypotensive lipids irritate the eye more than a β-blocker, at least unless given as a suspension. The order of tolerability from good to worse appears to be latanoprost, travoprost and bimatoprost. This is supported by a study by Parrish et al, who compared these three substances in a double-masked clinical trial. However, differences were relatively small. The author has not enough personal experience to comment on the tolerability of unoprostone in comparison with the other hypotensive lipids.

Cystoid macular oedema (CME)
Following widespread use of latanoprost, cystoid macula oedema was reported in a number of cases. All studies so far have failed to quantify the exact risk of developing cystoid macular oedema following the administration of latanoprost. However, it appears that the risk is only increased if either the natural lens is missing or there is destruction of the posterior capsule of the eye. Although this is still a matter of dispute, the author of this chapter, along with many others, recommends caution in the use of latanoprost in cases of a missing natural lens or destruction of the posterior capsule of the eye. However, it appears that cystoid macular oedema in connection with latanoprost also resolves after discontinuation of the prostaglandin. Thus, cystoid macular oedema seems to be only a transient effect. Because of the low incidence the use of hypotensive lipids appears to be justified to some authors, even in high risk eyes.

Reactivation of herpes simplex virus keratitis
Several cases have been reported in which herpes simplex keratitis or kerato-uveitis has been reactivated after treatment with latanoprost or bimatoprost. The nature of this process is not yet completely understood. It has also been claimed that unoprostone will not induce these reinfections, although it binds to receptors similar to those for latanoprost. In all, there are very few case reports of recurrence of herpes keratitis but, nevertheless, this should be a consideration when choosing one of the drugs.

Increased length of eyelashes
This is probably the most minimal and possibly also the most wanted side-effect of prostaglandins. It was reported that patients using topical latanoprost developed longer and also stronger lashes, that also became curly at times. This does not appear to bother any patient. On the contrary, some would like to use latanoprost in the not affected eye to
stimulate growth of relatively short and thin lashes.

*Iris pigmentation changes*

Iris pigmentation has been one of the most intriguing side-effects. Fairly soon after initiating clinical studies, it was discovered that unilateral treatment with latanoprost led to
darkening of the iris on that side. The risk is higher in irides of mixed colour than in totally blue, grey or brown irides. The incidence was found to be as high as 69.7%. Clinical data suggest so far that the darkening of the iris is irreversible. Two histologic, prospective studies have investigated this phenomenon, both by Pfeiffer and collaborators: the Mainz I study and the Mainz II study. Both studies suggest the darkening of the eye to be due to an increased content of melanin but not to cell proliferation. Thus, the worst fears that malignant melanoma might be induced do not appear to be justified in the light of these studies. The strength of both studies was their well-controlled design. However, they looked at iridectomies of patients who had been treated with latanoprost for 3 or 6 months only and not for longer periods. Thus, the effects of continued treatment with hypotensive lipids need to be investigated.

In summary, hypotensive lipids carry a minimal risk of systemic side-effects. They are, however, accompanied by previously unknown topical side-effects which underline their nature as a very new and special group of substances.

Is there a best drug for a specific patient?

Until recently all hypotensive lipids were labelled for the lowering of increased IOP if first line drugs, usually β-blockers, were ineffective. Thus, in theory, their use was relatively limited. Current sales figures suggest that many ophthalmologists deviate from that recommendation and are using hypotensive lipids more liberally than previously. Quite obviously, latanoprost has the largest share in this market. Rescula is available, but only in a few countries and it plays a minor role. Travoprost and bimatoprost have smaller but enlarging shares in the market. Recently, latanoprost has received the labelling ‘first-line drug’ both in Europe and the USA, which is likely to support its share in the market. However, Travatan is also to receive that labelling. Is there any scientific evidence to favour one or the other drug?

Unoprostone has undisputedly the lowest IOP-lowering activity. Thus, it appears to be inferior in its ability to stabilize pressure-induced loss of visual function. However, it might be indicated in patients not responsive to other hypotensive lipids, because a differential response was shown when it was compared to latanoprost. Further differences include its postulated mechanism of action, which appears to be directed towards an increase in conventional outflow more than uveoscleral outflow. Whether a possible stimulating effect on ocular blood flow influences the clinical course of glaucoma needs to be shown.

A comparison is more difficult to make for the three other hypotensive lipids. Two studies compared IOP-lowering activity of latanoprost and bimatoprost and found no or minimal difference. A study by Parrish and collaborators compared latanoprost, travoprost and bimatoprost in a masked parallel prospective study of 3 months’ duration. So far, this is the only study to make a parallel comparison of these three hypotensive lipids. IOPs were taken at 8 a.m., 12 p.m., 4 p.m. and 8 p.m. at baseline and at 12 weeks and
mean diurnal IOPs (the means of the three measurements) were compared. There was no statistically significant difference in mean IOP reductions at 8 a.m., being 8.6±0.3 mm Hg for latanoprost, 8.0±0.3 mm Hg for travoprost and 8.7±0.3 mm Hg for bimatoprost. These findings are in line with those of previous studies. The mean reductions from baseline to week 12 at noon, 4 p.m. and 8 p.m. were not statistically significantly different either. Thus, there is no statistically significant difference, although latanoprost and bimatoprost fared slightly better in this study as compared to travoprost. However, there were differences concerning side-effects. Fewer latanoprost-treated patients (53.7%) reported ocular adverse events compared with bimatoprost (73.7%) or travoprost (64.5%), which was a statistically significant difference between latanoprost and bimatoprost. Also, fewer patients treated with latanoprost reported hyperaemia (47.1%) than with bimatoprost (68.6%) or travoprost (58.0%). In addition, the severity of the hyperaemia was generally lower in the latanoprost group as compared to the two other groups. However, generally the hyperaemia scores were low, 0.4 to 0.6 on a scale from 0 to 3.

**Conclusion**

The author’s general recommendation is as follows: if high IOP-lowering activity is of great importance, bimatoprost and latanoprost may be slightly superior to travoprost, although the clinical importance of this small difference is questionable. Latanoprost and travoprost may be more tolerable to the sensitive patient than bimatoprost. Unoprostone is inferior in IOP-lowering activity and is only recommended as adjunctive therapy or if better tolerable than the other hypotensive lipids. If one hypotensive lipid fails to show an adequate response, one of the other hypotensive lipids may, nevertheless, show adequate activity. They may, in rare cases, even be additive. Costs of treatment vary from country to country. However, hypotensive lipids, although relatively expensive, may contribute to better IOP control and subsequently less change in therapy, which has been shown to be associated with higher costs in medical glaucoma treatment.

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11.

COSOPT® VERSUS XALATAN®

Ann Hoste

Two strong risk factors in the development of glaucoma have currently been identified: increased intraocular pressure (IOP) on the one hand, and reduced blood flow in the back of the eye on the other. For this reason, each glaucoma medication should be evaluated for its potential to lower IOP, and for its possible vasoactivity in the posterior eye.

Cosopt is a fixed combination of timolol maleate 0.5% and dorzolamide 2%. In this chapter, an overview of the characteristics of both compounds is given, after which the IOP-lowering capacity and vasoactivity of Cosopt are compared to those of Xalatan.

Timolol

Timolol was the first β-blocker available in an ophthalmic solution. It was introduced on the market in 1978 and has since become the standard β-blocker in ophthalmology.

Mode of action in lowering intraocular pressure

The drug is a non-selective β-blocker with powerful β₁- and β₂-adrenoceptor binding capacity. The physiological basis for timolol to decrease IOP has not been unquestionably demonstrated. Timolol has no effect on outflow facility. It is generally believed that IOP reduction is achieved via decreased aqueous humor production, mainly through interaction with β₂-adrenoceptors in the ciliary processes and inhibition of the β-adrenergic stimulated synthesis of cAMP (that is, reduction of adenyl cyclase activity). In addition, timolol might act on β₂-adrenoceptors in the ciliary arteries to induce vasoconstriction, which in turn could contribute to the reduction in aqueous humor production. The β₂-adrenoceptor binding capacity of β-blockers however, may, not completely account for their therapeutic efficacy, as the β₁-selective blocker betaxolol is an effective IOP-lowering agent as well. Because calcium-channel blockers have been shown to have IOP lowering effects, the calcium-channel blocking activity of β-blockers might also be considered from this aspect. It is also possible that serotonin receptors are partly involved.

Clinical efficacy

Timolol exerts most of its IOP-lowering effects within 2 weeks of initiation of therapy.
although further minor decreases in IOP can be observed at 3 months.\textsuperscript{16,17}
The average percentage reduction in IOP induced by timolol 0.5% twice daily varies between clinical trials and is between 19% and 29%. A meta-analysis of 11 randomized controlled trials revealed that the mean percentage reduction in IOP from baseline produced by timolol was 26.9% (SE: 3.4%) at 3 months.

The non-responder’s rate is another matter of interest. If patients are considered to be non-responders when IOP reduction achieved by timolol is less than 6 mm Hg, or measured IOP remains above 20 mm Hg with timolol, the non-responder’s rate is about 20%.

The efficacy of timolol has not been surpassed by other β-blockers in ophthalmic solutions. Timolol is as effective in reducing IOP as the other non-selective β-blockers levobunolol, carteolol, and metipranolol. It is more potent than the β₁-selective drug betaxolol in most studies, although in some the two drugs were comparable with regard to efficacy in lowering IOP.

Long-term drift, that is an increase in IOP after long-term application of timolol, may in part be attributable to progression of the glaucomatous disease. On the other hand, a small loss of efficacy may be partly responsible for this phenomenon, as aqueous humor flow is somewhat higher after a year’s treatment than it was after a week’s treatment. In general, however, IOP control with timolol can be regarded as well maintained over several years.

If timolol is discontinued after long-term application, its effects will remain for at least 2 weeks. Discontinuation for up to 4 weeks may be required for complete disappearance of the timolol effect. Timolol can be detected in the aqueous humor up to 5 days after withdrawal, and even 42 days after withdrawal the drug can still be present in pigmented ocular tissues.

Timolol can be less efficacious in patients on concomitant systemic β-blockers, because systemic administration of β-blockers lowers IOP as well.

**Safety profile**

Timolol is generally well tolerated. It is the glaucoma medication with which we have had the most experience. In the 1980s, it was estimated that the use of topical timolol had increased to account for 70% of all glaucoma medications used and its use may not have diminished significantly until the arrival of new glaucoma medications. This yields the important advantage over newly developed medications in that side-effects have long been identified and consequently can mostly be avoided by careful patient selection. Chronic obstructive airways disease and cardiac conduction defects, in particular, are important contraindications for timolol that are related to its β₂- and β₁-adrenoceptor-blocking activity, respectively.

Congestive heart failure is currently still seen as another contraindication related to its β₁-adrenoceptor blocking effects. However, this clearly needs reconsideration. Contrary to long-held beliefs, systemic administration of β-blockers does not aggravate heart failure and
is even beneficial in the treatment of this disease.\textsuperscript{38,40–45} Beta-blockers have recently been shown to reduce morbidity and mortality in patients with mild, moderate and advanced heart failure. Patients with chronic heart failure have increased sympathetic
nervous system activity that contributes to deterioration of cardiovascular function over time. Long-term \( \beta \)-blocker therapy prevents such deterioration through inhibition of this neurohormonal pathway. The impressive survival data collected from several large studies have made \( \beta \)-blockers a component of standard heart failure therapy.

Timolol should be used with caution by pregnant women, as fetal bradycardia and cardiac arrhythmia have been reported.\(^4^6\) Furthermore, much higher concentrations of timolol can be retrieved in the milk of nursing mothers than in blood plasma.\(^4^7\)

Depression, fatigue, anxiety, confusion, worsening of Raynaud’s phenomenon or claudication, sexual dysfunction, unawareness or prolonged hypoglycemia in non-insulin-dependent diabetes, and impaired neuromuscular transmission have occasionally been reported,\(^3^6,^4^8\) and have been associated with the \( \beta \)-adrenoceptor blocking activity of timolol. However, an evidence-based assessment could not identify studies supporting the development of most of these adverse events, neither with systemic nor with topically applied \( \beta \)-blockers.\(^3^8\) According to this study, wide acceptance of such traditionally purported side-effects has been largely due to propagation of isolated case reports and short series.\(^3^8\)

Timolol may decrease high-density lipoprotein (HDL) cholesterol levels in plasma,\(^2^4,^2^5\) although there are currently no indications that this affects the clinical outcome of the patient. There are no important local side-effects arising with timolol. Punctate keratitis\(^3^6\) and allergic reactions occur rarely.

**Vascular effects in the posterior eye**

In most vessels, \( \beta_2 \)-adrenoceptor stimulation causes vasodilatation, whereas \( \alpha_1 \)-adrenoceptor stimulation causes vasoconstriction. Beta-blockers can generally be expected to induce vasoconstriction, as during \( \beta_2 \)-adrenoceptor blockade \( \alpha_1 \)-mediated effects of
Figure 11.1 The vessel myograph, isolation procedure. A ring segment of a posterior ocular vessel (such as retinal artery, shown here) is dissected free under a microscope. Subsequently, the segment is threaded on two thin wires, and the whole preparation is transported to an organ bath.
endogenous adrenergics are no longer opposed. Whether timolol and other β-blockers actually exert such vasoconstrictor action in the back of the eye depends on whether or not functional β-adrenoceptors are present in the posterior ocular arteries. This is suitably investigated with the vessel myograph, where drugs are added directly to isolated segments of these arteries in an organ bath (Figures 11.1 and 11.2). This technique facilitates highly precise measurements, under controlled conditions, of functional responses of posterior ocular arteries to the drug under investigation. To investigate the presence of β-adrenoceptors, the effects of β-adrenergic agonists (such as isoproterenol or isoprenaline) have been studied. These agonists have failed to induce significant relaxation (i.e. vasodilatation) in all studies of retinal, choroidal, long and short posterior ciliary and ophthalmic artery alike. Some experiments were performed on human short posterior ciliary arteries, which confirmed results obtained from various animal species such as cow, pig and cat. Thus, β-blockers (such as timolol) cannot have adverse vasoconstrictor effects in the back of the eye through their β-adrenoceptor blocking activity, because such receptors are too few in number in all posterior ocular artery types to affect vascular tone.

On the other hand, it has been shown in various studies that β-blockers can act as vasodilators in retinal and posterior ciliary artery. This has nothing to do with their β-adrenoceptor binding capacity, but is rather a direct effect on the Ca^{2+} channels in the
smooth muscle cell membrane. In other words, β-blockers have Ca$^{2+}$ channel blocking activity that underlies their vasodilator effects. Although this activity appears to be a more general property of β-blockers, each specific β-blocker can have it to a
greater or lesser extent. Propranolol (the standard β-blocker in pharmacology) and betaxolol both have significant Ca\(^{2+}\) channel blocking activity that is more powerful than that of timolol.\(^{12,51,53-56,59}\) For this reason, it is uncertain whether the latter drug could have any clinically relevant vasodilator effects in the patient.

**Dorzolamide**

Dorzolamide was the first carbonic anhydrase (CA) inhibitor available in an ophthalmic solution. It was introduced into the market in 1995 and was originally conceived as an alternative for oral carbonic anhydrase inhibitors (mainly acetazolamide) that are not well tolerated when administered chronically.

**Mode of action in lowering ocular pressure**

The reduction in IOP by dorzolamide is achieved exclusively via decreased aqueous humor inflow.\(^{60,61}\) Dorzolamide 2% is, however, less effective as a suppressor of aqueous humor flow than systemically administered acetazolamide\(^{60}\) or topical timolol 0.5%.\(^{61}\) Dorzolamide is a CA inhibitor with powerful effects on isoenzyme II, and to a lesser extent on isoenzyme IV.\(^{62}\) Isoenzyme II is present in the epithelium of the ciliary processes and plays a key role in aqueous humor production. Isoenzyme IV probably is not critical for aqueous humor production, as it was not observed to be present in human ciliary processes, although this issue has not been resolved unequivocally.\(^{62}\) All CA isoenzymes catalyze the transformation of water and carbon dioxide into bicarbonate through the following chemical reaction:

\[
H_2O + CO_2 \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-
\]

This reaction is a necessary step in the transportation of Na\(^+\) and water across the ciliary epithelial cell into the posterior chamber.

**Clinical efficacy**

The effects of dorzolamide are fully established after 2 weeks of treatment, as no significant further IOP decreases are observed at 3 months.\(^{63}\) The mean reduction in IOP after 3 months of application of dorzolamide 2% three times daily is 15.5% at morning trough (before drug instillation) and 19.8% at morning peak (2 hours postdose).\(^{63}\) Dorzolamide maintained an adequate reduction of IOP in 55% of patients after one year of treatment\(^{64}\) in one long-term study, and in a comparable 53.9% after 2 years of treatment in another study.\(^{65}\) Most patients who required add-on therapy did so within the first 6 months of initiating dorzolamide therapy.\(^{65}\)

The effect on IOP of dorzolamide 2% three times a day has not been surpassed by the only other topical CA inhibitor available, brinzolamide 1% at a regimen of two times a
Dorzolamide has no additive effects in patients on concomitant systemic CA inhibitors.67

Safety profile

Dorzolamide is generally well tolerated systemically. Since the drug is a sulfonamide, any hypersensitivity against sulfonamides represents an absolute contraindication as this may lead to lethal blood dyscrasia (aplastic anemia, thrombocytopenia, and agranulocytosis). This has been reported with systemic CA inhibitors, although fortunately not with topical ones so far. Since dorzolamide is excreted in urine, caution is required in patients with severe renal impairment. Nausea, indigestion, fatigue, headache, and paresthesia are side-effects commonly observed with systemic CA inhibitor treatment, but they are quite rare with dorzolamide.62 There are no adequate studies on pregnant and nursing women.

The most important causes of discontinuation of dorzolamide therapy are its local side-effects. These comprise bitter or abnormal taste related to the CA inhibitor activity, ocular stinging, burning, or other discomfort and allergic reactions.62,65 In a long-term study, drug-related adverse events occurred more frequently during the first year (29.7%) than during the second one (13.8%).65

Dorzolamide inhibits CA isoenzymes II and IV in the corneal endothelium where these enzymes are involved in fluid transport and thus determine corneal hydration.68 Though dorzolamide has no significant effects on corneal thickness and endothelial cell loss in healthy eyes up to one year of treatment,69,70 caution is required in a subset of glaucoma patients with severe corneal endothelial compromise.71,72 Dorzolamide might cause irreversible corneal edema in these patients.71

Vascular effects in the posterior eye

As mentioned above, CA catalyzes the transformation of water, and carbon dioxide, into bicarbonate. Inhibition of this enzyme results in accumulation of carbon dioxide (CO2), which is a well-known and potent vasodilator.73–79 Thus, the standard CA inhibitor acetazolamide is a well-known powerful vasodilator of, among others, cerebral blood vessels.78–88 The drug is used routinely in neurology and neurosurgery to measure the so-called ‘cerebrovascular reserve capacity’ in patients with cerebrovascular disease.78,79,83–88 That is, the ability of cerebral vessels to lower their resistance in response to decreases in cerebral perfusion pressure, expressed as change in cerebral blood flow from baseline under a maximum vasodilatory stimulus. As cerebral arteries are closely related to the ocular ones, acetazolamide can be expected to act as a vasodilator in ocular arteries as well. The drug has indeed been shown to increase blood flow in the ophthalmic artery,81 choroid81,89 and retina.90 The ophthalmic and central retinal arteries, however, appear less
responsive than the middle cerebral artery to acetazolamide.\textsuperscript{91}

Other CA inhibitors such as dorzolamide can be expected to have similar vasodilator properties. Moreover, experiments on rabbits do provide evidence that dorzolamide gets to the back of the eye after topical application.\textsuperscript{62,92} Furthermore, CA isoenzyme II was
observed to be present in the human retina. More specifically, CA isoenzyme II activity was observed in Muller cells, cones, and pigmented epithelium. Various in vivo studies of ocular blood flow have been undertaken to demonstrate vasodilator effects of dorzolamide in the human posterior eye. The non-invasive methods used include scanning laser ophthalmoscopy after fluorescein dye injection, color Doppler ultrasound imaging, laser Doppler velocimetry and flowmetry, and ocular pulse amplitude. Dorzolamide decreased the retinal arteriovenous passage time of injected fluorescein dye in the retinal vasculature and accelerated capillary dye transit in the macula and optic nerve head as well. Increases in blood velocity at these various locations suggest, but do not prove, that topically applied dorzolamide was enhancing perfusion. In another study, however, such increases could not be confirmed. In the aforementioned papers the drug left unaltered blood velocity or resistance index in the retrobulbar vessels (posterior ciliary, central retinal, and ophthalmic arteries) as analyzed by color Doppler imaging. In contrast, others reported that the resistance index was significantly lower in the ophthalmic and central retinal arteries after topical application of dorzolamide. Optic nerve head circulation seemed not to be affected by dorzolamide as assessed by laser Doppler flowmetry. Utilizing a similar technique, others have reported that dorzolamide failed to alter retinal blood flow, although the drug may not have had sufficient time to reach the retina as only a single drop of dorzolamide was applied. Dorzolamide increased ocular pulse amplitude, which primarily reflects increases in choroidal blood flow. It remains to be determined, however, whether this effect is related to increases of ocular perfusion pressure secondary to the fall of intraocular pressure or a vasodilator effect of the drug, or both.

Thus, while there is unquestionably a pharmacological rationale to indicate that CA inhibitors can increase blood flow, dorzolamide was observed to increase ocular blood flow in some studies, but not all. Conflicting findings point to a limited accuracy of currently used in vivo techniques to assess drug effects on blood flow, and to the multitude of uncontrolled parameters that can affect results. This makes the studies of oxygen tension in the vitreous next to the optic disc in the pig all the more important. In these studies, dorzolamide was found to increase oxygen tension at the optic nerve head after intravenous administration, while intraocular pressure was kept constant.

In the author’s own laboratory, we investigated the vasoactivity of dorzolamide under in vitro conditions, by using the vessel myograph described above (Figures 11.1 and 11.2). Dorzolamide could affect vascular tone through two distinct mechanisms. First, dorzolamide might cause accumulation of (the potent vasodilator) carbon dioxide in the retinal tissues surrounding the vessels, thus indirectly acting as a vasodilator. Alternatively, or in addition, the drug might have direct vascular effects, either through accumulation of carbon dioxide within the vessel wall or through a yet unknown mechanism of action. In order to investigate the latter direct vascular effect of dorzolamide, we (as usual) added the drug to isolated retinal arteries that were carefully dissected free of all surrounding retinal tissue. It appeared that dorzolamide had no pronounced effects under these conditions as only a minor, although statistically significant, relaxation (vasodilatation) was observed at the highest doses used.
Vasoconstriction was never observed. In
Figure 11.3 Direct effects of dorzolamide on isolated bovine retinal arteries that were carefully dissected free of all surrounding retinal tissue (n=6). Arteries were precontracted with $K^+$ 120 mM to allow demonstration of relaxant effects of dorzolamide. Increasing doses of dorzolamide were added after the $K^+$-induced contraction had stabilized. Control (tone=100%) was $K^+$-induced tone (or force) prior to dorzolamide application. The small relaxation observed during dorzolamide $3 \times 10^{-5}$ M was statistically different from time control experiments.

In order to study the indirect vascular effects of the drug we repeated the same experiment, this time with the surrounding retinal tissues still adherent to the arteries, allowing for carbon dioxide accumulation in these tissues. Under these conditions we again observed a small (although statistically significant) relaxation at the highest doses of dorzolamide used (Figure 11.4). This confirmed the minor direct relaxing effect we observed earlier, but we were unable to demonstrate any additive indirect effects, through carbon dioxide accumulation in the surrounding retinal tissue. Again, vasoconstriction was never observed.

Although we cannot attribute any clinical implications to the minor vasodilator effects we observed, our experiments do not at all exclude the possibility that carbon dioxide does accumulate in the retina in the in vivo situation and significantly increases blood flow in the glaucoma patient. The specific in vitro conditions used may have impeded vasodilator responses that may only be demonstrated under the in vivo condition. It is, for example, conceivable that carbon dioxide, which is a gas, diffused rapidly out of the organ bath before it had the chance to exert its vasodilator action. However, our experiments are reassuring in that we were able to demonstrate with certainty that dorzolamide has no vasoconstrictor effects.
**Figure 11.4** Experiments to study the indirect effects of dorzolamide on isolated bovine retinal arteries with adherent retinal tissue (n=6). Arteries were precontracted with K 120 mM to allow demonstration of relaxant effects of dorzolamide. Increasing doses of dorzolamide were added after the K-induced contraction had stabilized. Control (tone=100%) was K-induced tone (or force) prior to dorzolamide application. The small relaxation observed during dorzolamide 3 × 10^{-5} M was statistically different from time control experiments, and comparable with the one shown in Figure 11.3.

**Cosopt**

Timolol and dorzolamide are almost completely additive in their effects on aqueous humor flow, despite the fact that both drugs act by decreased aqueous humor production. Consistent effects were observed in the 1980s with timolol and the oral CA inhibitor acetazolamide. The timolol—dorzolamide combination appears to be more effective in this respect than the betaxolol—brinzolamide one. Thus timolol and dorzolamide have additive effects on IOP as well. After 3 months of treatment, the mean reduction in IOP was 22.2% for timolol alone, 15.5% for dorzolamide alone, and 27.4% for the combination, at morning trough (that is, just before drug instillation). At morning peak (i.e. 2 hours after drug application), IOP reduction was 22.6%, 19.8% and 32.7% for timolol, dorzolamide, and the combination, respectively. The addition of dorzolamide to timolol...
induced a further significant IOP reduction of 10% to 19%.\textsuperscript{105,108} In contrast, the addition of timolol to dorzolamide induced a further intraocular pressure reduction at peak and afternoon trough of 34% and 28%, respectively, after 1 week.\textsuperscript{110} The IOP-lowering effect of Cosopt (the fixed dorzolamide-timolol combination) twice
daily is comparable to that of dorzolamide three times daily plus timolol twice daily.\textsuperscript{111} No long-term drift is observed after a 1-year treatment period.\textsuperscript{111} Cosopt is generally well tolerated and there were no further safety issues with Cosopt versus the concomitant therapy with each of its components,\textsuperscript{63,109,111} while compliance is improved. The proportion of discontinuation of the combination therapy is comparable with that of dorzolamide, and is greater than that of timolol, as more patients receiving the combination report ocular burning, stinging, or a tearing eye.\textsuperscript{63,109}

\textit{Cosopt versus Xalatan}

Overall, Xalatan and Cosopt provide equal intraocular pressure reduction.\textsuperscript{112} The vascular effects of these medications differ significantly, however. Cosopt is unquestionably a safe drug where preservation of ocular blood flow is concerned. As described above, the possibility that timolol or dorzolamide has vasoconstrictor effects in the posterior ocular vessels can be excluded with certainty. In contrast, this obviously is not the case for latanoprost (Xalatan).

It may seem to the clinician that latanoprost is a vasodilator, because the drug clinically causes conjunctival-scleral hyperemia. This hyperemia, however, is probably mediated by branches of the sensory trigeminal nerve\textsuperscript{113} and thus occurs specifically in the ocular surface structures. The direct vascular effects of the drug are definitely of another kind. Latanoprost is a derivative of prostaglandin F\textsubscript{2α} (PGF\textsubscript{2α}), which is a well-known vasoconstrictor of various extraocular arteries, such as the cerebral,\textsuperscript{114–116} pulmonary,\textsuperscript{117} iliac,\textsuperscript{118} coronary,\textsuperscript{119–121} renal,\textsuperscript{121} mesenteric,\textsuperscript{121} uterine,\textsuperscript{122} and carotid\textsuperscript{122} arteries and the aorta.\textsuperscript{119} Both the author’s and others’ studies with the vessel myograph (Figures 11.1 and 11.2) have shown that PGF\textsubscript{2α} also acts as a vasoconstrictor in the retinal,\textsuperscript{123–129} anterior\textsuperscript{130} and posterior ciliary\textsuperscript{131} choroidal\textsuperscript{131} and ophthalmic\textsuperscript{132,133} arteries. In most of these papers PGF\textsubscript{2α} has not been the drug under investigation, but it has been used routinely as a contractile (i.e. vasoconstrictor) agent in these studies of physiopharmacological characteristics of posterior ocular vessels. These observations with the prototype drug PGF\textsubscript{2α} were pointed out in an ophthalmic journal soon after the introduction of latanoprost into the market, in 1997.\textsuperscript{134} It was, however, impossible at that time to investigate the in vitro effects of latanoprost itself because the active substance, latanoprost free acid, was not yet commercially available, the latanoprost in the ophthalmic solution being an inactive prodrug that needs activation by the ocular tissues. The first study of an ocular artery with the vessel myograph was conducted in 1998 by the manufacturer.\textsuperscript{135} This study showed that, as could be expected, latanoprost free acid acted as a vasoconstrictor in bovine posterior ciliary artery. This was confirmed by other investigators in the pig.\textsuperscript{136} The author’s group characterized the vasoconstrictor effects of PGF\textsubscript{2α} and latanoprost free acid on bovine retinal and choroidal arteries.\textsuperscript{137} We found that the vasoconstriction induced by either compound is
probably mediated by the TP prostanoid receptor, as it was significantly blocked in both retinal and choroidal arteries by a TP-receptor antagonist (Figure 11.5).

The latanoprost concentrations required for vasoconstriction are higher than the ones that are believed to reduce intraocular pressure, but on the other hand they are lower than the concentrations in the ophthalmic solution. Thus, while it might well be that latanoprost is unable to exert its vasoconstrictor action in patients with glaucoma, the possibility that it (sometimes) does, cannot be dismissed on purely theoretical grounds. A thorough theoretical discussion was held soon after the introduction of the drug into the market. The only way to enlighten our understanding was to measure vascular responses in the in vivo situation, after topical application of the latanoprost ophthalmic solution. Such studies have since tended to reassure us because not a single one showed any adverse effects with latanoprost. In the studies specifically referred to here, blood flow even increased. These are all studies of pulsatile ocular blood flow, which is an

Figure 11.5 Representative tracing showing the vasoconstrictor effects of latanoprost. Increasing doses of the active form of latanoprost, latanoprost free acid, were added to an isolated ring segment of bovine retinal artery. Latanoprost free acid induced a marked dose-dependent contraction, in this specimen from doses of $10^{-5}$M onward, although in other specimens contraction could be observed from doses of $10^{-6}$M onward. After washout of latanoprost free acid and subsequent full relaxation of the latanoprost free acid induced contraction, the selective TP receptor blocker ICI-192.605 was added. Increasing
doses of latanoprost free acid, added in the presence of the TP receptor blocker, failed to
induce any vasoconstriction, indicating that the TP prostanoid receptor mediates the
latanoprost-induced contraction.
estimate of total ocular blood flow. In view of our findings that latanoprost has vasoconstrictor activity, the most plausible explanation is that in fact increases of ocular perfusion pressure secondary to the fall of intraocular pressure were being measured, instead of direct vascular effects. Some authors of these studies came to similar conclusions.\textsuperscript{138,139,144} If the observed effects are sustained after long-term application of latanoprost, they could optimistically be regarded as beneficial. However, it should be noted that this overall effect on total ocular blood flow might mask focal choroidal vasoconstriction, for example due to (not inconceivable) local differences in the latanoprost diffusion rate. Even massive retinal vasoconstriction could go undetected by this technique, as the contribution of retinal blood flow to pulsatile ocular blood flow is merely 2 to 5%.\textsuperscript{145} Another remark on the in vivo data is that they were obtained from intact eyes. Reports of cystoid macular edema with latanoprost in eyes that underwent cataract surgery\textsuperscript{146} show that at least in this subpopulation of patients, diffusion of latanoprost was accelerated to such an extent as to induce pronounced biological effects in the posterior pole.

On balance, there is currently no experimental evidence that latanoprost will exert its vasoconstrictor effects in the in vivo situation. Still, it is hoped that future improvements in techniques to measure ocular blood flow will allow conclusive determination of whether long-term application of latanoprost is unable to impair ocular blood flow in all subpopulations of patients with glaucoma. There is no doubt that the direct vascular effects of latanoprost have no add-on value in the treatment of glaucoma.

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Introduction

Impairment of blood supply to the optic nerve head, retina and peripapillary choroid due to vascular dysregulation is considered an important cause of the progression of glaucoma. Pathological segmental vasoconstiction (ischaemia) followed by vasorelaxation (reperfusion damage) in the branches of the ciliary and the retinal arterioles represents the insufficiency of autoregulation. This, in addition to the fluctuation of the ocular perfusion pressure due to either intraocular pressure (IOP) spikes or transient decreases of the effective arterial pressure in the ophthalmic artery is considered a significant risk factor in glaucoma. In clinical practice, treatment of vascular dysregulation in the eye cannot be separated from the IOP-lowering medication, since no evidence-based special ocular vascular treatment is available at present. However, several of the IOP-lowering drugs do show vascular effects (beneficial or potentially dangerous for the glaucomatous eye) in in-vitro and in-vivo animal models. Knowledge of vascular effects of eye drops approved for IOP lowering in glaucoma has been increasing in the last years, although the published findings are sometimes contradictory, and some of the clinical techniques used to measure ocular blood flow require further development.

It is important to understand that great care is necessary to derive direct treatment conclusions from experimental studies on the vascular effects of the drugs used to reduce IOP, since most of the information necessary for such a decision is still missing. First of all a molecule with proven in-vitro vasoactive property may only exert its vascular effect in the human eye, if the molecule is delivered to the potential target tissues (retina, optic nerve head, peripapillary choroid, optic nerve) in a sufficiently high concentration, but without reaching a toxic systemic level. This concentration must be maintained in the target tissues for 24 hours a day, since a pathological vascular reaction may develop at any time. Until now very few systematic studies have addressed these fundamental questions, which means that the human ocular concentrations of most of the potentially vasoactive glaucoma medications are still unknown (Table 12.1). Since a part of the vasoactive molecule is bound to the cell membrane or to melanin in the target tissues, the
Table 12.1 Drugs approved for decreasing IOP in glaucoma, and their influence on ocular blood flow

<table>
<thead>
<tr>
<th>IOP-lowering molecule</th>
<th>Concentration in human retina, choroid and optic nerve head during chronic administration in clinical dosage</th>
<th>Clinicalo studies suggesting potentially beneficial effect on human ocular perfusion</th>
<th>Clinical studies suggesting potentially deleterious effect on human ocular perfusion</th>
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</thead>
<tbody>
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<td>Betaxolol</td>
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<td>No</td>
</tr>
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<td>Yes/No</td>
<td>Yes/No</td>
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<td></td>
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</tr>
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</tr>
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<td>Yes/No</td>
</tr>
<tr>
<td>Bromonidine</td>
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<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

*When the in-vitro effective concentration range is considered the reference value.

concentration of the unbound, pharmacologically active molecule remains unknown. The animal models are not necessarily informative for the human concentrations, since different species have different receptor profiles, different drug delivery systems with undetermined capacities, different metabolic activity and the body weight of the experimental animals including primates is considerably smaller than that of the human patients. Since a potential increase in the ocular perfusion pressure due to the drug-induced IOP decrease might always be a possible reason for any measured perfusion change in in-vivo or clinical studies on IOP-lowering drugs, and because of the limits of some non-invasive clinical blood flow measurement techniques, it is not always easy to separate the true vascular effects from the artefacts related to the measurement technique. On the other hand, an accelerated perfusion of the whole eye or the whole retina does not necessarily mean that the blood flow in the precapillaries and capillaries of the optic nerve head is improved. Since several topical
IOP-lowering drugs (especially some non-selective $\beta$-receptor blockers$^{3,4}$ and clonidine$^6$) have a clinically significant negative influence on
systemic perfusion, their direct effects on ocular perfusion might be compromised by their systemic cardiovascular effects. Finally, perfusion measurements during long-term studies may be influenced by modification of the topical and systemic medication, or the development of novel ocular and systemic diseases, which influence ocular perfusion or progression of glaucoma.

**Topical β-receptor blockers**

A selective β₁-receptor blocker: betaxolol

Betaxolol is a highly lipophilic β-receptor blocker, which is relatively selective for the β₁ receptors. In addition, the molecule has a special Ca²⁺ channel blocking property for the voltage-dependent (L-type) Ca²⁺ channels, which is independent from the β-receptor blocking property. By blocking the Ca²⁺ channels betaxolol diminishes the Ca²⁺ influx, which leads to a decreased intracellular Ca²⁺ concentration. Since vasoconstriction is mediated by an increased Ca²⁺ concentration in the vascular smooth muscle cells and the pericytes, betaxolol has a vasorelaxing property on the contracted vessels. Vasorelaxation can be evaluated by measuring the decrease in the vessel wall stretch and the increase in the vessel diameter on precontracted vessels in vitro. The vasorelaxing property of betaxolol was verified on both K⁺ precontracted vessel segments and on vessels exposed to 10⁻⁹ M endothelin-1 (ET-1). This latter finding is especially important, since ET-1 is considered a polypeptide with an important role in vascular dysregulation of the glaucomatous eye. The in-vitro vasorelaxing property of betaxolol seems to be a general feature found on many different arteries of several different mammalian species, including the human retinal arteries. Betaxolol-induced vasorelaxation was significant on preconstricted isolated retinal vessels from 10⁻¹² M a betaxolol concentration.

Because of the vasorelaxant potential of this molecule, extensive research has been performed in order to evaluate systematically the concentration of topically applied betaxolol in the eye. Betaxolol 0.25% ophthalmic suspension was instilled into one eye per animal at a clinical dosage (bid) in chronic experiments. The in-vivo studies were performed on pigmented rabbits and cynomolgus monkeys. In a later study, ocular betaxolol concentration was evaluated on enucleated eyes of glaucoma patients who had been treated with bid 0.25% betaxolol suspension for at least one month. Since the enucleated human eyes had no previous vitrectomy, trauma or ocular tumour this investigation provided unique information on the ocular distribution of a topically applied antiglaucoma drug. The concentration distribution of betaxolol was uniform in all studies; the plasma concentration was of magnitudes lower than the different ocular concentrations (Figures 12.1 and 12.2; Table 12.2), which suggests an accumulation of the lipophilic betaxolol molecule in the retina, optic nerve head, optic nerve and choroid. The concentration of betaxolol in these tissues (including the human samples) was magnitudes higher than the minimum
concentration necessary for vasorelaxation in vitro. In the study
on glaucoma patients the interindividual difference in betaxolol concentration was small for each human ocular tissue (Table 12.2), which suggests that the measured values probably represent concentrations typical for the glaucomatous human eye. In the animal studies the untreated fellow eyes also showed relatively high betaxolol concentrations, which suggests that one of the major transport routes is the circulating blood plasma, which delivers topically applied betaxolol after its systemic absorption. The low plasma betaxolol concentration is in accord with the results of the human studies on systemic β-receptor occupancy of topically applied betaxolol compared to that of topically applied non-selective β-receptor blockers.18–20

It is important to recognize that in the experiment on rabbits, in which betaxolol concentrations of the different ocular tissues were plotted against time elapsed from the last instillation, the ocular concentrations remained stable for at least 24 hours, while the plasma betaxolol concentration decreased rapidly (Figure 12.1 and 12.2). This suggests a local accumulation of the drug, which allows a continuous supply to the posterior ocular layers. The possibility for the formation of such a pool was shown in a human study21 in which β-receptor blocker concentrations of human trabeculectomy specimens obtained from eyes

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**Figure 12.1** Betaxolol concentrations of the plasma, choroid, and retina plotted against time elapsed from the last instillation after a 7-day bid treatment with 0.25% betaxolol suspension, in the rabbit. One eye per animal was treated, and the fellow eye remained untreated. Different animals were used for the different time periods (Alcon, data on file, with permission).
chronically instilled with timolol or betaxolol were measured. The high concentrations found suggest that these molecules may be distributed along the orbital septa to the posterior pole of the eye, and may penetrate into the eye there. Transcorneal pene-
Figure 12.2 Betaxolol concentrations of the plasma, optic nerve head, and optic nerve plotted against time elapsed from the last instillation after a 7-day bid treatment with 0.25% betaxolol suspension, in the rabbit. One eye per animal was treated, and the fellow eye remained untreated. Different animals were used for the different time periods (Alcon, data on file, with permission).

Table 12.2 Betaxolol concentrations in the posterior layers of the human glaucomatous eye and in the blood plasma of the same patients after bid treatment for at least 28 days with 0.25% betaxolol suspension. The table shows data on four phakic eyes.⑨

<table>
<thead>
<tr>
<th></th>
<th>Plasma</th>
<th>Retina</th>
<th>Choroid</th>
<th>Optic nerve head</th>
<th>Optic nerve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>0.53 (0.36)</td>
<td>64.0 (26.5)</td>
<td>1631 (1324)</td>
<td>38.6 (11.7)</td>
<td>5.89 (5.83)</td>
</tr>
<tr>
<td>Range</td>
<td>0.16–1.02</td>
<td>46.2–94.4</td>
<td>669–3542</td>
<td>26.1–54.4</td>
<td>2.80–14.2</td>
</tr>
</tbody>
</table>

In several clinical investigations using colour Doppler imaging,22–27 increased blood velocity and decreased resistive index were found in the retrobulbar and ocular vessels after the initiation of topical betaxolol medication. In some clinical studies improvement of visual
functions was also detected.\textsuperscript{26–28} In other investigations, however, the improvement of the ocular perfusion was not observed.\textsuperscript{29–32}

**Non-selective \(\beta\)-receptor blockers: timolol, levobunolol, carteolol and nipradilol**

In addition to their non-selective \(\beta\)-receptor blocking property, timolol and carteolol exert a \(\text{Ca}^{2+}\) channel blocking activity similar to that of betaxolol, but only in a considerably higher concentration.\textsuperscript{14,33,34} This effect is associated with a relatively weak, concentration-dependent, in-vitro vasorelaxing property.\textsuperscript{33–35} The potential influence of the intrinsic sympathomimetic activity of carteolol on the ocular perfusion remains unknown.\textsuperscript{23,36} In addition to its \(\beta\)-receptor blocking activity, nipradilol has selective \(\alpha_1\)-receptor blocking property and a nitric oxide donating effect.\textsuperscript{37} These factors may have a role in the transient increase of optic nerve head blood flow velocity induced by topical nipradilol in humans.\textsuperscript{37} This is supported by the periocular nipradilol concentration measured in monkeys 60 minutes after instillation. The measured value was in the concentration range of effective vasorelaxation by nipradilol on the isolated canine central retinal artery in vitro.\textsuperscript{37} In different animal experiments the lipophilic non-selective beta-receptor blockers showed a concentration ratio between the blood plasma and the ocular tissues similar to that seen after instillation of betaxolol.\textsuperscript{38–41} In the albino rabbit levobunolol was found in significantly lower concentrations in the vitreous, choroid-retina, and optic nerve specimens than timolol after a single instillation of the 0.5% solutions.\textsuperscript{42} In animal experiments the periocular and intraocular accumulation of the non-selective \(\beta\)-receptor blockers, their periocular transport to the deep orbital tissues and their presence in the contralateral eye were similar to those observed for betaxolol.\textsuperscript{39–41} Periocular accumulation of timolol after long-term topical medication was measured on human trabeculectomy specimens.\textsuperscript{21} Systematic studies on human ocular concentrations of these molecules, however, have not been presented.

The results of the clinical studies in which the influence of the topically applied non-selective \(\beta\)-receptor blockers on the ocular perfusion was studied are contradictory.\textsuperscript{43,44} Retinal vasoconstriction,\textsuperscript{45} reduction of the end-diastolic velocity in the ophthalmic artery\textsuperscript{46} and increased resistive index of the temporal posterior ciliary artery due to timolol medication\textsuperscript{23} were reported as well as no effect of this molecule on pulsatile ocular blood flow,\textsuperscript{47} and optic nerve head perfusion.\textsuperscript{48} Even a significant decrease in the resistive index and an increase in the end-diastolic velocity of the retrobulbar vessels were published after topical timolol treatment.\textsuperscript{49} Levobunolol instillation was associated with an increase in pulsatile ocular blood flow,\textsuperscript{50} but also with no change of ocular perfusion and resistive indices.\textsuperscript{23} Topical carteolol had no effect on perimacular haemodynamics with blue field entoptic stimulation,\textsuperscript{51} decreased the resistive index in the central retinal artery but not in the
retrobulbar vessels, increased the optic nerve head blood velocity with the laser speckle technique, and increased the pulsatile ocular volume in healthy volunteers.
Carbonic anhydrase inhibitors (CAIs) lower IOP by decreasing aqueous humour production of the ciliary epithelial cells. Systemic administration of acetazolamide induces an increase in the cerebral and retinal flow. A similar effect on the ocular circulation was found after acute or short-term topical or systemic application of dorzolamide and brinzolamide in in-vivo animal models, as well as following their topical administration to healthy volunteers, or to patients suffering from normal tension glaucoma or primary open-angle glaucoma. Brinzolamide, which is more lipophilic than dorzolamide or acetazolamide at physiological pH, was found in 0.338 μg equivalents/g in the retina of the pigmented rabbits after a single instillation. This concentration and its relatively long half-life in the retina suggest that this molecule (and probably also the other CAIs) may directly influence the retinal vessels. In a laser Doppler flowmetric study on rabbits, bid instillation of brinzolamide 1% or dorzolamide 2% for 7 to 14 days resulted in a similar, significant increase in optic nerve head blood flow, and a decrease in IOP. These changes were associated with a mild but significant decrease of the arterial pH. In contrast, in another study using bid dorzolamide 1% instillation for 20 days on rabbits, no change of the optic nerve head circulation was measured with laser speckle analysis. In studies on domestic pigs, intravenous administration of acetazolamide and dorzolamide caused a dose-dependent increase in oxygen tension at the optic nerve head. This effect of the intravenously injected dorzolamide was maintained despite the acute experimental elevation of IOP, which shows that the increase in oxygen tension is independent from the IOP decrease induced by these molecules.

In the human studies on topical CAIs, using intravenous fluorescein or indocyanin green dye injections and the scanning laser angiographic technique, the retinal arteriovenous transit time was found to be decreased and the macular capillary transport velocity increased. In the same study no change of the retrobulbar perfusion was measured with colour Doppler imaging. Other investigators, however, did find a significant decrease in the resistive index of the posterior ciliary arteries after topical CAI administration. Capillary flow as measured by scanning laser Doppler flowmetry on the supero-temporal neuroretinal rim of eyes suffering from primary open-angle glaucoma was found to be increased after topical dorzolamide treatment. In another study, the optic nerve head blood flow measured with the same technique and laser Doppler flowmetry remained unchanged in healthy volunteers after a similar treatment. In a study on previously untreated primary open-angle glaucoma patients, no alteration of the retrobulbar perfusion and no change in the retinal capillary perfusion were observed when the measurements taken after a 6-week tid dorzolamide medication were compared to the pretreatment baseline. Pulsatile ocular blood flow increased in the clinical studies on topical CAIs. In short-term studies, topical application of dorzolamide 2% was followed by an improvement in the central retinal
sensitivity as well as in
the contrast sensitivity under physiological hypercapnia or hyperventilation-induced hypocapnia. The short-term functional improvement is considered a consequence of the increased retinal perfusion. The clinical significance of this, however, remains unknown, since no long-term studies are available on the alterations of the visual functions of eyes on topical CAI monotherapy.

Compared to the findings on topical timolol 0.5% medication, an accelerated retinal perfusion in the superior retinal vasculature was found after the topical administration of the fixed combination of timolol 0.5% and dorzolamide 2%.75 This means that the potentially beneficial effect of dorzolamide on ocular perfusion is maintained when this carbonic anhydrase inhibitor is applied together with a non-selective β-receptor blocker. On the other hand, in the same study the visual field indices, the contrast sensitivity, or the blood velocity and the resistive indices of the retrobulbar vessels, remained unchanged.

The mechanism of the increase in intraocular oxygen tension measured in the animal experiments using carbonic anhydrase inhibitors or the acceleration of the retinal perfusion observed in humans after topical administration of CAIs remains unclear. Acidic changes in the intraocular pH or some direct but still unknown vascular effect of CAIs on the ocular vessels have been presumed.59,74

Prostaglandin analogue, prostaglandin metabolite analogue and prostamide drugs

Isopropyl unoprostone

Isopropyl unoprostone is a synthetic docosanoid, an analogue of the naturally occurring metabolite of docosahexaenoic and docosatetraenoic acids.76,77 This molecule has a low affinity for prostaglandin (PG) receptors but it has a strong Ca\(^{2+}\) channel blocking activity on L type Ca\(^{2+}\) channels and a stimulatory effect on maxi-K ion channels.76–78 These effects lead to a decrease in the intracellular Ca\(^{2+}\) level, which causes a dose-dependent relaxation of the precontracted contractile elements. This relaxing property of unoprostone was verified in in-vitro studies on ET-1-precontracted isolated vessel segments and trabecular meshwork strips,76–78 as well as in in-vivo animal models.79,80 The ocular concentration of unoprostone after a single instillation was measured in the pigmented rabbit.81 The maximum concentration in the different intraocular tissues was detected at 30 minutes to 60 minutes after the instillation. This was followed by a fast decrease between 2 hours and 6 hours after administration (Rescula\(^{®}\) Product Monograph, CIBA Vision AG, data on file). The peak concentration for the aqueous humour was more than 10 times higher than that for the retina and nearly 20 times higher than that for the choroid, in the pigmented rabbit.

Since the functional anti-endothelin effect of unoprostone might represent a feature important for clinical practice, clinical investigations were also performed on ocular blood
flow alterations induced by topically applied 0.12% or 0.15% isopropyl unoprostone. A single dose of topical unoprostone induced a transient increase in optic nerve head blood flow in healthy volunteers, and antagonised the ET-1-induced decrease in choroidal blood flow in cynomolgus monkeys. In a study of 21 days' duration, unoprostone-treated eyes in normal volunteers showed an increase in the perfusion of the optic nerve head and the retina—choroid, as measured with the laser speckle tissue circulation analyzer. In another study in healthy, young individuals the decrease in the choroidal blood flow induced with intravenously administered ET-1 was significantly and dose dependently blunted with repeated instillation of 0.12% unoprostone eye drops, as measured by laser Doppler flowmetry and laser interferometry. Interestingly, in another study in vasospastic normal-tension glaucoma patients, no alteration in the choroidal and optic nerve head blood flow was found by laser Doppler flowmetry and corneal temperature measurement (a new technique developed to characterize the intraocular perfusion), when measurements at baseline were compared to those obtained after a 1-week treatment with 0.15% unoprostone. In a study on open-angle glaucoma patients, bid 0.15% unoprostone medication for 28 days was associated with a significant improvement in mean deviation with the frequency doubling technique, but the threshold perimetry indices with standard perimetry as well as contrast sensitivity remained unchanged.

**Latanoprost, travoprost, and bimatoprost**

Natural prostaglandins have been shown to exert significant vascular effects in the whole body and in the eye. These effects, however, differ considerably among species, vascular area and different classes of prostaglandins. Both FP and EP1–4 prostanoid receptors are widely distributed in the human ocular tissues. Some of the EP receptors are especially responsible for the mediation of microvascular effects. Since the naturally occurring prostaglandins, including PGF2α, do not show high selectivity among the receptors, the ocular vascular effects of latanoprost, an analogue of PGF2α, were investigated in detail in different species before this molecule became used in clinical practice. In contrast to PGF2α, latanoprost did show a high selectivity for the FP receptors and consistently caused considerably less effect on blood flow and capillary permeability than the naturally occurring molecule. Latanoprost induced only a modest vasodilatation in the anterior segment and caused no vasoconstriction in the retina and choroid of the monkey eye in a dosage four to seven times higher than the clinical dosage. In an in-vitro study on isolated vascular segments, latanoprost relaxed the rabbit ciliary artery with the maximum effect at 100 μM concentration. This effect was independent from the endothelial function of the vessel or the release of nitric oxide, intrinsic PG or calcitonin gene-related peptide. In other similar in-vitro experiments on preconstricted isolated porcine ciliary arteries, latanoprost produced a relaxant effect at lower and a mild constriction effect at higher concentrations.
The latanoprost concentration in the human retina and choroid remains unknown. However, a potential zero concentration in these tissues would not necessarily mean that latanoprost has no effect on the posterior intraocular tissues, since secondary mechanisms
(for example nitric oxide production or secondary PG release from the anterior segment of the eye) cannot be excluded at present. The functional studies are therefore of special importance in this respect. Using the laser speckle velocimetry technique, topical latanoprost was shown to induce an increase in the optic nerve head blood velocity in the rabbit, which was abolished with intravenous indomethacin pretreatment. In the same study, repeated topical administration of latanoprost induced a similar but short-term effect on cynomolgus monkeys and healthy volunteers. This effect, as in rabbits, was abolished by indomethacin pretreatment in the monkey experiment. All these changes were independent of the marked and stable reduction in IOP, which was not influenced by indomethacin administration. This suggests that the vascular effects leading to an increased optic nerve head perfusion were mediated by a secondary mechanism. In a scanning laser Doppler flowmetric study in healthy volunteers no change was found in the parameters of capillary perfusion of the optic nerve head and the peripapillary retina after topical administration of 0.005% latanoprost.

Pulsatile ocular blood flow was consistently increased after the instillation of latanoprost, however, this alteration was related to the IOP decrease and lost its statistical significance after correction for the IOP change.

Travoprost is a new synthetic PGF$_2\alpha$ analogue with a high affinity for the FP receptors. Since this molecule has been used in clinical practice for only 2 years, little information is available on its vascular effects in the human eye. In a laser Doppler flowmetric study on rabbits (Alcon, data on file), travoprost 0.004% induced an increase in the optic nerve head blood flow.

Bimatoprost is a structural analogue of a naturally occurring prostamide. Since it was introduced in clinical use only 2 years ago, the information on the potential effects of this molecule or its metabolites on the vasculature of the human posterior ocular tissues is limited. In human retinal xenograft experiments, bimatoprost did not influence the diameter of the human arteries over the concentration range 0.1 nM to 10 000 nM.

\textit{\textbf{$\alpha_2$-Adrenoreceptor agonists: clonidine, apraclonidine and brimonidine}}

The most important mechanism by which the $\alpha_2$-receptor agonists lower IOP is the decrease in aqueous humour production. This is mediated by the activation of the ciliary $\alpha_2$-receptors, which results in a decrease of the cAMP level in the non-pigmented ciliary epithelial cells. Activation of other $\alpha_2$-receptors by these topical drugs, however, cannot be avoided in other ocular tissues. Since different vascular beds have different $\alpha_2$-receptor profiles, and even regional differences in the distribution of the $\alpha_2$-receptors have been shown between different parts of the same vascular bed, the potential danger of $\alpha_2A$-receptor-induced vasoconstriction due to $\alpha_2$-receptor agonist eye drops has been investigated in detail.
Clonidine is a relatively non-selective molecule, which may stimulate both the \( \alpha_1 \)- and the \( \alpha_2 \)-receptors.\(^{105} \) Since \( \alpha_1 \)-receptor activation causes vasoconstriction, it is not surprising that topical clonidine medication caused vasoconstriction or decreased flow in the retina, choroid, ciliary arteries, ophthalmic artery and optic nerve in experimental animals and in humans.\(^{5,105} \) In a group of primary open-angle glaucoma patients, perimetric indices deteriorated 2 hours after a single topical administration of 0.125% clonidine.\(^{106} \) The decrease in systemic blood pressure due to topical clonidine\(^{6} \) probably represents a special risk factor for the development of disturbed ocular perfusion in glaucoma patients.

Apraclonidine is also a relatively non-selective \( \alpha_2 \)-receptor agonist,\(^{105} \) which is recommended only for short-term use in clinical practice. Apraclonidine has significant vasoconstrictive properties, but mostly in the anterior segment of the eye.\(^{6,107,108} \) In a study using colour Doppler imaging in healthy volunteers, blood velocity indices decreased and the resistive index increased in the ophthalmic artery 4 hours after a single instillation of 1% apraclonidine.\(^{109} \) The parameters for the central retinal artery, however, remained unchanged.\(^{109} \) Topical medication with bid 0.5% apraclonidine eye drops resulted in a significant decrease in pulse amplitude in normal volunteers.\(^{110} \) In another study in healthy subjects, capillary perfusion of the optic nerve head and peripapillary retina remained unchanged after a single application of 0.5% apraclonidine, as measured by scanning laser Doppler flowmetry.\(^{108} \)

In contrast to clonidine and apraclonidine, brimonidine is selective for the \( \alpha_2 \)-receptors. This molecule has 790-fold greater selectivity for \( \alpha_2 \)-receptors than for \( \alpha_1 \)-receptors.\(^{105} \) The intravitreal concentration of topically applied brimonidine 0.2% was investigated in human vitrectomy specimens obtained at 4 to 14 days of tid brimonidine medication.\(^{111} \) The concentration varied from 1.4 nM to 1836 nM (median 15.1 nM) and the aphakic and pseudophakic eyes had a tendency for higher values compared to the phakic ones. These figures are in accord with the result of a study on monkeys, in which a brimonidine concentration of 100 nM to 170 nM was found in the vitreous body after a 14-day-long bid medication period.\(^{112} \) The vitreous concentration of brimonidine after topical application seems to be too low (approximately \( 10^{-8} \) M) to activate the \( \alpha_1 \)-receptors in the posterior ocular tissues.\(^{111,112} \) This was supported by in-vitro studies on human retinal vessels.\(^{105,112,113} \) The calibre of the vessels exposed to brimonidine remained unchanged, even when the brimonidine concentration was increased to \( 10^{-5} \) M. In contrast to the lack of vasoconstriction of the human retinal vessels, brimonidine was found to be strongly vasoconstrictive on the isolated porcine ciliary artery.\(^{104} \) but exerted no effect on the perfusion of the short posterior ciliary arteries and the optic nerve head in the rabbit.\(^{114} \) This might be explained by the different receptor profiles of different vessels in different species.

In the human studies, brimonidine medication did not alter the ocular pulse amplitude or the pulsatile ocular blood flow.\(^{100,115} \) Blood flow velocities in the ophthalmic artery,
temporal and nasal ciliary arteries and central retinal artery also remained unchanged.\textsuperscript{116} Retinal capillary perfusion of ocular hypertensive subjects investigated by scanning laser Doppler flowmetry showed no alteration for brimonidine medication.\textsuperscript{73,117,118} These clinical studies
suggest that topical brimonidine therapy is not associated with vasoconstriction in the posterior ocular tissues or in the retrobulbar vessels of the glaucoma patient.

Conclusions

It is not easy to summarize the experimental and clinical data regarding the influence of the widely used IOP-lowering drugs on ocular perfusion. The results of the functional investigations are not infrequently conflicting, the human intraocular concentration of most of these drugs is unknown and the conclusions derived from adequately designed, long-term studies are missing. However, the ophthalmologist requires guidelines on this field since the drug-induced changes of the ocular blood supply are of clinical importance. Table 12.1 provides a simplified summary of the most relevant information in this area. Further long-term and adequately controlled studies are necessary to clarify the role of the presently available and future antiglaucoma drugs in the treatment of glaucomatous vascular dysregulation.

References


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13.
NON-INTRAOCULAR PRESSURE-LOWERING GLAUCOMA MEDICATION

Konstantin Gugleta

Introduction

Glaucoma is an optic neuropathy with characteristic changes in the optic nerve head and/or typical visual field defects. In glaucoma, the rate of retinal ganglion cells (RGC) diminution is higher than in physiological aging. The aetiology and the exact mechanism of this accelerated decay are still poorly understood.

A number of terms are currently used to address the treatment of non-IOP risk factors, most commonly vasoprotection and direct and indirect neuroprotection. In general, every treatment that reduces the rate of RGC deaths, including the IOP lowering, is a form of indirect neuroprotection. Direct neuroprotection usually refers to interfering with a cascade of programmed cell death, that is apoptosis.

The definition of an ideal glaucoma drug is simple. It must be able to reduce the IOP, to improve the perfusion of neuroretinal tissue and to act neuroprotectively at the cellular level. Creating or finding it is another story. To date there is no such proven drug. This chapter is an overview of non intraocular pressure-lowering glaucoma medications, those in use today and those in the pipeline. A rationale for use is offered for each group.

Non-IOP-lowering effects of primarily IOP-lowering medications

Because common antiglaucoma drugs have a variety of effects beside intraocular pressure (IOP) reduction, the first subsection will address their vascular effects, with the emphasis on human data, and their neuroprotective features (Figure 13.1). Results of in vitro and animal model studies are not readily transferable to humans. In addition, the issue of penetration to the posterior pole of topically applied drugs is still a matter of debate. When assessing ocular blood flow effects, one should not forget a possible confounding effect of IOP reduction.
Figure 13.1 Graphically depicted vasoprotective (effects on human ocular circulation) and neuroprotective characteristics (animal models) of common antiglaucoma medications and calcium channel blockers. Dashed line=weaker effect, full line=stronger effect; green=positive effect (vasodilation, neuroprotective effect), grey=no effect measured, red=negative effect (confirmed decrease of human ocular circulation on several occasions).

Common antiglaucoma medications and ocular blood flow

Beta-adrenergic antagonists have been in use as glaucoma medication for more than 25 years. The main mode of ocular hypotensive action is inhibiting the β2-receptors in the epithelial cells in the ciliary processes. Since much of the ocular vasculature is relatively devoid of β-adrenoceptors, one could expect theoretically only a minimal β-adrenergic effect in the retinal vasculature. Regarding a possible influence on systemic cardiovascular glaucoma risk factors, topical, but not systemic, β-blockers may have an adverse effect on vasospastic tendency. Nocturnal hypotension may be provoked and/or worsened with the evening β-blocker eye drop. An overview of effects on ocular blood flow is given in Table 13.1.

Carbonic anhydrase inhibitors block carbonic anhydrase II in the ciliary epithelium. For relevant IOP reduction, 99% of carbonic anhydrase must be blocked. The prime effect on vessels is similar to that of carbon dioxide. Ocular blood flow effects are presented in Table 13.1.

For topical prostaglandin analogues and prostanoids, the available data from the literature
are summarized in Table 13.1.

Due to absence of $\alpha_2$-receptors in the posterior pole,\textsuperscript{63} theoretical expectations of topical alpha$_2$-agonists are low. The data on ocular blood flow effect in humans are available for brimonidine and apraclonidine (Table 13.1).

Parasympathomimetics are nowadays rarely used. The ocular blood flow is not affected.\textsuperscript{21,69,70}
Table 13.1 Ocular blood flow effects of common antiglaucoma medications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Ocular blood flow effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beta-adrenergic blockers</strong></td>
<td></td>
</tr>
<tr>
<td>Timolol</td>
<td>Timolol is a non-selective β-adrenergic antagonist whose prime effect is to increase peripheral resistance by inhibiting β&lt;sub&gt;2&lt;/sub&gt;-receptors on the vascular smooth muscle cell membrane. Various blood flow measuring techniques were applied, and thus different vascular beds, investigated. Haemodynamic effects were not convincing: in healthy subjects in three series of experiments an improvement observed, in three there was no effect, in seven the flow was reduced. In glaucoma patients, four experiments demonstrated improvement, and 11 no effect or slight reduction of blood flow.</td>
</tr>
<tr>
<td>Betaxolol</td>
<td>Betaxolol is a selective β&lt;sub&gt;1&lt;/sub&gt;-adrenergic antagonist with calcium channel blocking properties. Its prime effect on arteries is relaxing. As for timolol, various techniques were employed an and the results were equally contradictory, with predominantly weak positive or no effect on the ocular circulation.</td>
</tr>
<tr>
<td>Carteolol</td>
<td>Carteolol also demonstrated variable and inconclusive effects on circulation in healthy eyes as well as in glaucoma.</td>
</tr>
<tr>
<td>Metipranolol</td>
<td>Metipranolol improved circulation in healthy retina.</td>
</tr>
<tr>
<td>Levobunolol</td>
<td>Levobunolol failed to improve retrobulbar circulation in primary open-angle glaucoma patients.</td>
</tr>
<tr>
<td><strong>Carbonic anhydrase inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>Dorzolamide</td>
<td>Dorzolamide generally accelerated the arteriovenous dye transit, and increased the ocular pulse amplitude, reflecting mostly the choroidal blood flow, in healthy and glaucomatous subjects. Variable success was reported for the retrobulbar vessels. Laser Doppler flowmetry failed to detect blood flow change in the optic nerve head of the healthy subjects. A combination of timolol and dorzolamide (Cosopt) accelerated the arteriovenous dye transit, but only in the superior retinal vasculature, as compared to timolol.</td>
</tr>
<tr>
<td>Brinzolamide</td>
<td>Brinzolamide failed to influence retinal vessels and optic nerve head blood flow in healthy and glaucomatous subjects.</td>
</tr>
<tr>
<td>Acetazolamide</td>
<td>Systemic carbonic anhydrase inhibitor, acetazolamide, is no longer a first-line drug for the chronic application in glaucoma, primarily due to its side-effects (potassium loss, paresthesia, nausea, diarrhoea etc.). It improves the retinal and choroidal circulation.</td>
</tr>
</tbody>
</table>
Reports convincingly demonstrate, with only one exception, that latanoprost improves the pulsatile ocular blood flow, in both healthy and glaucomatous subjects. The increase in pulsatile blood flow is most likely the consequence of an IOP decrease, and the question remains how this increase reflects the perfusion of the optic nerve head. In healthy humans latanoprost did, however, improve the optic nerve head blood flow velocity, as measured by the laser speckle technique. Scanning laser Doppler flowmetry in healthy and colour Doppler imaging in glaucomatous subjects, and use of the retinal vessel analyzer in both, failed to detect ocular blood flow improvement with latanoprost.
Drug	Occular blood flow effects

Prostanoids
Upperstone improves, with less efficiency than latanoprost, the pulsatile occular blood flow in normal tension glaucoma patients,51 improves lesser speckle parameteres in the optic nerve head and/or choroid-retina in healthy volunteers;59–61 however, laser Doppler floemetry failed to detect any change in the choroid normal-tension glaucoma patients.62

Alpha₂-adrenergic agnosists
Brimonidine
There are conflicting reports on the effect of brimonidine on pulsatile ocular blood flow.32,50,63 No impact on ocular hypertensive and glaucomatous subjects.9,34,64–68
Apraclonidine
Topical apraclonidine most probably does not influence other ocular haemodynamic in humans.33,65

Neuroprotective properties of common antiglaucoma medications
Regarding the possible neuroprotective ability, Melena et al.30 analysed the effect of β-blockers, brimonidine, latanoprost, dorzolamide and pilocarpine on voltage-dependent calcium channels, and found only betaxolol to have significant blocking properties, which could explain its observed superiority to timolol in visual field preservation in glaucoma patients.71,72 However, apart from betaxolol in rats and rabbits,73–75 the neuroprotective effect was also reported in rats for brimonidine,76–78 and even for timolol.79

Optimizing the blood pressure
While IOP is very weakly correlated with the blood pressure,80 the involvement of low blood pressure, especially nocturnal hypotension, in the development and progression of glaucomatous optic neuropathy has been consistently reported for a long time.80–88 Not only does hypotension lead directly to a decrease in perfusion pressure, but the systemic vascular disorder that leads to arterial hypotension also affects the autoregulation capacity of ocular circulation.89 This subsection will focus on possible therapeutic measures.

The ambulatory 24-hour blood pressure monitoring is nowadays the integral part of glaucoma diagnostic, especially if ocular pressure-independent mechanisms of glaucomatous damage are suspected. One looks for low blood pressure at day and night, and for an increase in magnitude and number of blood pressure dips at night. A blood pressure reading under 101/61mmHg (day) and 86/48mmHg (night) is considered low.90 A decrease in blood pressure at night of between 10% and 20% is considered normal.91 Lack of a nocturnal fall of pressure is also a sign of abnormality.83,86

If a low blood pressure and/or conspicuous dips are identified in a glaucoma
patient/suspect, the first step is to exclude the iatrogenic, drug-induced, hypotension. An overtreated hypertension can produce detrimental effects in the eye. Hypnotics can contribute to the nocturnal hypotension. Decision-making involves the treating physician. Even the common glaucoma medication, β-adrenergic antagonists, especially with an evening drop, can produce a significant nocturnal hypotension. If no such relation can be established, experience in treating orthostatic hypotension is helpful. An increased salt and fluid intake and moderate aerobic exercise (see also later in a separate subsection) should be initially attempted. If symptoms of orthostatic hypotony are present (dizziness, nausea, syncope, muscle weakness, blurred vision), elastic stockings and abdominal bands to prevent venous blood pooling, several small meals to avoid postprandial hypotension and physical countermanoeuvres instead of motionless standing are of help. A cold exposure, balneotherapy, may produce vasospasms.

Should conservative approaches fail, there is a large list of drugs that may be used (Table 13.2). Most of these drugs are not suitable for glaucoma patients, because of their side-effects, the most prominent being a direct vasoconstrictive effect on ocular blood vessels. Fludrocortisone is promising, however the long-term effect on visual function in appropriate glaucoma patients remains to be elucidated.

Regulating the vascular dysregulation

A large body of evidence points to the involvement of vascular dysregulation in the pathogenesis of glaucoma. Vascular dysregulation implies either an arteri(ol)ar vasospasm or an inadequate dilation when necessary. It may occur globally rather than being confined to one or a group of organs, hence the term vasoconspastic syndrome, which in turn can be grouped as primary or secondary. The underlying disorder might be a vascular endotheliopathy and increased levels of circulating endothelin-1. The ocular circulation is affected through an associated low blood pressure, but also through disturbed autoregulation of ocular vessels and thus the higher susceptibility to IOP. The proposed leading mechanism of damage is the reperfusion injury, a consequence of the hit-and-run nature of vascular dysregulation.

It makes sense routinely to treat one risk factor only if interventional studies show a clear benefit to the patient. Evidence is available that vasodilatory treatment with CCB, both short—and long-term, or with carbon dioxide, is beneficial for the visual field of glaucoma patients. This is merely indirect evidence, as ocular vascular dysregulation, unlike readily measurable blood or IOP, has so far escaped direct quantitative expression. We recently developed a test for choroidal vascular reactivity to isometric exercise, based on the observation that this reactivity is higher in the presence of positive history of cold extremities. Moreover, in daily routine we apply the nailfold capillary microscopy as a diagnostic and treatment follow-up parameter. A history of cold hands and migraine could in itself give us some hint about vascular dysregulation in a patient.
Table 13.2 Drugs in the therapy of orthostatic hypotension: mode of action, applicability and caveats in glaucoma

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mode of action and caveats in glaucoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fludrocortisone</td>
<td>Fludrocortisone is a mineralocorticoid commonly used as a first-line drug in orthostatic hypotension treatment. Fludrocortisone improves not only low blood pressure, but also the vasospastic tendency in primary open-angle glaucoma patients. The starting dose is usually 0.1 mg twice weekly; adverse effects are avoided with this low dosing. A dose can be gradually increased if necessary; it must be kept in mind that the drug requires several weeks for a full pressor action. Adverse effects described in the literature are: hypokalemia, peripheral oedema, weight gain, headache, supine hypertension, infection masking, even an IOP increase; however, so far the author has observed no adverse effects.</td>
</tr>
<tr>
<td>Midodrine</td>
<td>Midodrine, an α₁-adrenergic agonist, is often used in autonomic failure and neurocardiogenic syncope. The use of this drug in glaucoma is hindered by its vasoconstrictive properties.</td>
</tr>
<tr>
<td>Amezinium</td>
<td>An inhibitor of monoamino oxidase and noradrenaline uptake. Similarly to amezinium, it promotes an α-adrenergic activity in blood vessels and is thus probably unsuitable for use in glaucoma.</td>
</tr>
<tr>
<td>Yohimbine</td>
<td>Aα₂-antagonist. Similarly to amezinium, it promotes an α-adrenergic activity in blood vessels and is thus probably unsuitable for use in glaucoma.</td>
</tr>
<tr>
<td>Clonidine</td>
<td>Central α₂-agonist used for hypertension treatment, but also for IOP reduction; it also shows peripheral α₁ and α₂ antagonism.</td>
</tr>
<tr>
<td>Dehydroergotamin</td>
<td>Dehydroergotamin is used for the treatment of orthostatic hypotension, however it may induce an unwanted ocular vasoconstriction.</td>
</tr>
<tr>
<td>Desmopressin</td>
<td>Desmopressin, a vasopressin analogue, may also induce unwanted ocular vasoconstriction.</td>
</tr>
<tr>
<td>Erythropoietin</td>
<td>Erythropoietin was proven successful in reversing anaemia and improving orthostatic hypotension.</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>Metoclopramide, a peripheral dopaminergic antagonist, improves the drop in blood pressure upon standing in diabetic patients with orthostatic hypotension.</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Indomethacin, a cyclo-oxygenase inhibitor, can increase postural blood pressure in Shy-Drager syndrome patients.</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitors</td>
<td>Selective serotonin reuptake inhibitors are used in neurally mediated syncope.</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Caffeine, a phosphodiesterase inhibitor, is still used to treat post-prandial hypotension; however, it can increase IOP.</td>
</tr>
</tbody>
</table>

Other quantitative methods to evaluate vasospastic tendency, for example the Hettinger vibration test, are also described in the literature. Magnesium and calcium channel blockers (CCBs) are currently used in the treatment of vascular dysregulation.
Magnesium in glaucoma treatment

Even though magnesium is the least abundant serum electrolyte, it is extremely important for the metabolism of calcium, potassium, phosphorus, zinc, copper, iron, sodium, lead, cadmium, hydrogen chloride, acetylcholine, NO, for many enzymes, for intracellular homeostasis and for activation of thiamine and, therefore, for a very wide gamut of crucial body functions. Magnesium deficiency can present with many signs and symptoms.\textsuperscript{128} Magnesium is also a naturally occurring calcium antagonist. The literature on its use in glaucoma patients is scarce.\textsuperscript{129} Depending on adverse effects, primarily gastrointestinal disturbances, we dose magnesium between 5 mM once daily and 10 mM twice a day. Should magnesium fail to improve nailfold capillary microscopy findings, the next step is the CCBs.

Calcium channel blockers in glaucoma

The CCBs are a diverse group of drugs originally developed for the treatment of angina pectoris.\textsuperscript{130} Their modes of action and biological effects are versatile. The flux of calcium across the cell membrane, the plasmalemma, occurs through voltage-dependent calcium channels, loosely referred to as calcium channels, receptor-operated calcium channels and sodium—calcium exchangers. The effect in a smooth muscle cell is a contraction. Transport of calcium between endo(sarco)plasmic reticulum and cytosol is governed by second messengers and thus the release of calcium from intracellular stores and the calcium-sensitivity modulation of the contractile apparatus are still areas of possible research breakthroughs.\textsuperscript{4} However, the maintenance of ocular vascular tone relies almost exclusively on extracellular calcium.\textsuperscript{4} On the other hand, a voltage-dependent calcium channel antagonist can directly block the release of glutamate and influx of calcium and thus counter-act the detrimental effects of glutamate-receptor overactivation.\textsuperscript{30} Moreover, L-type voltage-dependent calcium channels exist both in the ciliary body epithelium and in the trabecular meshwork.\textsuperscript{131,132} All these provide the theoretical basis for the vasoprotective, neuroprotective and ocular hypotensive roles of CCBs in glaucoma.

Indeed, various drugs from this group have demonstrated, with very few (some only partial) exceptions,\textsuperscript{133–136} both short-term and long-term beneficial effects on visual function, primarily visual field but also contrast sensitivity in a few studies, in healthy and normal-tension glaucoma subjects.\textsuperscript{121,137–145}

In some studies CCBs failed to demonstrate a long-term protective effect on the optic nerve head appearance in glaucoma patients.\textsuperscript{135,146} The neuroprotection of RGC by CCBs, and the mechanisms involved, have been well described.\textsuperscript{30,147–149}

Systemic CCBs can decrease IOP in humans,\textsuperscript{150,151} however this effect is not always observed.\textsuperscript{152,153} Topical CCBs are effective in IOP reduction in animals,\textsuperscript{154–157} and also in healthy human subjects;\textsuperscript{158,159} nevertheless, there also negative reports in animals.\textsuperscript{160}
Interesting for glaucoma is the antiproliferative effect of CCBs on human Tenons fibroblasts.\textsuperscript{161} Unfortunately, topical verapamil failed to show a postoperative benefit after glaucoma filtration surgery.\textsuperscript{162}
The data on ocular blood flow effects of CCBs in humans are abundant in the literature (Table 13.3). However, despite the ample literature data, a veil of controversy still surrounds the use of CCBs in glaucoma. Possible adverse side-effects are many (peripheral oedema, palpitations, transient hypotension with dizziness or lightheadedness, nausea, headache, weakness, nasal or chest congestion, diarrhoea or constipation); however, none with the low dosing. Nifedipine increases the mortality rate in patients with coronary heart disease, although this was debated. Bleeding can be provoked. Even an increased risk of cancer was observed in patients receiving CCBs. Again, none of these grave complications was described with the low drug dosing. In general, vascular dysregulation requires lower doses of CCBs than arterial hypertension, and patients with dysregulation are generally more sensitive to vasoactive drugs.

Table 13.3 Ocular blood flow effects of calcium channel blockers

<table>
<thead>
<tr>
<th>Drug</th>
<th>Ocular blood flow effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nifedipine</td>
<td>Nifedipine can bypass the blood-neural tissue barrier due to the tissue architecture between the choroid and ONH. Nifedipine almost uniformly failed to improve ocular haemodynamic parameters in healthy and glaucomatous subjects. However, several studies unveiled the selectivity of nifedipine's action. It improved ocular perfusion and/or visual field only in some, generally more vasospastic, glaucomatous patients. Furthermore, although also not improving the baseline perfusion, nifedipine was able to reverse the endothelin-1 effect on healthy ocular vessels in vivo and gluteal vessels of normal tension glaucoma patients in vitro.</td>
</tr>
<tr>
<td>Nimodipine</td>
<td>Nimodipine, a lipophilic centrally active CCB, failed to improve the optic nerve blood flow in healthy and perimacular perfusion in subjects with normal tension glaucoma; however, the same studies demonstrated an improvement of contrast sensitivity and visual field, respectively.</td>
</tr>
<tr>
<td>Nilvadipine</td>
<td>Nilvadipine unequivocally improved the retrobulbar and optic nerve blood flow in normal tension glaucoma patients. Moreover, a carbon dioxide induced vasodilation predicted similar effect of nivadipine in normal-tension glaucoma patients.</td>
</tr>
<tr>
<td>Felodipine</td>
<td>Single-dose felodipine did not improve the retinal, choroidal and optic nerve rim haemodynamic parameters in healthy subjects.</td>
</tr>
<tr>
<td>Flunarazine</td>
<td>In contrast to felodipine, 3 months’ long flunarazine therapy improved retrobulbar haemodynamics and visual field in normal-tension glaucoma patients.</td>
</tr>
<tr>
<td>Iganidipine</td>
<td>Iganidipine improved optic nerve head blood flow in rabbits.</td>
</tr>
<tr>
<td>Lomerazine</td>
<td>Lomerazine, apart from its neuroprotective effect, also improved optic nerve head blood flow in rabbits.</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>Nicardipine demonstrated a tissue selectivity between retina/choroid and optic nerve head in rabbits and cats.</td>
</tr>
</tbody>
</table>
Semotiadil demonstrated an inverse to nicardipine tissue selectivity between retina/choroid and optic nerve head in rabbits.\textsuperscript{179}
The issue of perfusion decrease due to tempering with blood pressure, especially at night, and possible provocation of the blood steal-phenomenon from the atherosclerotic vessels, was raised with the use of CCBs. However, atherosclerosis is less commonly encountered in glaucoma patients, as opposed to vascular dysregulation. Although an ideal candidate for this therapy would have glaucoma and arterial hypertension, vascular dysregulation is rather associated with hypotension. Nevertheless, CCBs can improve the ocular perfusion despite the drop in blood pressure.

The choice of a specific CCB (central/peripheral, stronger/weaker) is tailored to the individual patient. These drugs should be taken in the morning hours, to avoid the nocturnal hypotension. We currently recommend to appropriate glaucoma patients low nilvadipine doses, 2 mg once daily. Our clinical endpoint is the improvement in capillary microscopy and choroidal vascular reactivity results, with strict control of blood pressure. The CCBs are certainly a viable treatment option in selected glaucoma patients.

**Neuroprotection in glaucoma treatment, a brief overview**

The neuroprotection will be discussed in extenso elsewhere in this volume. This is a short overview of possible treatment and its rationale. Neuroprotective properties of CCBs and common antiglaucoma medications have already been addressed.

The concept of neuroprotection views glaucoma as a chronic optic neuropathy. The therapeutic strategy is to fight the programmed death, apoptosis, of RGC. Apoptosis can be induced in several ways, for example:

(a) By the lack of neurotrophic factors due to the interruption of axoplasmatic flow, mediated either mechanically through increased IOP or through an acute vascular event.

(b) Chronic optic nerve ischaemia and subsequent reperfusion are, most likely through free radicals, associated with RGC apoptosis.

(c) The excitatory neurotransmitter of the retina, glutamate, allegedly elevated in the vitreous of glaucomatous patients, can lead to apoptosis of RGC.

(d) An inducible nitric oxide (NO) synthase is present in the astrocytes of glaucomatous patients and in ocular hypertonic rats. Overproduction of NO can in turn, through peroxynitrite and hydroxyl radicals, provoke apoptosis.

In accordance with these triggers of apoptosis, various treatment modalities have been proposed:

(a) A brain-derived neurotrophic factor promotes ganglion cell survival in cats and rats.
(b) Free radical scavengers, like gingko biloba extract\textsuperscript{205} or vitamin E\textsuperscript{206} do have neuroprotective properties.

(c) A glutamate receptor (N-methyl-D-aspartate) blocker, memantine, achieved relative preservation of RGC in rats and monkeys with experimental glaucoma\textsuperscript{207,208} A large study is currently investigating memantine in glaucoma.

(d) NO can be scavenged by melatonin\textsuperscript{209} which shows a neuroprotective effect in ischaemia,\textsuperscript{210} and by gingko.\textsuperscript{211} Inhibitors of inducible NO synthase prevent loss of RGC in rats.\textsuperscript{212,213}

There are also other approaches to neuroprotection. Cannabinoids may modulate glutamatergic excitotoxicity,\textsuperscript{214} but they may also act downstream of glutamate stimulation.\textsuperscript{215} Preconditioning with subneurotoxic levels of glutamate can be protective to RGC.\textsuperscript{216} The same group found that increased immunity to myelin can increase RGC survival, that interleukin-6 knockout mice are protected from glutamate toxicity and that vaccination with self antigen increases RGC survival.\textsuperscript{217} The intraocular delivery of the neurotrophin ciliary neurotrophic factor increases ganglion cell axon growth into peripheral nerve grafts.\textsuperscript{218} Maintaining mitochondrial membrane potential can prevent the release of apoptosis-inducing factors.\textsuperscript{219} A number of other drugs and treatment modalities have also been investigated.\textsuperscript{197,220} Despite innumerable positive animal results, neuroprotection trials in stroke and head injury have uniformly failed to prove clinical benefit. Large studies of neuroprotection in glaucoma are underway.

Other primarily non-IOP-lowering medications in glaucoma treatment

Endothelin antagonists in glaucoma treatment

The idea of endothelin involvement in the pathogenesis of glaucoma was given credence because of compelling direct and indirect evidence.\textsuperscript{117,169,221–232} In the anterior segment, endothelin actions are consistent with the IOP reduction,\textsuperscript{233–235} however not in the presence of injury/inflammation.\textsuperscript{236} In the posterior segment, it can negatively affect perfusion\textsuperscript{226,228–230} and axonal transport\textsuperscript{222} and it can cause proliferation of optic nerve head astrocytes,\textsuperscript{237} which, as astrocytes in glaucoma patients express iNOS\textsuperscript{198} and endothelin can induce NOS expression in ciliary epithelium,\textsuperscript{238} may also be of relevance for glaucoma. Endothelin receptor antagonists are in the pipeline for glaucoma; their ocular vascular actions have been examined in healthy subjects.\textsuperscript{239,240} However, endothelin plays a role in the development of neural crest cells,\textsuperscript{241} which may exclude women of child-bearing age, the likely candidates for endothelin-blocking in glaucoma.\textsuperscript{242} Fortunately, a number of other medications, such as nifedipine, unoprostone, betaxolol and bunazosine, can antagonize
Furthermore, the potential use of endothelin-converting enzyme (ECE) inhibitors in glaucoma deserves scrutiny due to ECE-1 distribution in human eyes.246
**Nitric oxide in glaucoma treatment**

Nitric oxide plays a role in the pathogenesis of glaucoma.\(^{225,247}\) Possible therapeutic interventions are many, but complex due to the versatility of the functions of NO and its synthases. NO substrates, such as L-arginine, can reduce IOP and increase ocular blood flow.\(^{248}\) NO donor substances affect IOP\(^{249}\) and ocular blood flow.\(^{250–252}\) Along the same line, the NO synthase inhibitor N-monomethyl-L-arginine (L-NMMA) reduces baseline choroidal blood flow.\(^{253}\) In contrast to therapeutically positive effects of NO release on IOP and ocular blood flow, as mentioned before, an inducible NO synthase is present in astrocytes of glaucomatous patients,\(^{198}\) and inhibitors of inducible NO synthase prevent loss of RGC in rats.\(^{212,213}\) Selective blockade of an appropriate NO synthase isoform holds promise for the future.\(^{254}\)

**Serotonin in glaucoma—to antagonize or to agonize?**

Various types of 5-hydroxytryptamine (5-HT) receptors are present in the eye.\(^{255}\) Stimulation of 5-HT\(_{1a}\) receptors reduces IOP in rabbits\(^{256}\) and is also neuroprotective applied both topically in rabbits\(^{257}\) and systemically in rats.\(^{258}\) On the other hand, serotonin may be involved in glaucomatous pathogenesis by promoting vasospasm and thrombocyte aggregation.\(^{259}\) Treatment with the 5-HT\(_{2}\) antagonist naftidrofuryl improves optic nerve head blood flow in glaucoma patients\(^{260}\) and visual function, but only in normal-tension glaucoma patients.\(^{261,262}\) The response to serotonin of blood vessel in normal-tension glaucoma patients is enhanced.\(^{169}\) Another 5-HT\(_{2}\) antagonist, ketanserin, improves peripheral blood flow in vasospastics\(^{263}\) and reduces IOP.\(^{264}\) The latter effect is perhaps mediated through the pro-\(\alpha_1\)—adrenergic affinity of ketanserin.\(^{257}\) Nevertheless, the potential use in glaucoma of a modulation of serotonin biological action remains elusive to date.

**Renin—angiotensin system antagonists in glaucoma treatment**

An orally administered angiotensin-converting enzyme (ACE) inhibitor, Ramipril, showed beneficial effects on the visual function of glaucoma patients after 3 months’ therapy.\(^{265}\) The ACE inhibitor captopril and the angiotensin-II receptor subtype-1 blocker losartan were successful in lowering IOP in healthy and glaucoma subjects\(^{266,267}\) after systemic application. Topical applications of the ACE inhibitor SCH-33861 also demonstrated an ocular hypotensive effect,\(^{268}\) in contrast to the topically applied angiotensin-II receptor blocker CGP-48933.\(^{269}\) ACE inhibitors relaxed porcine ciliary arteries in vitro.\(^{270,271}\) Nevertheless, losartan failed to influence choroidal blood flow in healthy humans\(^{272}\) after a single oral dose. Therapeutical modulation of the renin—angiotensin system in glaucoma deserves further research.
**Alpha\textsubscript{1}-blockers in glaucoma treatment**

Topical application of the selective $\alpha\textsubscript{1}$-antagonist bunazosine decreased IOP in healthy humans\textsuperscript{273} In rabbits, it increased the choroidal blood flow at baseline\textsuperscript{274} and reversed the effect of endothelin-1 on optic nerve head blood flow.\textsuperscript{245} Topical dapiprazole is useful in IOP reduction in pigmentary glaucoma\textsuperscript{275} Nicergoline can be neuroprotective\textsuperscript{276} and is
beneficial for retinal and cortical electrophysiological parameters and ocular blood flow in glaucoma patients, however it can cause nephritis. Nipradilol, an \( \alpha_1 \)- and \( \beta \)-adrenoceptor blocker and NO donor, has neuroprotective and moderate ocular vasodilative properties in animals.

**Adenosine antagonists in glaucoma treatment**

Adenosine and its receptors are involved in vascular regulation, but also in neuroprotection. Antagonists of the type-3 adenosine receptor could have a role in glaucoma treatment.

**Dipyridamole in glaucoma treatment**

Dipyridamole, a phosphodiesterase-blocker and an adenosine uptake blocker, has vasorelaxing properties both in vitro and in retrobulbar vessels of ocular vascular patients. No long-term treatment of glaucoma patients has been reported.

**Alternatives in glaucoma treatment**

**Ginkgo biloba extract in glaucoma treatment—a serendipity?**

Ginkgo biloba extract has several biological actions that combine to make it a potentially important agent in the treatment of glaucoma. It improves peripheral and retrobulbar circulation, improves pre-existing visual field defects in normal tension glaucoma patients, scavenges free radicals and NO, possibly inhibits NO production, relieves vasospasm of cerebral vessels, prevents light-induced damage in photoreceptors and inhibits glutamate excitotoxicity and apoptosis. Still, ginkgo biloba extract can cause dangerous bleeding. This herb certainly deserves further scrutiny as a glaucoma therapeutic.

**Cannabis in glaucoma**

Some time ago the expectations from cannabis application in glaucoma were high. Inhaled or as topical cannabinoids, it can reduce IOP. Some cannabinoid derivatives reduce glutamate excitatory neurotransmission. In its cannabis form it was abandoned as a glaucoma drug due to lung and mental side-effects.

**Chinese herbal medicine in glaucoma**

Many compounds found in Chinese herbs improve retinal and choroidal circulation in
animals,\textsuperscript{304–306} facilitate retinal recovery after ischaemic insult,\textsuperscript{307–309} and even improve the visual field in glaucoma patients.\textsuperscript{310} However, they are not entirely harmless—renal fibrosis\textsuperscript{311} and even urothelial carcinoma have been described.\textsuperscript{312}
Vitamins in glaucoma treatment

Long-term supplementation of vitamin B₁₂ (cobalamin) demonstrated beneficial and protective effects in Japanese glaucoma patients. Vitamin C can reduce IOP with massive systemic doses, but also after topical administration. However, this was not reproducible at all times. In vitro ascorbic acid inhibits Tenons fibroblasts; however, no association between ocular ascorbic acid level and trabeculectomy failure could be demonstrated. Vitamin E (α-tocopherol) protects against retinal light damage and also protects cortical neurons during ischaemia-reperfusion injury. Vitamin E alone, while decreasing serum lipid peroxidation products, and in combination with the B-vitamin complex, proved beneficial for the visual field of glaucomatous patients. Subconjunctival injection of vitamin E improved filtration surgery results in rabbits. The use of vitamins in glaucoma requires controlled studies.

Therapeutical implications of the involvement of rheological factors in glaucoma

An association between increased blood viscosity and glaucoma could be demonstrated in a number of studies, but not in all. The hyperaggregability of erythrocytes leads to decreased optic nerve blood velocity. Some studies succeeded and some failed to show decreased erythrocyte deformability in glaucoma. An association of increased aggregability of thrombocytes with glaucoma, but not directly with visual field damage progression, has been observed. On the same line, a hypercoagulable state in untreated glaucoma patients has been reported; however, an activated protein-C resistance, that usually accompanies venous thrombosis elsewhere, was not found in patients with nerve fibre layer haemorrhages or central venous thrombosis. Therapeutical implications of these findings are scarce. Doxium was shown to be beneficial for glaucoma patients. In general, application of low doses of acetylsalicylic acid could remove most of the described risk factors. Acetylsalicylic acid influences neither the IOP nor its fluctuations. Interaction with carbonic anhydrase inhibitors can produce adverse effects.

Therapeutical implications of the association of glaucoma with sleep apnoea syndrome

An association was observed between various types of glaucoma and sleep apnoea syndrome. The possibility of sleep apnoea involvement should be considered in therapy-resistant cases of glaucoma, as the mainstay therapy in this syndrome, nasal continuous positive airway pressure, can sometimes also be beneficial for glaucoma.
Physical exercise in glaucoma

Physical exercise produces an IOP drop that is more pronounced in glaucoma patients.\textsuperscript{348} In addition, a consistent decrease occurs after chronic exercise.\textsuperscript{349} Various mechanisms of IOP reduction have been postulated.\textsuperscript{350,351} Exercise can be,\textsuperscript{352} but is not always beneficial for the visual field.\textsuperscript{353} Exercise can decrease blood flow in some
eyes, sometimes dramatically. It can also produce relative pupillary block and pigment dispersion in susceptible subjects, which is preventable by pilocarpine. Although in general beneficial for the cardiovascular status, caution and only moderate aerobic exercise are advisable in glaucoma.

**Carbon dioxide inhalation**

Hypercapnia increased the optic nerve head blood flow in healthy subjects, unlike the retrobulbar circulation, which improved only in glaucomatous subjects. Higher responsiveness to hypercapnia in one subgroup of patients in the ocular pulse amplitude study was coupled to a visual field improvement. Response to carbon dioxide can predict a vascular effect of some drugs by identifying a residual vasodilatory capacity in selected patients. Although a safe system for carbon dioxide delivery has been described, in the author’s experience inhalation of any carbon dioxide enriched air mixture is always accompanied by hyperventilation, hyperoxia and by stimulation of the sympathetic nervous system. Caution should be exercised when interpreting vascular responsiveness to carbon dioxide. A routine therapeutical application is currently not in sight.

**Sildenafil (Viagra) in glaucoma**

Of possible interest for glaucoma, sildenafil dilates retinal arteries and veins in healthy humans, while not affecting the IOP.

**Optic nerve sheath decompression**

As a possible alternative approach to glaucoma therapy, results to date are not convincing.

**Future directions in glaucoma treatment**

**Therapeutic implications of immune system involvement in the pathogenesis of glaucoma**

The immune system regulates cell death in response to RGC stress. Autoantibodies have been intensively investigated in glaucoma. Autoimmune damage to the optic nerve head may occur directly, due to autoantibodies, or indirectly, when a sensitizing antigen provokes a ‘mimicked’ autoimmune response injurious to RGC. Practical therapeutical measures are currently not available.

**A word on gene therapy for glaucoma**
There is a growing body of evidence that mutations of genes and/or altered gene expression may play a crucial role in glaucoma, and their manipulation can bring therapeutic breakthroughs. A number of delivery systems can be used, generally by means of intracameral or intravitreal injection: adenoviruses, adenoassociated viruses, herpes
simplex viruses, lentiviruses—feline and human immunodeficiency virus, liposomes and naked DNA. Target tissues are the trabecular meshwork, ciliary epithelium and muscle, RGC and Muller cells. Various genes comprise a target group, for example myocilin, metalloproteinases, neurotrophin and its receptors, optoneurin, etc. By modifying the structure and/or expression of these genes, a decreased aqueous production and increased trabecular/uveoscleral aqueous outflow as well as improved ganglion cell survival can be attempted. Furthermore, animal models of glaucoma can be improved. Knock-out and knock-in animal models could improve our basic understanding of glaucoma pathogenesis. This fast developing field is probably the most promising one in glaucoma treatment.

Comment

The increased IOP is no longer the integral part of the glaucoma definition due to the fact that there are glaucoma patients with the IOP in the statistically normal range, as well as individuals with their IOPs outside this range, yet with no glaucoma. Several well-designed large clinical trials have been published recently, demonstrating the importance of IOP reduction in halting the progression or the onset of the glaucomatous damage.\(^{379-383}\) Albeit reaffirming the role of IOP in the pathogenesis of glaucoma, these studies

![Hypothetical representation of pressure-mediated (blue bars) and pressure-independent pathogenetical mechanisms (red bars) in glaucoma along the intraocular pressure](image-url)
spectrum.
also confirm the involvement of other risk factors. For example, about 30% of patients showed progression of damage within 4 years despite the pressure reduction in the Early Manifest Glaucoma Study.\textsuperscript{379} In the Collaborative Normal Tension Glaucoma Study, approximately one-third of progressive patients (12% compared to 35% in the control group) did so despite the successful large reduction of IOP.\textsuperscript{383} Obviously, along the wide IOP spectrum there are glaucomas resistant to pressure reduction (Figure 13.2). In general, risk factors other than IOP may act independently of IOP, but may also render the optic nerve head more sensitive to IOP, and alleviating them would enhance an effect of IOP reduction. Our primary goal is to slow down the rate of RGC disappearance, using all the available methods. Therefore, it is the identification of risk factors, and not simply the lack of increased IOP in a progressive glaucoma patient, that should govern the potential use of non-IOP-lowering glaucoma medications.

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14.
EARLY SURGICAL TREATMENT OF GLAUCOMA

T.Zeyen

Introduction

It is accepted practice today for a patient with newly diagnosed glaucoma to be treated with medication first, to continue with laser trabeculoplasty if medical treatment is insufficient and only to consider surgery as the last option. Several randomized prospective studies have led to question this traditional stepladder and to favour early surgery.

It is widely accepted that, in the treatment of angle-closure glaucoma, early surgery is often necessary. In the case of an acute angle-closure attack, for example, an iridectomy should be performed within 48 hours when the intraocular pressure (IOP) cannot be reduced medically and corneal oedema and/or a shallow anterior chamber preclude a laser iridotomy.1

In chronic angle-closure glaucoma a phacoemulsification often normalizes the IOP,2 especially when no or only a few goniosynechiae are present.

Early filtering surgery for the treatment of primary open-angle glaucoma, however, is more controversial. Cairns,3 who invented the trabeculectomy, suggested this intervention as the primary therapy of choice. In the 1970s and 1980s the use of early filtering surgery was supported by clinical trials carried out in the United Kingdom.4,5 In 1988 Jay and Murray showed,6 in a randomized prospective study, that early surgery for open-angle glaucoma provided a more stable control of the IOP and a better protection of the visual field than conventional medical treatment. Those results were confirmed by Migdal et al.,7 who compared primary filtering surgery with medicine and laser trabecuoplasty in a randomized prospective study. When considering primary filtering surgery versus medical or laser treatment of glaucoma several important questions should be addressed.

Can we obtain IOPs in the low teens more easily with surgery?

We learned from the Advanced Glaucoma Intervention Study (AGIS) that IOP readings <18 mm Hg throughout the study could prevent visual field loss.8 Those patients had a mean IOP of 12.3 mm Hg. In general, lower IOPs can be obtained with filtering surgery.
than with medications. In the Moorfields study, the Collaborative Initial Glaucoma Treatment Study (CIGTS), and the Ocular Hypertension Treatment Study (OHTS) mean IOPs of 17–18 mm Hg were obtained with medications. In contrast, several long-term studies have shown that IOPs between 14 and 16 mm Hg can be obtained with a trabeculectomy with or without 5-fluorouracil. Shaarawy et al and Ambresin et al published similar results with non-perforating deep sclerectomy, although 50% of the cases were converted into a microperforating operation after Yag-laser goniopuncture.

To obtain IOPs in the low teens we probably need to use antimetabolites, such as 5-fluorouracil or mitomycin-C. Those drugs, however, can induce side-effects like hypotony, leakage, blebitis and endophthalmitis. Newer and less harmful antifibrotic medications such as anti-TGF-β will soon become available and might replace the more toxic mitomycin-C. IOP fluctuations >5 mm Hg are considered an additional risk factor for the development of glaucoma. The above-mentioned studies have also shown that filtering surgery not only reduced the IOP more than medications, but that surgery had a lower diurnal variation in IOP than medical patients. Unfortunately good IOP reduction does not always prevent further visual field loss over the years, suggesting that lowering the IOP may only slow down the rate of damage, but not always stop it.

**Can medical therapy be harmful?**

Medical therapy can be harmful because of the possible side-effects, local as well as systemic. Local side-effects such as burning, stinging and visual disturbance are frequent, but overall well tolerated. They may, however, influence compliance and quality of life. This will be addressed later on. Moreover, topical medications can be potentially dangerous. Topical β-blockers can produce severe cardiovascular and pulmonary adverse reactions and in the USA even deaths were reported, attributed to the use of timolol eye drops. Aplastic anemia has been attributed to carbonic anhydrase inhibitors, administered systemically as well as topically. Alpha2-agonists can produce somnolence and lack of concentration, and prostaglandin analogues can probably provoke asthma. Selective β-blockers may have fewer systemic side-effects but are less effective at lowering the IOP. Low-dose, non-selective β-blockers (for example timolol 0.1%) are reported to have fewer side-effects without losing their IOP-lowering property.

Medical therapy can also have an effect on future surgery. Failure of filtration surgery is believed to be secondary to postoperative fibrosis. An increased number of inflammatory cells and fibroblasts have been found in the conjunctiva of patients receiving longterm topical antiglaucoma therapy. This fibrosis may be induced by the drug or by the preservatives. Preoperative treatment with non-steroidal anti-inflammatory drops or fluorometholone 0.1% may reduce the risk of conjunctival scarring in patients with long-standing use of antiglaucomatous eyedrops.
Problems related to early surgery

Bleb discomfort can be a problem after filtration surgery. The CIGTS reported a higher proportion of local eye symptoms in the surgical than in the medical group.\textsuperscript{27} Morbidity and even mortality can be related to retrobulbar anaesthesia. Retrobulbar haemorrhage is probably the most common complication, occurring in 1–3\% of the retrobulbar injections.\textsuperscript{28} The incidence of inadvertent globe perforation was estimated to be 1 in 140 injections in eyes with an axial length of 26 mm or longer.\textsuperscript{29} Those complications can be avoided by performing surgery under topical anaesthesia. The CIGTS showed that the probability of having a cataract operation 5 years after filtering surgery was approximately 20\% (twice the rate observed in the medicine group).\textsuperscript{9} Although clear cornea phacoemulsification might affect some bleb function, it is a highly successful procedure that almost always restores a patient’s vision. Endophthalmitis remains a vision-threatening complication occurring in 0.5–1\% of the cases after trabeculectomy.\textsuperscript{30} Both cataract formation and endophthalmitis seem to be less frequent after non-perforating filtering surgery.\textsuperscript{31}

Quality of life and cost of therapy

The drug effects mentioned above can significantly affect the quality of life.\textsuperscript{32} Although we assume that patients prefer medical to surgical therapy, some patients with bilateral glaucoma, randomized to the surgical group in the Moorfields study,\textsuperscript{7} after several years of medical therapy to the second eye, spontaneously inquired for surgical therapy in that eye as well. Two factors that may affect quality of life of the patient are compliance and the cost of therapy. Compliance with therapy was always an issue in glaucoma treatment. Patients are more likely to remember to take their medication shortly before their office visit than at other times.\textsuperscript{33} This can give the ophthalmologist the false impression that the target pressure is obtained and lead to visual field progression despite apparently low IOPs. Precious time may be lost since it is reasonable to think that the earlier we intervene to reduce the IOP effectively, the less apoptosis will be induced. Even if compliance is influenced by the drug regimen, prescribing a more convenient medication with fewer side-effects does not eliminate defaulting.\textsuperscript{33} We may, however, expect a better compliance with a once-a-day regimen of a well-tolerated drug.\textsuperscript{34}

The cost of therapy becomes an increasingly important issue, especially in times when governments impose stringent budgets to screen and treat our patients. It is very difficult to evaluate and compare the cost of medical versus surgical treatment of glaucoma in various countries. In 1987 Kooner et al reported that the average annual cost to a patient on antiglaucoma drugs in the USA was $644–1101.\textsuperscript{35} The cost of surgery was reported to vary between $4000 and $7000. After 7 years of treatment the cost of surgery equals the cost of medications. Similar proportions were reported by Ainsworth and Lay,\textsuperscript{36} who
found that the total cost for medical treatment of bilateral glaucoma during 8 years was £2560 compared to £2570 for early surgery. These calculations were made on the basis of fewer drugs than are now available, and with surgery performed on an inpatient basis. On the other hand, the cost for surgery did not include long-term postoperative complications. However, it is likely that with more expensive topical medications on one side and outpatient surgery with improved techniques under topical anaesthesia on the other side, the difference in cost between medical and surgical therapy will be reduced. Since glaucoma is a chronic disease with patients sometimes treated for decades it therefore seems reasonable, from a cost analysis point of view, to treat patients with early surgery.

**Indications for primary filter or tube**

As presented above there are good reasons to perform filtering surgery as initial treatment of primary open-angle glaucoma. However, concerns about potential poor results will prevent a total shift from initial medical to initial surgical therapy. There are, however, specific indications for initial filtering surgery:

- Patients with high IOP non-responding to medication;
- Patients with intolerance to medication;
- Non-compliant patients;
- Patients who cannot afford medical treatment;
- Patients with advanced glaucoma who need a low target.

Additionally there are a few indications for a primary tube implantation:

- Neovascular glaucoma non-responding to cyclodestructive procedures;
- Patients with extensive conjunctival scarring (e.g. after multiple vitrectomies);
- Iridocorneal endothelial (ICE) syndrome;
- Chronic uveitis, especially in younger patients.

**References**

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15. STATE OF THE ART ON LASER TREATMENT

John Thygesen

Introduction

Laser therapy has become the method of choice for treating many forms of glaucoma, especially when medical modalities prove inadequate or patient compliance with medical regimens is poor. In angle-closure glaucoma with papillary block, for example, neodymium: yttrium—aluminium—garnet (Nd: YAG) or argon laser iridotomy (ALT) has almost replaced surgical iridectomy. Argon laser trabeculoplasty has advanced the treatment of primary open-angle glaucoma by providing a safe and usually effective means of achieving intraocular pressure reductions with fewer complications than invasive surgical procedures such as trabeculectomy. In cases of medically and surgically uncontrollable glaucoma, Nd: YAG and diodelaser cyclophotocoagulation of the ciliary body have proven effective.

Laser energy can be delivered in a variety of wavelengths and time durations. The effect of laser energy on tissue depends on the amount and duration of energy absorbed, which are dependent on tissue pigmentation, wavelength, amount of energy delivered, exposure time and the size of the laser spot.

Laser therapy may be divided into three different treatment modalities:

• Laser treatment for outflow obstruction

  Laser trabeculoplasty

  Laser filtration procedures

• Laser treatment for internal flow block

  Laser iridotomy

  Laser iridoplasty

• Laser cyclodestructive procedures
Laser treatment for outflow obstruction

Laser trabeculoplasty (LTP)

Introduction

Argon laser trabeculoplasty (ALT) is a firmly established, well-tolerated procedure used to lower intraocular pressure (IOP) in various types of open-angle glaucoma. Laser treatment of the human trabecular meshwork by puncturing Schlemm’s canal was performed initially by Krasnov in 1973, but the lower IOP he described was short—lived. In 1979 Wise and Witter reported that the placement of small, evenly spaced, non-penetrating argon laser spots consistently lowered IOP in phakic eyes that have open-angle glaucoma. Laser trabeculoplasty (LTP) is most frequently performed using the argon laser (ALT), although other types of thermal-effect lasers like the diode laser have proved to be equivalent. The treatment consists in targeting the trabecular meshwork (TM) with laser applications via a goniolens. It lowers the IOP, causing an increased outflow facility. The precise mechanism of action is not established and accepted theories include scarring at the site of the laser impact with subsequent tightening of the trabecular beams around it, activation of endothelial cells, release of endothelin and changes in the extracellular matrix. With optimal patient selection an average 25% IOP decrease from baseline can be expected. Such an effect, however, appears to fade with time, with approximately 50% of the eyes still controlled after 5 years and only 20% after longer follow-up.

Treatment modalities for glaucoma consist of topical and systemic medication, laser treatment and conventional surgical procedures. Traditionally, maximum-tolerated medical therapy has been used before laser trabeculoplasty, and laser treatment has preceded conventional surgery. This approach was designed primarily to reduce the risks of therapy for the patient. However, results from the Glaucoma Laser Trial indicate that laser trabeculoplasty is a safe and effective form of treatment when used as initial therapy for glaucoma. After a follow-up of 2 years, fewer patients treated initially with laser trabeculoplasty require the addition of glaucoma medications compared with patients initially treated with timolol.

AGIS report 9 showed a borderline evidence (p=0.04) that African-American patients had a 32% lower risk of initial ALT failure than white patients. Analysis of ALT as second intervention show race to have a negligible effect on the risk of failure (p<0.9).

Selective laser trabeculoplasty (SLT) Since 1998, selective targeting of the trabecular meshwork has been reported using a Q-switched 532-nm Nd: YAG laser; the technique is called selective laser trabeculoplasty or SLT. SLT lowers intraocular pressure by using short pulses of an Nd: YAG laser to target melanin granules within the cells in the trabecular meshwork, resulting in increased fluid outflow. The process is called selective photothermolysis. The limitations of ALT are primarily related to its coagulative effect, which leads to scarring of the trabecular meshwork, SLT is said to retain the therapeutic benefit of laser treatment—reduced intraocular pressure, without the collateral thermal
damage to non-melanin-containing cells and to the trabecular meshwork structure. The SLT procedure requires a 532 nm frequency doubled, Q-switched, Nd: YAG laser with a 3 ns pulse duration and a 400 μm spot. In total, 50 spots are placed over 180° of the trabecular meshwork at energies of 0.4 to 1.4 mJ/pulse. The Coherent’s Selecta 7000 laser and SLT received FDA clearance in 2001.

It is too soon to comment with any certainty on the safety or effectiveness of this new technology. The advantages of SLT seems to be less disturbance of the trabecular anatomy, the possibility to treat eyes where argon laser trabeculoplasty failed and the possibility to repeat the treatment without the risk of damaging the functioning part of the meshwork. However, there is still a need for more comprehensive and long-term studies. The laser can only be used for SLT procedures at this time.

**Indications for LTP**

Laser trabeculoplasty is indicated in primary open-angle glaucoma (POAG), exfoliative glaucoma and pigmentary glaucoma when a lower IOP is advisable. Positive and negative predictors for LTP success include diagnosis, pigmentation of the trabecular meshwork, age and angle configuration. The trabecular meshwork must be visible with a Goldman type indirect goniolens. If the angle approach is narrow, peripheral laser iridoplasty can be applied to stretch the iris and flatten the peripheral bowing, facilitating better visualization of the trabecular meshwork. In pseudoexfoliation the initial effect is usually greater than in POAG, however failures can occur earlier. The role of laser trabeculoplasty has changed during the last decade, owing to the results of prospective clinical trials and to the retrospective analysis of long-term data on a large number of patients.\(^4\)–\(^14\) When introduced, it was to be applied only when patients were ready for a filtering operation, with the aim to avoid surgery. LTP is now considered as effective as medications for the initial treatment of primary open-angle glaucoma (POAG).

**Contraindications**

For patients younger than 50 years of age, LTP is not recommended unless they have pigmentary or pseudoexfoliation glaucoma. Secondary glaucomas, both open—and closed-angle, and primary angle-closure glaucoma are contraindications for LTP. Juvenile glaucomas or glaucomas associated with angle dysgenesis or malformations do not respond well to laser trabeculoplasty.

**Treatment technique**\(^7\)

The patient’s informed consent must be sought after a thorough discussion of the goal of therapy and potential complications.

**Preoperative preparation**

- IOP spikes prevention: topical apraclonidine/brimonidine, pilocarpine and oral acetazolamide 1 hour prior to the procedure and immediately afterwards can be used,
depending on the individual.

- Topical anaesthesia is instilled immediately before the procedure.
Laser procedure

**Lens** Goldmann type gonioscopy lens or Ritch trabeculoplasty lens\(^\text{©}\) or CGA\(^\text{©}\) Meridian with antireflective coating. Methylcellulose is used as a coupling agent between the cornea and the lens.

**Laser** Argon laser (green or blue/green) or diode laser. The argon green laser appears to be effective and less likely to cause photoreceptor injury to the treating physician than the argon blue-green laser. The diode laser also has been used with comparable results, but the tissue reaction is less pronounced and thus it is harder to judge the endpoint.

**Laser parameters**

- Diameter: 50 \(\mu\)m
- Exposure time: 0.1 s
- Power: 300–1200 mW according to the trabecular meshwork reaction
  - Optimal reaction: blanching or small bubble
- Number of burns: 30 to 60 spots, evenly spaced over 180\(^\circ\)
  - 60 to 120 applications for 360\(^\circ\) in one or two sessions
  - When electing to perform two sessions of 180\(^\circ\), make sure not to repeat the treatment in the same quadrant.

**Postoperative management**

- Check the IOP during the first 1–6 hours. If it is not possible, treat with oral CAI to prevent IOP spikes.
- Topical corticosteroids or non-steroidal antiinflammatory drugs four times daily are prescribed for 7 days, and the patient is reviewed after 1 week. If anterior uveitis is present at 1 week, topical corticosteroids are continued.
- Close monitoring is suggested in the following cases: advanced glaucomatous nerve damage with severe field loss, one-eyed patients, high prelaser IOP, exfoliation syndrome and previous laser trabeculoplasty.

**Treatment guidelines**

It is crucial to focus the laser beam accurately on the anterior portion of the meshwork (Figure 15.1), Posterior treatment increases the formation of peripheral anterior synechiae and postoperative inflammation. The trabecular meshwork always lies between two white lines (Schwalbe's line and the scleral spur). The procedure begins with the goniolens at the 12 o'clock position (inferior angle) and the lens is rotated clockwise; the temporal portion of the right eye and the nasal portion of the left eye are photocoagulated first. The laser spots are placed at the junction of the pigmented and non-pigmented trabecular meshwork, with a gap of about the diameter of two laser spots between spots.\(^7\)

The advantage of treating only half of the circumference is a lower risk of postoperative IOP spikes, and it is preferable when severe damage of the optic nerve head is present and/or when an IOP rise occurred after the treatment of the first eye or the first session of the same
eye.
If the angle is closed or narrow, a laser iridoplasty or a peripheral iridectomy is performed beforehand to deepen and allow better visualization of the angle; a laser iridoplasty is often performed simultaneously with the LTP, but when a peripheral iridectomy is performed, then the LTP is done a week later because of possible anterior chamber debris.

**Retreatment**

Laser trabeculoplasty can be repeated. The effect on IOP is expected to be modest and not significant if the initial effect from the first treatment was poor. **(Figure 15.2)**

**Complications**

- Transient decrease in visual acuity due to gonioscopy contact fluid;
- Early and transient pressure elevations;
- Visual field loss as a consequence of IOP spikes;
- Inflammation;
- Transient iritis;

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**Figure 15.1** Laser trabeculoplasty. A: Schwalbe’s line. B: Laser burns. L: Laser light. S: Scleral spur. C: Schlemm’s canal. (Reprinted with permission from Highlights of Ophthalmology.)
• Transient corneal epithelial burns can be observed;
• Peripheral anterior synechiae, especially for posterior placed burns;
• Late pressure rise due to loss of effect;
• Encapsulated blebs after filtration surgery may be seen more frequently in eyes that have had LTP.
The most common risk is IOP spikes, but these may be limited effectively using apraclonidine or brimonidine. In one study, approximately 3% (10 of 300 eyes) of patients affected by primary open-angle glaucoma had sustained a persistent elevation of at least 5 mm Hg after LTP, which did not return to normal prior to surgical intervention. A late progressive IOP rise is more common with longer follow-up and can involve up to 80% of the cases 10 years after treatment.

**Long-term effect of ALT**

A period of at least 4–6 weeks after ALT is required before the final result can be evaluated. In two long-term studies, ALT maintained IOP control in 67–80% of eyes for 1 year, in 35–50% for 5 years and in 5–30% for 10 years (that is, an attrition rate of 6–10% per year). The Glaucoma Laser Trial, a multicentre, randomized clinical trial designed to assess the efficacy and safety of initial treatment for primary open-angle glaucoma using ALT versus standard topical medication, concluded that initial ALT is at least as efficacious as initial treatment with topical medication. A study on long-term functional outcome after early surgery compared with laser trabeculoplasty and medicine in open-angle glaucoma showed the same efficacy using medicine and laser in early treatment of POAG, whereas the
efficacy was less than in early surgery.\textsuperscript{12} A Norwegian study showed that primary ALT gives a long-lasting and favourable effect in chronic open-angle glaucoma
where two-thirds of the eyes still managed without additional medication for 8 years.\textsuperscript{13} The success in pseudoexfoliation glaucoma was even higher in the first 3 years, and kept above 50% for 5 years. This makes laser a valuable option as first choice of therapy in glaucoma. Predictors of a better effect on IOP are a favourable outcome in the first eye, older age, pseudoexfoliation and heavier trabecular pigmentation.\textsuperscript{14} The efficacy is limited in pseudophakia and after filtration surgery (Figure 15.3).

**Laser filtration procedures**

Laser energy can be delivered either internally (ab interno) or externally (ab externo) to produce a direct opening into the anterior chamber through limbal tissue to achieve filtration. The laser energy may be delivered using a probe (contact) or via a gonioscopy lens (non-contact). The rationale for laser sclerostomies is the desire for a glaucoma

![Figure 15.3](image)

**Figure 15.3** Kaplan-Meier probabilities of failure of interventions.

*Estimated cumulative failure rates at 5 years are:*

*ALT as 1st intervention: 35.5% (30.6–40.4)*

*ALT as 2nd intervention: 42.4% (29.0–55.9)*

*Trabeculectomy as 1st intervention: 17.9% (13.9–21.9)*
Trabeculectomy as 2nd intervention: 20.7% (13.0–28.2)

Trabeculectomy as 3rd intervention: 34.4% (17.6–51.1)

(95% confidence intervals)

filtration procedure that is simple, quick, limits the wound healing response and minimizes complications.

**Ab externo technique**

*Thulium-holmium-chromium:yttrium-aluminum-garnet (holmium) laser sclerostomy*

The holmium ab externo sclerostomy was generally found most suitable for the creation of blebs in eyes that had heavy conjunctival scarring. Ab externo holmium laser sclerostomy was performed by delivering laser energy through a fibreoptic probe via a subconjunctival approach. A 1–2 mm conjunctival incision 8–10 mm away from the intended sclerostomy site and 6 mm from the limbus was made. The probe was then inserted under Tenon’s capsule and advanced carefully toward the limbus. With the probe tip held tangential to the limbus, the probe was rotated so that the aiming beam was as parallel as possible to the iris. The laser was then fired at a repetition rate of 5 pulses/second (80–100 mJ/pulse in previously unoperated eyes and 100–120 mJ/pulse in previously operated eyes) until a filtering bleb was seen. The success rate of the holmium laser ab externo sclerostomy ranged from 49–55% at 1 year, 39–44% at 2 years to 29–36% at 3 years. Hypotony, iris incarceration and cystic blebs were the most frequent complications. Due to these complications very few procedures are now being performed.

*Intrastromal holmium laser keratostomy*

To avoid hypotony, iris incarceration and cystic blebs, a new filtering procedure, intrastromal holmium laser keratostomy (ILK), has been developed. A laser canal is created intrastromally in the cornea anterior to Schwalbe’s line in the floor of a corneoscleral tunnel incision made with a knife from the corneal site. Complete surgical success without medication and reoperations was reached in 63% of the eyes, with a mean observation time of 22.5 months (range: 16.6–26.7 months). Only 13% of the eyes had early iris incarcerations; there were no late incarcerations. Twenty-five per cent had temporary shallow anterior chambers. As the holmium laser probe was not available for a longer period, because of the above-mentioned results of the holmium laser sclerostomy, the ILK procedure has now been transformed into the filtering clear-cornea, micropenetrating surgery, intrastromal diathermal keratostomy (IDK), in which a diathermy needle is used instead of the laser probe to make the canal into the anterior chamber from the corneoscleral tunnel incision.

**Ab interno technique**

*Neodymium: yttrium—aluminum—garnet laser sclerostomy*

Ab interno Nd: YAG laser sclerostomy is performed using laser energy delivered through a fibreoptic probe via a transcameral approach. The laser energy exits from the tip parallel to the long axis of the probe. Viscoelastic or balanced salt solution is injected subconjunctivally, using a 30 gauge needle, to elevate conjunctiva adjacent to the proposed sclerostomy site. A
sharp steel blade or diamond knife is used to create a peripheral
corneal paracentesis, approximately 1.5 mm in length, 90–180° away from the proposed sclerostomy site. Viscoelastic is injected intracameraly through the paracentesis site. The laser probe is introduced through the paracentesis and is passed across the anterior chamber until the tip is in contact with the sclera in the region of Schwalbe’s line. A gonioscopy lens can be used to aid visualization. The aiming beam may transilluminate the sclera in the vicinity of the limbal sulcus. Between 3 and 5 pulses of 200 mJ (10 W, 0.2 s) are required to achieve filtration. The laser probe is advanced until the probe tip is visualized in the subconjunctival space. Penetration through full-thickness sclera is evident when an adjacent bleb enlarges, and the probe is withdrawn.

**Complications** Iris incarceration is the most frequent complication of laser filtration procedures, especially in phakic eyes and in those with narrow angles. The risk of this complication can be reduced by performing the sclerostomy over a prior peripheral iridectomy or by the creation of a peripheral iridectomy at the time of the sclerostomy. Laser sclerostomy procedures are associated with overdrainage complications found in other full-thickness procedures, which include hypotony, shallow anterior chamber, choroidal effusion, choroidal haemorrhage and cataract formation.

The role of laser sclerostomy in glaucoma filtration surgery as a primary or secondary procedure has lessened.

**New investigational procedures**

*Excimer laser trabecular ablation ab interno (ELT)*

As several experimental and clinical studies have shown that permanent perforation of the trabecular meshwork cannot be achieved with photodisruptive lasers, the further development of certain infrared lasers offered a useful alternative method for a filtering procedure. The excimer laser trabecular ablation ab interno procedure is designed to remove corneoscleral trabecular meshwork to open Schlemm’s canal and thus facilitate outflow. An excimer laser (λ=308 nm) with a 150–250 μm fibre is used. The procedure begins with a 1 mm corneal incision using a precalibrated 20-gauge knife, followed by introduction of viscoelastic into the anterior chamber to deepen the angle in the area where the excimer laser ablation is performed. An angulated fibreoptic is then introduced and a series of four to eight laser shots is applied to the trabeculum from 150 μm to 250 μm.

*Erbium: YAG laser trabecular ablation*

Laser trabecular ablation (LTA) is an ab-interno approach with the purpose to improve outflow facility by removing trabecular tissue and to open Schlemm’s canal. In an application of erbiumr: YAG LTA, 12 neighbouring single laser pulses (5–7 mJ pulse energy, 200 μs pulse duration) were applied to the trabecular meshwork. Light microscopy revealed neither marked scarring nor endothelial proliferation in the treated trabecular meshwork. However, most of the recognizable ablation craters failed to open Schlemm’s canal. Although limited scar formation within the trabecular meshwork after LTA is a promising aspect, the present technique of Er: YAG LTA still needs technical and surgical improvements to guarantee
reliable and reproducible opening of Schlemm’s canal.\textsuperscript{21}
Laser suturolysis

Following drainage surgery, laser suturolysis can be helpful in encouraging aqueous flow if the scleral trapdoor has been sewn down too tightly. To facilitate such a technique, long bites with the 10–0 nylon sutures through the sclera offer a longer possible pathway for laser access.

Laser treatment for internal flow block

Peripheral laser iridotomy

Introduction

Von Graefe introduced surgical iridectomy for glaucoma in 1857; iridectomy was shown to be effective for angle-closure but not for open-angle glaucoma. In 1956, Meyer-Schwickerath demonstrated that an iridectomy could be created without the need for an incision, using xenon arc photocoagulation. This method failed to gain popularity, however, because of frequent lens and corneal opacities. Argon laser iridectomy and, more recently, Nd: YAG laser iridectomy have essentially replaced surgical iridectomy in the vast majority of cases.

Indications for laser iridotomy

Laser iridotomy is the established procedure of choice for angle-closure glaucoma associated with pupillary block—whether primary or secondary; acute, intermittent or chronic. Laser iridotomy is indicated for the following types of glaucoma:

- Acute angle closure with pupillary block;
- Chronic (creeping) angle closure with pupillary block;
- Iris bombé;
- Prophylaxis of occludable angle (indicated for high-risk patients who are young, have a positive family history of angle closure or need frequent, dilated examinations, e.g. diabetics);
- Pigmentary dispersion syndrome (laser iridotomy for this indication remains controversial, since the procedure changes the anatomy of the iris posterior bowing, but the long-term clinical advantage remains unproven).

Laser iridotomy also aids in the diagnosis of aqueous misdirection (malignant glaucoma).

Contraindications

Laser iridotomy is contraindicated in patients who are unable to sit and cooperate at the slit lamp, and in eyes that have a cloudy cornea, widely dilated pupil and flat anterior chamber with iridocorneal touch. Care must be used in nanoflalmus: ciliary block or ‘uveal effusion’ (malignant glaucoma) might occur. As an alternative, laser iridoplasty may be used. Patients
on treatment with anticoagulants drugs or acetylsalicylic acid should be off treatment for a few weeks to avoid bleeding from the iridotomy site.
Treatment technique

The patient’s informed consent must be sought after a thorough discussion of the goal of therapy and potential complications.

Argon versus neodymium: yttrium—aluminum—garnet

Both lasers are effective for the creation of iridotomies. The argon laser requires uptake of light energy by the pigment (thermal effect), but the Nd: YAG laser does not and works well on all iris colours (photodisruptive effect). The most preferred laser is the Nd: YAG because it is quicker, requires less energy to create a patent peripheral iridectomy and is associated with fewer late closures than the argon laser.

The Nd: YAG laser, however, does not coagulate tissue, and small haemorrhages occur more frequently with this modality. Therefore, in eyes that have prominent unavoidable vessels or in patients affected by a bleeding diathesis combined treatment is preferred, first with an argon laser (to ablate vessels in the area), followed by a Nd: YAG laser (to establish a patent peripheral iridectomy).

Patient preparation

The patient’s informed consent must be sought after a thorough discussion of the goal of therapy and potential complications.

- Aceclidine 2% or pilocarpine 2% to 4% single instillation (unfolds the iris, reduces the iris thickness, facilitates the perforation).
- IOP spikes prevention: Oral acetazolamide Topical apraclonidine 1% 1 hour prior to the procedure and immediately afterwards diminishes frequency and magnitude of the acute postoperative IOP rise and decreases bleeding by a vasoconstrictor effect. Remember to ask for known drug intolerance or other systemic problems.
- Topical anaesthesia is instilled immediately before the procedure, both to the treated eye and to the contralateral eye to reduce blinking, which may disrupt treatment.
- Topical glycerine, intravenous mannitol or oral hyperosmotic agents should be considered if the cornea is oedematous

Lens

- Wise laser iridotomy lens (ocular+103 D);
- Abraham (+66 diopters);
- CG© Meridian.

The Abraham lens has a 66D plano-convex button. The Wise lens has a 103D planoconvex button, which concentrates the laser energy more than the Abraham lens because it minimizes the spot and magnifies the target even more; however, because of the higher power of the Wise lens, it is more difficult to focus. The other advantage of the Abraham lens is that energy delivered to both cornea and retina is four times lower than that delivered to these
tissues by the Wise lens.27
Iridotomy site

- Superior quadrants of the iris covered by the upper lid, to prevent monocular diplopia;
- Avoid the 3 o’clock and 9 o’clock positions for discomfort and iris vessels;
- Avoid visible vessels;
- As far peripherally as possible within the arcus senilis;
- Choose a thinner looking area or a crypt;
- Electively superonasal to reduce the likelihood of macular injury when using the Argon laser;
- The optimal size of the iridotomy is 100 to 500 μm;
- Transillumination through the pupil or the iridotomy is not a reliable indicator of success.

Laser parameters

Nd: YAG laser iridotomy

Power: Start with 1.5–6 mJ (according to iris colour: brown iris>blue iris)
Spot size: 50–70 μm (constant for each laser model)
Pulses per burst: 1–3

The beam should be focused within the iris stroma rather than on the surface of the iris. Lens capsule damage is possible at energy levels above 2 mJ. The least amount of energy that is effective should be used. An iridectomy in the range 100–200 μm in diameter is ideal.²⁸
Argon laser iridotomy

When no Nd: YAG laser is available, the Argon laser may be used. There is no single group of laser parameters for all types of iris and for all surgeons. The laser parameters need to be adjusted intraoperatively.

Preparatory stretch burns

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Penetration burns

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<thead>
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<th>Diameter:</th>
<th>50 μm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure time:</td>
<td>0.2 s</td>
</tr>
<tr>
<td>Power:</td>
<td>800–1000 mW</td>
</tr>
</tbody>
</table>

Long pulses (0.2 s) are used for light-coloured irides (blue, hazel, light brown), while short pulses (0.02–0.05 s) are used for dark-brown irides. The rest of the treatment parameters are the same for both long and short pulses, that is a power of 1000 mW and a spot size of 50 μm.

Combined argon/Nd: YAG laser technique

Both argon and Nd: YAG lasers can be used in sequential combination for dark-brown irides, or for patients who are on chronic anticoagulant therapy. First, the argon laser (shortpulse mode) is used to attenuate the iris to about one-fourth of the original thickness and to coagulate vessels in the area. Then the Nd: YAG laser is used, with the beam focused right at the centre of the crater; one or more bursts of 1–3 pulses and 3–6 mJ are used to complete the iridectomy.

Complications

- Temporary blurring of vision;
- Corneal epithelial and/or endothelial burns with argon;
- Intraoperative bleeding, usually controlled by a gentle pressure applied to the eye with the contact lens;
- Transient elevation of the IOP;
- Postoperative inflammation;
- Posterior synechiae;
- Late closure of the iridotomy;
- Localized lens opacities;
- Endothelial damage;
• Rare complications include retinal damage, cystoid macular oedema, sterile hypopion, malignant glaucoma.
**Corneal injury** Focal laser damage to the epithelium, to Descemet’s membrane or to the endothelium occurs frequently, but is usually transient. A shallow anterior chamber, pre-existing corneal oedema or pathological conditions of the cornea (i.e. guttata) makes corneal injury more likely.

**Bleeding** Postlaser hyphema is not uncommon after use of the Nd: YAG laser and is generally minimal and self-limited. Brisk bleeding may be stopped by the application of direct pressure to the cornea using the contact lens, to tamponade the bleeding site temporarily.

**Intraocular pressure spikes** Elevated IOP occurs in approximately one-third of eyes after treatment with either laser,\(^1^8\) but the use of apraclonidine 0.5% or brimonidine 0.2% significantly decreases this risk, except for people already on chronic apraclonidine treatment.\(^2^9\),\(^3^0\)

**Laser-induced inflammation** Laser-treated eyes may suffer transient iritis because of breakdown of the aqueous-blood barrier.\(^2^8\) Occasionally, inflammation may be quite severe and posterior synechiae may develop. Prednisolone drops four times daily for 4–7 days may be used postoperatively.

**Iridectomy failure** An iridectomy may fail because the opening created is too small or because perforation is not achieved when a residual iris pigmented layer is present. Theoretically, functional failure may be avoided with a peripheral iridectomy of diameter at least 50 \(\mu\)m; an iridectomy in the range 100–200 \(\mu\)m in diameter is ideal.\(^2^8\)

**Diplopia** Diplopia or ‘ghost images’ is an occasional complaint, especially when the peripheral iridectomy is placed in the horizontal meridian or it is not covered perfectly by the upper eyelid. In some patients, diplopia (alleviated when the lid is lifted away from the eye) may result despite an iridectomy that is well covered by the upper eyelid. This probably results from a prism effect created by the tear meniscus or the upper eyelid. Intolerable monocular diplopia may be resolved by placing a cosmetic contact lens, which blocks the light from the peripheral iridectomy but not the pupil.

**Lens opacities** The lens rarely may be damaged directly from laser irradiation or indirectly because of deficient nourishment of the lens. If directly laser induced, the opacities tend to remain focal in the area of the peripheral iridectomy, away from the visual axis.

**Postoperative management**

• Check the IOP after 1–3 hours and again after 24–48 hours. When this is not possible, give prophylactic treatment to avoid IOP spikes.
• Topical corticosteroids for 4–7 days.
• Repeat gonioscopy to determine whether or not the angle has deepened.
• Pupillary dilatation to break posterior synechiae.
• Verify the patency of the peripheral iridotomy.
If the peripheral iridectomy remains patent after 4–6 weeks, the opening usually remains open unless an active inflammatory response (uveitis, neovascularization, etc.) is present.

*Laser iridotomy treatment guidelines*

The purpose of the laser iridotomy procedure is to obtain a full thickness hole of sufficient diameter to resolve the pupillary block. Perforation is assumed when pigment, mixed with aqueous, flows into the anterior chamber. The iris falls back and the peripheral anterior chamber deepens. Patency must be confirmed by direct visualization of the lens through the iridotomy. The optimal size of the iridotomy is 100 to 500 μm. Transillumination through the pupil or the iridotomy is not a reliable indicator of success.

The iridectomy is placed in the peripheral iris under the upper eyelid to avoid ghost images that may arise through the iris hole. Such ghost images may be accentuated by the tear meniscus. The 12 o’clock position is avoided when the argon laser is used, since bubble formation hinders further visualization of the target area. Iris crypts represent thinner iris segments and, as such, are penetrated more easily. The superonasal position (at 11 and 1 o’clock), since it directs the laser beam furthest from the macula, is the best position to use to help prevent inadvertent irradiation of the fovea.

One patent iridectomy is almost always sufficient to relieve pupillary block. In rare instances in which the long-term patency of the opening is uncertain or in the presence of inflammatory (uveitic) pupillary block, a second iridotomy may be made at the same sitting.

*Outcome*

If the peripheral iridectomy remains patent and a new attack of IOP elevation occurs, it is imperative to perform an indentation gonioscopy to evaluate whether a plateau iris or a chronic angle closure with synechiae is present. In case of a plateau iris, an iridoplasty is needed. In case of a chronic angle closure with synechiae, IOP-lowering therapy is needed.

*Laser iridoplasty*

Laser iridoplasty consists of the placement of a circumferential ring of non-penetrating contraction burns at the far iris periphery, just inside the limbus, to contract the stroma and widen the angle. Laser iridoplasty is indicated in cases of pre-argon laser trabeculoplasty of narrow angle (to increase visibility of the angle anatomy), in angle closure for which peripheral iridectomy cannot be performed because of corneal clouding and the closure is unresponsive to medical treatment, and in the plateau iris syndrome.

*Indication*

- To widen the angle approach by shrinking the peripheral iris using a thermal effect.
- Plateau iris syndrome.
- In mixed pupillary block/plateau iris cases where YAG iridotomy has not opened the angle.
- In preparation for ALT when the angle approach is narrow, in order better to visualize the trabecular meshwork.
- Angle closure in nanophthalmos.
Treatment technique

The patient’s informed consent must be sought after a thorough discussion of the goal of therapy and potential complications. Patients should be warned that one treatment may not suffice and that a second treatment may be necessary to obtain a permanent effect (that is, posterior positioning of the peripheral iris). Patients should be told ahead of time that the treatment might cause slight permanent dilatation of the pupil and that it will cause delayed discoloration of the peripheral iris.

Preoperative preparation

- IOP spikes prevention: topical apraclonidine/brimomdine, pilocarpine and oral acetazolamide 1 hour prior to the procedure and immediately afterwards can be used depending on the individual.
- Topical anaesthesia is instilled immediately before the procedure.

Lens

- Laser contact lenses;
- Abraham lens;
- Goldmann type lens, aiming through the central part, not the mirrors.

Contraindications

- Severe corneal oedema or opacification;
- Flat anterior chamber;
- Synechial angle closure.
Figure 15.5 Argon laser iridoplasty.
Pupillary block

1A
Eye with imminent pupillary block

1B
same eye after indentation gonoscopy

Laser iridotomY is indicated

Plateau iris

2A
Eye with plateau iris and imminent angle closure

2B
Same eye after indentation gonoscopy Still imminent angle closure

Argon laser iridoplasty is indicated

Eye with plateau iris and imminent angle closure

Same eye after YAG-iridotomy Still imminent angle closure

Argon laser iridoplasty was indicated as first line therapy
Figure 15.6

Argon laser iridoplasty was indicated as first line therapy

UBM photos showing iris and anterior chamber
Courtesy: Kessing SV & Jensen PK. Copenhagen University Hospital
Laser parameters

Contraction burns

Diameter: 300-500 µm
Duration: 0.2-0.5 seconds
Power: 200-400 mW
Location: the aiming beam should be directed at the most peripheral portion of the iris

The goal of treatment is contraction of the peripheral iris with flattening of the peripheral iris curvature. The ideal number of impacts is 20 to 50 applications over 360°, leaving 2 beam diameters between each spot and avoiding visible radial vessels.

Complications

• Mild iritis
• Corneal endothelial burns
• Transient postoperative IOP elevation
• Posterior synechiae of the pupil
• Permanent pupil dilation

Postoperative treatment

• Topical steroids for 4–7 days.

Postoperative control

• The patient is reviewed after 1 week. If anterior uveitis is present at 1 week, topical corticosteroids are continued.
• Gonioscopy to check whether the peripheral iris curvature has flattened.

Laser cyclodestructive procedures

Cyclodestructive procedures are generally reserved for eyes that have poor visual potential, eyes in which other glaucoma procedures failed or are not applicable (for example extensive conjunctival scarring), eyes in which filtering surgery has a high failure rate (for example neovascular glaucoma, aphakic and pseudophakic glaucoma and glaucoma associated with silicone oil), and patients who, for medical reasons, are unable to undergo filtration surgery.32

In most clinics, cyclocryotherapy has now been exchanged with either the neodymium:yttrium-aluminum—garnet (Nd: YAG) laser or semiconductor diode transscleral cyclophotocoagulation (wavelength 810nm). The exact mechanism most probably involves
destruction of the epithelium of the ciliary processes with simultaneous destruction of the ciliary body vasculature.\textsuperscript{33} Other techniques currently under investigation include laser endocyclophotocoagulation and endoscopic cyclophotocoagulation.
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16.
CYCLODESTRUCTION IN THE TREATMENT OF GLAUCOMA
Ahti Tarkkanen, Päivi Puska and Tero Kivelä

Introduction

Partial transscleral contact cyclodestruction to lower intraocular pressure (IOP) in therapy-resistant glaucomas is one of the controversial methods in ophthalmology. Cyclodiathermy and cyclocryocoagulation now belong to the past because of their severe side-effects, such as intense postoperative pain, an abrupt rise in IOP, intraocular haemorrhage and phthisis. The side-effects of Nd: YAG laser cyclophotocoagulation are similar but milder. Consequently, these methods are being replaced by contact transscleral infrared 810 nm diode laser, red 647 nm krypton and red 670 nm diode laser cyclophotocoagulation. The latter lasers are excellently absorbed by melanin pigment, which explains the good clinical results with low amounts of energy. In order to produce a similar coagulation effect in the rabbit ciliary body, only half as much energy is required with the 647 nm krypton laser as compared to the 1064 nm Nd: YAG laser. The red lasers do not impair the sensitivity of the cornea, they do not injure corneal subbasal nerves and they do not change tear secretion. Diode laser equipment is not costly, mostly portable and easy to use.

The location of the pars plicata of the ciliary body is variable and it must be identified before cyclophotocoagulation by transscleral illumination or high frequency ultrasonography. The fibreoptic probe must be held perpendicular against the scleral surface, and it has to be pressed firmly against the sclera to enhance penetrance of the laser beam. The laser energy at the scleral surface is usually 1.0 to 2.0 W with the 810 diode laser, whereas with the 670 nm diode laser it is no more than 0.35 to 0.43 W. The application times are 1.5 to 2.0 seconds for the 810 nm and 10 seconds for the 670 diode laser.

The fall in IOP after diode laser cyclophotocoagulation is most probably due to a combination of reduction in the aqueous inflow and an increase in the uveoscleral outflow. Transscleral diode laser cyclophotocoagulation is indicated for therapy-resistant glaucoma, which has failed to respond to maximally tolerated medical therapy, laser trabeculoplasty and filtering glaucoma surgery. Other indications are patients with very poor vision and elevated IOP, pain relief for blind eyes and for patients whose general medical condition precludes filtering surgery or who refuse traditional glaucoma surgery.
Non-penetrating and penetrating cyclodiathermy

In 1925, Curran\textsuperscript{1} cauterized the sclera over the ciliary body using a red-hot galvanocautery loop. He aimed to lower intraocular pressure (IOP) by creating an artificial staphyloma to increase filtration through its spongy sclera. Weve,\textsuperscript{2} in 1932, observed that the IOP remained low after extensive diathermy over the region of the ciliary body. He used non-penetrating cyclodiathermy to treat infantile glaucoma.

Vogt\textsuperscript{3} introduced penetrating cyclodiathermy in 1936. He used a 1-mm-long needle 0.2 mm in diameter. Up to 100 scleral punctures were made 1.5 to 3.5 mm from the limbus to the lower quadrants. Because it caused necrosis of the peripheral cornea in many cases, the method was modified. The new needle was only 0.5 mm long and 0.16 to 0.18 mm thick. The scleral perforations were made at least 2.5 mm from the limbus by application of a 60 mA current for 0.5 to 1 seconds. A conjunctival flap was not prepared.

The rationale of cyclodiathermy was to heat tissues to the level of vascular thrombosis to cause scarring and atrophy of the ciliary epithelium. This procedure became the cyclodestructive method of choice.\textsuperscript{4} The main complications consisted of conjunctival necrosis and an abrupt rise in IOP to as high as 80 to 100 mm Hg because of scleral shrinkage during or soon after the procedure.

In 1970 Walton and Grant\textsuperscript{5} reviewed a series of 100 operations of modified penetrating cyclodiathermy performed on 26 adults and 27 children. Their study documented only a 5% chance of a long-lasting, useful reduction in IOP and about the same chance of inducing phthisis. Cyclodiathermy was soon to be replaced by cyclocryotherapy.

Cyclocryocoagulation

Freezing of the ciliary body to lower IOP was suggested by Bietti\textsuperscript{6} in 1950. However, it took more than 15 years before it was shown that this method was useful in treating patients with advanced chronic glaucoma. The results were improved if the treatment was repeated\textsuperscript{7,8} Fewer complications were described, the most serious being marked intraocular haemorrhage.

In human and primate eyes treated with cryocoagulation, the epithelial and vascular elements of the ciliary processes were destroyed and replaced by fibrous tissue. However, both the trabecular meshwork and Schlemm’s canal were also affected histologically.\textsuperscript{9} It was suspected that their damage could counteract lowering of the IOP. In addition, breakdown of the blood—aqueous barrier was observed, accounting for chronic aqueous flare.

Specific indications for cyclocryotherapy once it became the cyclodestructive procedure of choice in the 1970s were neovascular, inflammatory and aphakic glaucomas.\textsuperscript{10} The standard probe tip freezes to \(-80^\circ\) C. The first application is made 3 mm posterior to the limbus at the 12 o’clock position, with or without opening the conjunctiva. The probe is pushed firmly against the globe and the development of the ice ball is noted. It usually
reaches maximum size in 45 to 60 seconds. Freezing is then stopped. The probe is allowed to thaw slowly without irrigation because this will enhance the clinical effect. Subsequent cryoapplications are placed at 3, 6, 9, 1:30, 4:30, 7:30 and 10:30 o’clock positions, in total eight applications.

Cyclocryocoagulation gives favourable results in neovascular glaucoma.\textsuperscript{11,12} Visual outcome may be poor and pain relief in 90\% of patients is the main benefit.\textsuperscript{13,14} Good results have been obtained in the treatment of aphakic open-angle glaucoma\textsuperscript{15} as well as in glaucoma after penetrating keratoplasty.\textsuperscript{16,17} These findings have been confirmed in two 10-year follow-up studies.\textsuperscript{18,19}

The most frequent complications of cyclocryocoagulation are intense postoperative pain for several days, transient IOP elevation, hyphaema and secondary uveitis. Postoperative pain may be reduced by performing the operation after conjunctival peritomy. Strong analgesics are nevertheless often needed. In one study,\textsuperscript{20} the IOP rose to 60 to 80 mmHg during the freezing phase, but decreased to baseline during thawing. Postoperatively, the IOP again rose up to 60 mmHg and peaked 6 hours after the procedure. Chronic aqueous flare is later found in all eyes. Phthisis is a well-known and feared complication. In another study,\textsuperscript{19} the overall incidence of phthisis after cyclocryocoagulation was 12\%. Of eyes with neovascular glaucoma, 22\% ended up having this feared complication.

After the advent of ingenious new methods of cyclodestruction, cyclocryotherapy is now seldom practised. It is mainly used in case equipment for when cyclophotocoagulation is not available.

\textit{Transscleral cyclophotocoagulation}

\textbf{Xenon arc}

In 1961 Weekers and associates\textsuperscript{21} used light energy for the first time for cyclodestruction and founded the concept of cyclophotocoagulation. They applied the xenon arc transsclerally over the ciliary body.

The IOP declined both in normal rabbit eyes and in patients suffering from chronic open-angle and aphakic glaucomas. Histopathological studies showed intravascular thrombosis and loss of pigment from the ciliary processes. Their method did not gain popularity, however.

\textbf{Ruby laser}

In 1969, Smith and Stein\textsuperscript{22} and Vucicevic and associates\textsuperscript{23} reported the use of the ruby laser for cyclophotocoagulation. In rabbit eyes, the former investigators observed a doserelated local destruction of the ciliary body accompanied by vitreous coagulation, haemorrhage and secondary retinal detachment.

The first report on the efficacy of the ruby laser in intractable glaucoma was published in
1972,$^{24}$ and a year later the neodymium laser was used for this purpose.$^{25}$ In a 10-year follow-up study, the overall success rate for lowering IOP with transscleral ruby laser
cyclophotocoagulation was 62%. Most eyes maintained their preoperative visual acuity. Postoperative pain was considerably reduced in comparison to cyclocryotherapy. The main complications were chronic hypotony in 17% of eyes and phthisis in 17% of eyes.

**Nd: YAG lasers**

The introduction of neodymium: yttrium—aluminum—garnet (Nd: YAG) lasers markedly increased the popularity of cyclophotocoagulation. These lasers can be operated in continuous wave, thermal and pulsed, free-running modes. The ciliary processes can be approached through the pupil, by endoscopy or most often by the transscleral route. For the transscleral approach, non-contact and contact techniques have been developed; they yield comparable clinical results.

The continuous mode is used for transscleral contact cyclophotocoagulation and the probe is placed over the sclera 0.5 to 1 mm from the limbus without making a peritomy. Constant force must be applied to the probe on the sclera, in the range 0.25 to 0.40 N, to decrease absorption of laser energy during transit to the ciliary body. Pushing the probe will result in a more localized coagulation effect. The probe has to be held perpendicular to the scleral surface, because a misalignment of 15° off perpendicular will direct the beam away from the ciliary processes. Between 30 and 40 applications are made using 5 to 7 J energy. A good response has been reported also after 16 applications using 2 J each. The 3 and 9 o’clock positions are usually spared to avoid damage to the long posterior ciliary arteries.

In one study, 62% of the patients had an IOP below 21 mm Hg after treatment, whereas 11% had to be retreated. Very satisfactory results were obtained in refractory glaucoma following penetrating keratoplasty. In a series of 52 eyes, the mean pretreatment IOP was 38.7 mm Hg and after therapy it had fallen to 15.8 mm Hg. Seventy per cent had a post-treatment IOP of 21 mm Hg or less. If necessary, only half of the original number of applications is recommended to avoid phthisis.

As mentioned, complications of transscleral Nd: YAG cyclophotocoagulation resemble those seen after cyclocryotherapy, but they are less severe. After treatment using 16 to 50 burns and laser energy from 3 to 7 J, the most common complications were anterior uveitis (42 %), conjunctival injection (36 %) and pain (30 %). There are occasional reports of sympathetic ophthamalia after Nd: YAG cyclophotocoagulation. In cases with histopathological confirmation, the exciting eye had undergone perforating incisional surgery. Hence, eyes without visual potential should be treated cautiously, with this feared complication borne in mind.

**810 nm diode laser**

Infrared diode lasers operate within the 780 to 850 nm spectrum, in contrast to the 1064 nm wavelength delivered by the Nd: YAG laser. The near infrared light generated by the diode laser has an excellent scleral penetration and a better melanin absorption than the longer wavelength produced by the Nd: YAG laser.

The histopathological effects of the contact semiconductor diode laser and transscleral
Nd: YAG cyclophotocoagulation are similar in living rabbit\textsuperscript{38} and human autopsy eyes.\textsuperscript{39} However, the diode laser requires less energy than the Nd: YAG to cause similar ciliary body damage. Both non-contact and contact modes are available. The contact mode is preferred because of the smaller amount of energy required.

In the first clinical study,\textsuperscript{40} published in 1992, the mean IOP of 34.8 mmHg in eyes with refractory glaucoma had reduced to a mean of 24.3 mmHg 6 months after a single treatment session. The authors used a non-contact technique, in which the laser was attached to a slit lamp.

The standard outpatient transscleral contact diode laser cyclophotocoagulation procedure commences with local anaesthesia, which can be subconjunctival, subtenon, peribulbar or retrobulbar. The pars plicata of the ciliary body is localized by using transscleral illumination or high frequency ultrasound. The fiberoptic probe is pressed against the sclera at the site of the pars plicata and 10 to 15 applications are made. No more than 180° to 270° is treated using 2.0 W energy and 2.0 second application time settings.\textsuperscript{41} The probe has to be perpendicular to the sclera, because a misalignment of 15° may markedly lessen the effect.\textsuperscript{29} Topical antibiotic and either corticosteroid or non-steroidal antiinflammatory medications are prescribed postoperatively. Glaucoma medication is continued initially and then gradually withdrawn, starting from oral carbonic anhydrase inhibitors.

In addition to therapy-resistant glaucoma, transscleral infrared diode laser cyclophoto-coagulation has been used as first-line treatment for primary open-angle glaucoma.\textsuperscript{42} After 13 months, the drop in IOP was 20 % or more in 47 % of eyes. A target pressure of 22 mm Hg or less was achieved in 48 % of eyes.

In treating various types of refractory glaucoma, about 70 % achieved a final IOP of 21 mm Hg or less.\textsuperscript{41,43–45} The number of medications could be decreased and loss of visual acuity was not a problem. Favourable results were also obtained in treating glaucoma associated with uveitis.\textsuperscript{46} After 12 months, the IOP was controlled in 77 % of eyes. Repeated treatment was necessary in 64 % of eyes. Reactivation of uveitis, persistent hypotony and phthisis were not observed.

In paediatric refractory glaucoma, the success rate is lower than in adults and the younger patients may relapse more rapidly.\textsuperscript{47} After repeat cyclodiode treatment, 72 % of eyes showed clinically useful reduction of the IOP for at least a year. Meta-analysis suggested that higher total energy was associated with a higher percentage of patients achieving an IOP of 21 mmHg or less.\textsuperscript{48} This was not associated with an increased risk of complications or visual loss.

The complications of transscleral contact diode laser cyclophotocoagulation are mild. Even repeated procedures are well tolerated.\textsuperscript{42} Many patients consider laser treatment to be less frightening than incisional surgery such as trabeculectomy. Postoperative pain has been minimal. Most patients will have a mild uveitis lasting for 2–4 weeks. Hyphaema and phthisis are reported in 6.8 % of patients. Of eyes treated because of neovascular glaucoma, 1.9 % developed phthisis.\textsuperscript{43}
Red 647 nm krypton and 670 nm diode lasers

Experimental and clinical studies showed that red krypton at 647 nm is a promising wavelength for transscleral cyclophotocoagulation. Lesions in the pars plicata of the rabbit eye similar to those obtained using the contact Nd: YAG laser were produced by using only half the energy. Melanin absorption of the short wavelength laser energy is superior when compared with 1064 nm Nd: YAG lasers and even somewhat better than that of the 810 nm infrared diode lasers. Poorer transit of the krypton laser energy through the sclera can be overcome by pressing the probe firmly against the sclera.

The long duration of the red lasers allows use of lower power settings and in this way explosive reactions or ‘puffs’ in the ciliary body can be avoided. With red lasers the power at the scleral surface is 0.35 to 0.43 W, whereas with the 810 nm diode laser it is 1.5 to 2.0 W. The duration of each application with red lasers is 10 seconds, whereas with the 810 nm laser it is 1.5 to 2.0 seconds. Hyperthermia caused by the low-power, long-duration lasers may explain the mild postoperative side-effects such as the almost total absence of pain and mild uveitis.

To avoid a postoperative IOP rise, the patient is given a drop of 1 % topical apraclonidine, an oral carbonic anhydrase inhibitor or both. The shadow of the pars plicata of the ciliary body is identified using transscleral illumination. Peribulbar anaesthesia is administered. Conjunctival peritomy is not needed. The first treatment is applied 180° in the inferior quadrants. About 10 applications are applied per single quadrant, using 0.3 to 0.5 W power with the krypton or 0.40 to 0.45 W with the 670 nm diode laser. The exposure time is always 10 seconds.

After treatment the patient is given a topical corticosteroid and antibiotic. Previous antiglaucoma medications are tapered according to the therapeutic response. In case the procedure needs to be repeated, the temporal 180° is treated, i.e. one quadrant is retreated. If a third treatment is needed, the inferior nasal 90°and superior temporal 90° receive retreatment, that is the superior nasal quadrant is left untouched.

In the treatment of therapy-resistant posttraumatic glaucoma with the transscleral contact krypton laser, an almost 40 % drop in IOP at 2 months after treatment was achieved. In one of 18 eyes, phthisis developed. In the treatment of refractory glaucoma in children and young adults, an IOP level of 8 to 21 mm Hg or a decrease in IOP of more than 30 % was obtained after one or more krypton cyclophotocoagulations in 64 % of eyes at 2 years postoperatively. One-third were treated once, one-third twice, 18 % three times, 9 % four times and one patient even eight times. Still none of the eyes developed permanent hypotony, phthisis or other severe complications.

Thirty patients with neovascular glaucoma were treated with the transscleral contact 670 nm red diode laser combined with transscleral peripheral retinal cryocoagulation. One to two rows of cryoapplications, 15 to 40 in number, were applied posterior to the ora serrata under indirect ophthalmoscopic control. An IOP level of 8 to 21 mm Hg or a fall in IOP of 30 % or more was achieved in 87 % of eyes 17 months postoperatively. Another aim has been to relieve pain in blind eyes as a palliative measure. One eye out of 30 developed permanent hypotony and one developed phthisis.
The effects of transscleral contact diode laser cyclophotocoagulation on corneal innervation, mechanical sensitivity and tear fluid secretion have been studied.\(^{55}\) With the use of in vivo confocal microscopy, no changes were noted in the corneal layers or subbasal nerves one month postoperatively. Corneal sensitivity was tested with the Cochet—Bonnet esthesiometer. No abnormality was found in any part of the cornea. Normal values for tear fluid secretion were obtained.

These results lend strong support for the clinical observations on the mild postoperative complications. Only occasional patients report slight pain, and no systemic analgesics are needed postoperatively.\(^{55}\) Transient anterior uveitis occurred in 40\% of eyes. Subconjunctival haemorrhage was rare. The red krypton and 670 nm diode lasers seem well suited for the treatment of various types of treatment-resistant glaucomas.

### Mechanism of intraocular pressure reduction

The mechanism of IOP reduction after cyclophotocoagulation is debated. The accepted goal is ablation of the ciliary epithelium to minimize aqueous production.\(^{53,56–59}\) Alternative theories include damage of the ciliary vascular supply,\(^{59}\) postoperative uveitis with reduced aqueous production\(^{60}\) and increased uveoscleral outflow,\(^{56–58,60}\) and increased uveoscleral outflow from ciliary epithelial damage.\(^{56–58,60}\) In monkey eyes, deliberate treatment of the pars plana instead of the pars plicata gave a comparable reduction in IOP. Neuroepithelial defect has also been suggested to explain the reduction of IOP.\(^{61}\)

An eye with therapy-resistant chamber angle recession glaucoma was successfully treated with transscleral contact krypton cyclophotocoagulation.\(^{62}\) When the eye was examined at autopsy 10 months later it was found that effective ablation of the ciliary processes had been achieved. Only a slight chronic inflammation was present at that time. The experience from transscleral cyclocryocoagulation supports the view that nonconventional outflow routes are increased after cyclodestruction.\(^{63}\)

Histopathological studies have identified loss of ciliary muscle from the treated volume as an ubiquitous late effect of cyclophotocoagulation, whether it is performed at red or infrared wavelengths.\(^{62}\) Even though this potentially reduces accommodative capacity in young individuals, this has not been a problem in clinical practice. Another potential complication is neovascular growth to the vitreous cavity, if the ciliary epithelium is disrupted.

### Indications for partial cyclodestruction

Transscleral contact, the near infrared 810 nm diode laser, the red 647 nm krypton laser and the red 670 nm diode laser are currently preferred over cyclocryotherapy and even to the non-contact and transscleral contact Nd: YAG laser, whenever available. With the
former techniques, the risk of severe postoperative complications is low. Most of the units are also portable and less expensive than Nd: YAG lasers.

Cyclophotocoagulation is indicated for patients with therapy-resistant glaucoma who have failed maximum tolerated medical therapy, laser trabeculoplasty and filtering surgical procedures, for patients with minimal useful vision or no visual potential and for relief of severe pain from intractable glaucoma. Eyes without visual potential should be treated cautiously if they have undergone previous surgery because of isolated reports of presumed sympathetic ophthalmia after Nd: YAG cyclophotocoagulation.

Cyclophotocoagulation can also be useful for patients whose general medical condition precludes incisional surgical procedures and who refuse a traditional filtering operation or placement of a stent.

References


COMBINED SURGERY FOR GLAUCOMA AND CATARACT: VISCOCANALOSTOMY, PHACOEMULSIFICATION AND FOLDABLE INTRAOCULAR LENS IMPLANTATION

Ke Yao

Introduction

Antiglaucomatous filtering bleb fibrosis may occur soon or later postoperatively, because of scarring of the conjunctiva and Tenon’s capsule. Studies show that it is especially prevalent in black people, in whom fibrosis can occur in up to 80% of trabeculectomy cases\(^1\)–\(^3\). Since the 1980s several nonpenetrating surgical techniques have been introduced to resolve the problem\(^4\)–\(^8\). The aim is to reduce intraoperative and postoperative complications, such as hypotony, shallow anterior chamber, inflammatory reaction and bleb fibrosis. Recently, such surgical techniques have become quite popular, particularly when combined with phacoemulsification\(^9\)–\(^11\),\(^14\),\(^15\).

Viscocanalostomy is one of the non-penetrating glaucoma filtration surgical techniques, first carried out by Robert Stegmann. The main purpose is to avoid wound-healing-related bleb failure.\(^12\) The principal mechanism is possible leakage of the aqueous into the intrascleral pool from the extremely thin Descemetic window, the position of the excised inner scleral flap, covered with the superficial scleral flap. The Descemetic window consists of the anterior layer of corneoscleral trabecular meshwork and Descemet’s membrane. The aqueous collected in the intrascleral pool may flow into the collecting duct and episcleral vein through Schlemm’s canal, which is dilated by high viscosity viscoelastic material (Figure 17.1). In addition to the above-mentioned hypothesis, many surgeons have observed that filtering blebs, that is the aqueous in the intrascleral pool, might pass the scleral flap margins into the conjunctiva and Tenon’s capsule.
Figure 17.1 The hypothetic mechanism of viscocanalostomy. The aqueous humour flows into the intrascleral pool through the Descemet’s window and then into the collecting duct and episcleral vein through Schlemm’s canal.

Indication and contraindications

The major indication of viscocanalostomy (combined with phacoemulsification or not) is open-angle glaucoma and the major contraindication is neovascular glaucoma and angle-closure glaucoma. In neovascular glaucoma, the angiofibrous membrane, preventing aqueous flow, cannot be compensated with the dilated Schlemm’s canal. In angle-closure glaucoma, the Schlemm’s canal dilated by viscoelastic material may increase the risk of iris incarceration or cause dysfunction of the filtering of the Descemetic window. It is necessary to perform basal iridectomy or laser iridectomy through a new incision on the patients with
angle-closure glaucoma (the angle is not closed completely). The author only performs this procedure on patients with primary open-angle glaucoma combined with cataract.

**Surgical techniques**

**Anaesthesia**

Viscocanalostomy combined with phacoemulsification may be performed under local anaesthesia. Fixation of the eyeball by means of retrobulbar or peribulbar anaesthesia is helpful for preparing the scleral flap if there are no contraindications. Alternatively, topical anaesthesia (4% lidocaine and 0.5% tetracaine) combined with intraocular anaesthesia (2% lidocaine) may also be used. A subconjunctival injection of lidocaine should be administered if the desired effect cannot be achieved.

**Conjunctival flap**

A 6 mm wide fornix-based conjunctival flap including Tenon’s capsule is dissected superiorly. A superior rectus bridle suture is required to obtain adequate visualization if there
is poor exposure. Bipolar cautery can be used to stop bleeding of individual vessels one by one, but not to coagulate the episcleral vessels so as to preserve their function in aqueous drainage. Any damage of episcleral vessels should be avoided as far as possible.

**Superficial scleral flap**

A superficial scleral flap is better placed between two venous collectors, which may be parabolic, square or rectangular, according to the surgeon’s preference. The author prefers a square flap, 4×4 mm, 200–250 μm in thickness, dissecting 1 mm into the clear cornea.

The outline of the superficial scleral flap can be cut using different instruments, such as diamond micrometer, 30° to 40° angle ruby or metal blade. A metal blade with fixed thickness is now available, by which the flap can be cut 200–250 μm in thickness. The flap is usually dissected by a tongue-like, crescent shaped or spoon-like blade, which is so sharp that the flap can be dissected exactly parallel and the thickness can be easily controlled.

A suture of 8–0 silk can be used to fix the superficial flap for facilitating dissection of the inner scleral flap and obtaining good visualization, but it is not necessary.

**Inner scleral flap**

The dissection of the inner scleral flap, that is the deep scleral flap, is the key step of the procedure. Only by dissecting the inner flap to the correct depth is identification of Schlemm’s canal possible.

An inner flap is dissected for 0.5 mm inside the border of the superficial flap to attain adequately tight closure when suturing the superficial flap at the end of the procedure. It is advisable to use a blade with a scale for flap dissection, because the depth of dissection is hard to determine in advance, due to individual differences in scleral thickness. In the author’s experience, the plane of the dissected flap should be apposed to choroids as closely as possible, that is the blue-grey background can be seen through a thinner layer of the residual scleral fibres during dissection. At that time increased magnification of the microscope is required to obtain a more detailed view to secure the depth of flap. The instruments are the same as used in superficial flap creation.

If the depth is correct, Schlemm’s canal is unroofed as the flap is dissected forward to the canal in which the roof is adhering to the inner face of the deep flap. The canal looks like a dark line in front of the scleral spur under the microscope, just a notch on the anterior margin of the scleral bed. After the flap is extended to the clear corneal limbus, the trabecular meshwork of typical granular structure may be seen.

**Dilation of Schlemm’s canal**

With the inner scleral flap hanging for dilation of Schlemm’s canal, a finely polished cannula with an outer diameter of 165 μm and an inner diameter of 90 μm (Grieshaber) is used to inject high molecular weight viscoelastic material, such as Healon GV. The cannula is introduced carefully into the canal and viscoelastic material injected into the canal for 0.5–1.0 mm in order to avoid a tear caused by sudden increased pressure. The procedure has to be changed to trabeculectomy if this step fails.
Stegmann reported that the diameter of Schlemm’s canal increased to more than 200 μm (230 μm) from its usual diameter of 25–30 μm. The colour of the superficial scleral vessels may occasionally turn to pale after the injection. To gain the maximum dilation, Stegmann suggested that the injection should be repeated three times. The viscoelastic material is believed to persist inside the canal for about 6 days.

**Phacoemulsification**

Phacoemulsification may share the same incision with viscocanalostomy or be performed through another new incision on the superior temporal, superior nasal or temporal clear cornea.

In combined surgery sharing one incision, phacoemulsification is performed before viscocanalostomy and creation of Descemet’s window. A clear corneal tunnel incision, 2 × 3 mm wide, is constructed under the superficial scleral flap after reposition of the inner flap to the former scleral bed. Then appropriate viscoelastic material is injected into the anterior chamber through the side-port incision tract to maintain IOP before making a puncture into the tunnel incision.

The tunnel incision is better located between the superficial and deep flap. Because the superficial flap has been dissected 1 mm into the clear cornea, it is essential that the diamond or metal blade is extended forward 1 mm more (a total of 2 mm) into the clear cornea and then introduced to penetrate the anterior chamber. The width of the incision depends on the calibre of the tip of the hand-piece and the dimension of the intraocular lens (IOL).

In fact, the author prefers combined surgery through different incisions ([Figure 17.2](#)). After unroofing of the canal, the inner flap is extended into the clear cornea for 1 mm. We introduce the cannula into the canal for 0.5–1.0 mm, both left and right, to inject Healon GV slowly. The injection is repeated three times at both lumens of the canal. When the tissue of Descemet’s membrane is removed with a sponge and forceps, the aqueous percolation occurs through the Descemetic window and then the inner flap is excised by means of blunt-tipped scissors. The space of excised inner flap (intrasceral pool) is filled with appropriate Healon GV. The superficial flap is sutured with 10–0 nylon sutures on two sides of the margin and the conjunctival flap as well. Then the tunnel incision of phacoemulsification is constructed on the superior temporal or superior nasal clear cornea close to the flap. The temporal clear cornea incision is only generally applied in is patients with high astigmatism.

The ‘stop and chop’ technique is most popular for phacoemulsification, by which surgeons save time and power. A foldable IOL should be applied as far as possible, since the tunnel incision has to be expanded and sutured by 10–0 nylon sutures at the end of surgery if a rigid IOL is implanted.

When the shared-incision technique is applied, the miotic injection of chamber is necessary, which will reduce the risk of iridoptosis in the creation of the Descemetic window.
The shared-incision technique has two advantages over the separate-incision technique:

- The surgeon does not have to change position.
- The normal IOP is easy to obtain after suturing the superficial flap by the end of surgery, and the risk of shallow anterior chamber caused by leakage from the incision can be avoided.

Selection of the separate-incision technique is reasonable if the surgeon is not familiar with viscocanalostomy or postoperative astigmatism needs to be considered. In addition, the separate-incision technique is the choice in patients with a density cataract, whereby the risk of incision burning can be reduced.

**Descemetic window**

The Descemetic window needs to be created after phacoemulsification and IOL implantation with the shared-incision technique.

In order to prevent prolapse of the iris during creation of the Descemetic window after
viscoelastic material injection, aqueous may be drawn off through the side-port incision to reduce the IOP.

A sharp instrument should not be applied when creating the Descemetic window, which may enter the anterior chamber. Applying gentle pressure to the anterior boundary of the trabecular meshwork with a sponge, and pulling the inner flap softly, is sufficient to remove the thin layer of loose connective tissue by blunt dissection.

The anterior portion of the intact Descemetic window is formed by Descemet’s membrane and the posterior portion is the remaining trabecular meshwork tissue. The aqueous percolation should be observed when the window is constructed. If percolation
is absent or insufficient, a thin non-toothed forceps is helpful in teasing the thinner wall of Schlemm’s canal and the trabecular meshwork tissue exposed in the window to increase the aqueous exudation. The key point of this step is to avoid perforation. Once perforation exists, the advantage of viscocanalostomy is lost and the procedure has to be shunted to trabeculectomy.

**Excision of the inner flap and suture**

The inner flap is excised using Vannas scissors with blunt tips once the Descemetic window is showing good percolation. The action should be very gentle to avoid rupture of the Descemetic window by the tip of the scissors.

Closure of the parabolic superficial scleral flap needs five stitches with 10–0 nylon sutures, and the rectangular or square flap two or four stitches. High molecular weight viscoelastic material is injected into the intrascleral pool in order to avoid sinking of the flap. The conjunctiva and Tenon’s capsule on both sides are sutured in order to be fixed on the corneal limbus.

**Comparison of viscocanalostomy and trabeculectomy combined with cataract surgery**

The author compared the outcome of phacoemulsification-foldable IOL implantation combined with viscocanalostomy (P-C group) with that of phacoemulsification-foldable IOL implantation combined with trabeculectomy (P-T group).

**Patients**

Twenty-one eyes of 19 patients in the P-C group and 18 eyes of 18 patients in the P-T group operated on between January 2001 and March 2002 were included in the study. The inclusion criteria for the study were cataract and advanced, medically uncontrolled primary open-angle glaucoma with an IOP>21 mm Hg, without previous ocular surgery.

All patients were examined at 1 week, 1 month and 6 months postoperatively, to assess the best corrected visual acuity, IOP, diopter, corneal topography, corneal endothelium and complications.

**Intraocular pressure**

The IOP of both groups was below 21 mm Hg in the follow-up at 6 months (**Table 17.1**). The IOP of the P-C group was reduced by 9.73 mm Hg at 6 months. The difference between preoperation and postoperation was statistically significant ($t=8.512$). The IOP of the P-T group was reduced by 9.18 mm Hg at 6 months and the difference was also statistically significant ($t=9.144$). There was one eye in the P-C group (4.76%) with an IOP of 24 mm Hg, which could be controlled below 21 mm Hg by medical therapy. There was one eye in the P-T group (5.56%) with an IOP of 25 mm Hg, which could also be
Table 17.1 Main preoperative and postoperative IOP of the P-C and P-T groups

<table>
<thead>
<tr>
<th>Group</th>
<th>No of eyes</th>
<th>Preoperative IOP</th>
<th>IOP 1 week postoperatively</th>
<th>IOP 1 month postoperatively</th>
<th>IOP 6 months postoperatively</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-C</td>
<td>21</td>
<td>25.53±4.59</td>
<td>11.82±3.38</td>
<td>14.25±2.35</td>
<td>14.80±2.63</td>
</tr>
<tr>
<td>P-T</td>
<td>18</td>
<td>24.27±4.28</td>
<td>10.75±3.51</td>
<td>14.28±2.64</td>
<td>15.09±2.53</td>
</tr>
</tbody>
</table>

controlled under 21 mm Hg by medical therapy. Preoperatively and 1 week, 1 month and 6 months postoperatively, the difference in the average IOL between the two groups was not statistically significant by the t-test ($t$=0.187, $p=0.853$, 0.338, 0.970, 0.725).

**Visual acuity**

There were 16 eyes (76.2%) in the P-C group with visual acuity $\geq 0.5$ at 1 week post-operatively, and 13 eyes (72.2%) in the P-T group. The difference of the two groups was not statistically significant ($\chi^2=0.080$, $p=0.777$). There were 17 eyes (80.95%) in P-C group with visual acuity $\geq 0.5$ at 6 months (80.95%), and 14 eyes (77.78%) in the P-T group. The difference of the two groups was not statistically significant ($\chi^2=0.060$, $p=0.807$).

**Complications during and after operation**

In two eyes the Descemet’s window was punctured and in another two eyes, the inner walls of Schlemm’s canal were torn during operation in the P-C group. Four eyes were all performed in the earlier period of the study. Three eyes (14.29%) had transient increased IOP in the postoperative 24 hours. The inflammatory reaction was gentle with Tyndall (+) and no eye had hyphaema, shallow anterior chamber or choroidal detachment. Four eyes had functional filtering blebs.

There were also no severe complications in the P-T group. However, two eyes (11.1 %) had Tyndall (++), one eye (5.56%) Tyndall (+++), one eye (5.56%) had slight hyphaema and one eye (5.56%) choroidal detachment.

**Conclusion**

Viscocanalostomy combined with phacoemulsification and IOL implantation is a safe, efficacious and replicable surgery for open-angle glaucoma with cataract, not only showing the advantages of phacoemulsification, but also controlling the IOP of open-angle glaucoma and successfully decreasing postoperative complications. Therefore, this surgery facilitates more convenient ambulatory nursing for the patients.

The most frequent complication during the surgery is perforation of Descemet’s
membrane. A tiny perforation can be neglected; however, the procedure has to be changed
to trabeculectomy if a wide perforation occurs. The incision of phacoemulsification may be shared with the viscocanalostomy; however, the aqueous exudation from tunnel incision may be misinterpreted as leakage or perforation of Descemet’s membrane. Moreover, the Descemetic window is too thin to be ruptured during surgery. According to the author’s experience, it is safer to operate through different incisions, because after the accomplishment of viscocanalostomy, the superficial scleral flap is sutured and then phacoemulsification is performed through a new clear corneal incision.

In the combined surgery there are very few complications in viscocanalostomy, just some routine complications in phacoemulsification. The transient increased IOP may be related to the Healon GV inside the Schlemm’s canal in the first few days.

References

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18.
TRABECULECTOMY -THE GOLDEN STANDARD

RA Hitchings

Introduction

For the past 25 years, should topical medical therapy fail, glaucoma surgeons have routinely employed the operation of trabeculectomy when they wish to achieve adequate reduction in intraocular pressure (IOP). It is the purpose of this chapter to describe the origin of the operation, to see how it achieved its present pre-eminence, to look at the results and complications and then to judge whether the same operation, or one of its descendants, will be in use 25 years from now.

Origin in

Several eminent glaucoma surgeons can justly claim to have independently developed the idea of using a lamella sclerectomy to overlay a sclerostomy in the anterior chamber, as a method of restricting bulk outflow of aqueous after glaucoma surgery. Their methods introduced a surgical procedure designed to lower IOP safely. Three of these, Linner, Cairns and Watson presented their techniques at the Masters Symposium of the Ophthalmic Society of the United Kingdom in 1969 (Figure 18.1), while the fourth, Fronimopoulos described his version of a guarded sclerostomy at a similar time. From these descriptions a standard operation was derived that involved a lamellar (superficial) scleral flap and then a deep sclerostomy, sited at the angle of the anterior chamber. By common consent this refined version is no longer designed to remove trabecular mesh-work, often peripheral corneal tissue is removed instead. This operation, by retarding the bulk flow of aqueous from the anterior chamber in the immediate postoperative period, immediately reduced the peri-operative complications associated with the trephine operation and the thermal sclerostomy (Scheie’s) procedure. It became widely adopted and provided good long-term control of IOP for most ethnic groups suffering from chronic glaucoma. The current procedure differs only from this standardized approach in the instrumentation used to produce the lamellar flap and the deep sclerostomy (Figure 18.2). The operative results have been enhanced by postoperative manipulation of the
Figure 18.1 Early trabeculectomy procedures. (a-c) Stages in the procedure as described by Cairns.\(^2\) Note the posteriorly hinged lamellar scleral flap, absence of iridectomy and tight suturing of the lamellar flap. Aqueous drainage was considered to be circumferential around the canal of Schlemm. (d) Modification of the trabeculectomy by Watson.\(^3\) Note the extent of the deep scleral flap, extending posteriorly to the scleral spur. This cydodialysis could on occasion lead to late hypotony.
Figure 18.2 Modern trabeculectomy. Note the use of a dissector pocket knife to make a scleral tunnel, preplaced releasable sutures and the use of a scleral punch.
bleb, either by increasing bulk outflow of aqueous, by means of releasable sutures\textsuperscript{5} or laser suturelysis\textsuperscript{6} or by reducing the postoperative healing response using antiproliferative drugs such as 5-fluorouracil or mitomycin (see below).

**Complications**

Complications associated with this operation may be seen early with inadequate suturing of the flap and an excess of bulk outflow and hypotony,\textsuperscript{7} or excessive tightening of the flap with postoperative hypertension.\textsuperscript{8} Flat anterior chambers and aqueous misdirection are seen in eyes with comorbidity, such as Sturge Weber syndrome and chronic closed-angle glaucoma, respectively. However the incidence of ‘early’ complications in primary open-angle glaucoma is low and should be below the 1% level.

Late complications are becoming increasingly recognized, although their incidence is probably unchanged. Excessive wound healing leading to scar formation around the sclerostomy causes failure with an increase in intraocular pressure; this can be seen either as a heightened wound healing response in the early postoperative period or with ‘keloid’ formation in the late period.\textsuperscript{9} The risk of ‘early’ failure is increased when there is a tendency for a more aggressive wound healing response, such as in the young or in those with prior conjunctival surgery or with conjunctival inflammation.\textsuperscript{10–12} Randomized controlled trials have demonstrated that the trabeculectomy procedure is liable to produce cataract,\textsuperscript{13,14} while the routine use of antiproliferative agents, particularly mitomycin C, has increased the risk of late postoperative hypotony and infection of the fistulizing bleb (Figure 18.3).\textsuperscript{15–18}

**Results**

Two randomized controlled trials from the United Kingdom dating from the 1980s demonstrated that, over 5 years, a standard trabeculectomy can produce predictable intraocular pressure reduction to the mid teens in the majority of naïve patients (Figure 18.4).\textsuperscript{19,20} These long-term IOP results have been replicated in naïve patients with the CIGTStrial.\textsuperscript{13} The interaction of 5-fluorouracil and later mitomycin has increased the long-term IOP control in eyes with additional risk factors for failure (that is comorbidity, youth, black race and prior surgery).\textsuperscript{21,22} The Moorfields Laser Medicine Surgery Trial\textsuperscript{23} and the US CIGTS Trial\textsuperscript{13} demonstrated the greater efficacy in lowering IOP from primary trabeculectomy to conventional medical therapy. Retrospective reviews have shown how subsequent cataract surgery has an adverse effect on the success of the trabeculectomy procedure, often resulting in loss of IOP control.\textsuperscript{24}
**Figure 18.3** Complications of trabeculectomy (data derived from Membrey et al\textsuperscript{18}) depicting number of eyes on the y-axis and type of complication arising after different antiproliferative treatments.

**Figure 18.4** Long-term IOP control after trabeculectomy (data derived from Migdal et al\textsuperscript{23}). Note the SD for each IOP point on the graph. The study patients had not received prior medical
therapy. Compare this with the similar time scale graph from the CIGTS report.\textsuperscript{13}
Future development

Recognition of late complications that follow the trabeculectomy procedure has stimulated the development of successors. Previous attempts at alternative procedures have been tailored to Third World countries with the use of primary (Ahmed) tubes and trans-scleral cyclodiode. Avoidance of conjunctival wound healing has been tried with a transcorneal approach to the trabeculectomy procedure. The former is not applicable in Western nations and the latter has proved too great a technical challenge for the non-specialist ophthalmic surgeon to adopt.

The re-introduction of non-penetrating surgery, such as non-penetrating deep sclerectomy and viscocanalostomy, has followed recognition of the need to avoid both the early and late complications noted above. Randomized controlled trials comparing both viscocanalostomy non-penetrating deep sclerectomy with trabeculectomy have shown that the trabeculectomy procedure is likely to provide lower IOPs (see Tan and Hitchings for review). These studies have not been in existence for long enough to demonstrate that either viscocanalostomy can produce a lasting reduction in IOP, although sequential case series reported from both procedures suggest that a lasting reduction in IOP can be achieved.

However, results from one randomized controlled trial suggest that non-penetrating deep sclerectomy combined with YAG laser trabeculopuncture will produce the same levels of IOP as trabeculectomy without the same risk of cataract formation (Gandolfi, personal communication, Marrakesh, 2002).

At the present time, much effort is being directed towards preventing the two major complications of trabeculectomy surgery and its adjunctive antiproliferative treatments. Approaches that can halt fibroblast in-growth without killing off Tenon’s capsule and surface epithelium would greatly minimize the risk of late infection and hypotony. The preliminary studies by Peng Khaw’s wound healing group with human antigrowth factor beta-2 antibody suggest an alternative approach to wound healing. A second research line has to be directed towards the identification of those factors that hasten development of cataract years after trabeculectomy surgery.

Parallel with the research programmes that are directed towards minimizing adverse reactions to trabeculectomy surgery are the studies that are currently assessing the long-term efficacy of non-penetrating procedures. If it can be demonstrated that perhaps with YAG goniopuncture, good long-term IOP control can be obtained with deep sclerectomy then this would be a viable alternative to the guarded sclerostomy. Only the future will hold the answers to these particular questions.

References

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19.
DEEP SCLERECTOMY (OR THE WORDS OF HIRAACLITUS)

Tarek Shaarawy and André Mermoud

Introduction

The first suggestion of a disease associated with a rise in intraocular pressure (IOP) and thus corresponding to what is now known as glaucoma seems to occur in the Arabian writings of Shams-ad-Deen of Cairo, the 13th century Egyptian ophthalmologist, who described a ‘headache of the pupil, an illness associated with pain in the eye, hemicrania and dullness of the humours, and followed by dilatation of the pupil and cataract; if it becomes chronic, tenseness of the eye and blindness supervened’. Ever since, the mainstay of glaucoma therapy remained a battle to lower IOP, medically or surgically.

Trabeculectomy has been the golden standard of glaucoma surgery ever since Sugar in 1961 and Cairns in 1968 suggested a shift from the then widely practised full-thickness, glaucoma-filtering procedures. The use of a superficial flap was of paramount importance in creating a resistance to aqueous outflow, lowering the incidence of postoperative hypotony as well as offering a protection against the catastrophic occurrence of endophthalmitis. Throughout the years evidence mounted, showing that trabeculectomy is perhaps not the ‘holy grail’ of the quest for an ideal surgery for glaucoma. Most surgeons prefer to delay surgery because of the potential vision threatening complications of classical trabeculectomy, with or without antimetabolites. Complications include hypotony, hyphaema, flat anterior chamber, choroidal effusion or haemorrhage, surgery induced cataract and bleb failure. In spite of the tendency to delay surgery, it remains a very effective way of lowering IOP. Some authors hypothesize that if the safety margin of glaucoma surgery could be increased significantly without sacrificing efficacy, surgical intervention for glaucoma might be considered earlier.

Mikhail Leonidovich Krasnov, of the former USSR, paved the ground for non-penetrating filtering surgery, when he published his pioneer work on what he called sinusotomy. Several techniques have since evolved, probably the most popular of which are deep sclerectomy with collagen implant (DSCI) and viscocanalostomy.
Principles of non-penetrating filtering surgery

The main idea behind non-penetrating filtering surgery is somehow to surgically enhance the natural aqueous outflow channels, rather than to create a new and possibly overly effective drainage site. The avoidance of penetration into the anterior chamber should allow the anterior segment to recover more quickly, with less risk of hypotony and its sequelae.

In primary and in most cases of secondary open-angle glaucoma, the main aqueous outflow resistance is thought to be located at the level of the juxtacanalicular trabeculum and the inner wall of Schlemm’s canal. These two anatomic structures can be removed. This technique was first proposed by Zimmermann, and he used the term ab-externo trabeculectomy to describe it.

Another way to increase the aqueous outflow in a patient with restricted posterior trabeculum outflow is to remove the corneal stroma behind the anterior trabeculum and Descemet’s membrane. This has been called deep sclerectomy and was first described by Fyodorov and Kozlov. After deep sclerectomy, the main aqueous outflow occurs at the level of the anterior trabeculum and Descemet’s membrane, the so-called trabeculo-Descemet’s membrane (TDM).

In viscocanalostomy, described by Stegmann et al., the aqueous filters through the TDM to the scleral space, as in deep sclerectomy, but it does not form a subconjunctival filtering bleb because the superficial scleral flap is tightly closed. From the scleral space, the aqueous reaches the Schlemm’s canal ostia, which are surgically opened and dilated with a viscoelastic substance.

Surgical technique of non-penetrating glaucoma surgery

In deep sclerectomy (Figure 19.1), the conjunctiva is opened either at the limbus or in the fornix. The limbal incision offers a better scleral exposition but needs a more careful closure, especially when antimetabolites are used.

The sclera is exposed and moderate haemostasis is performed. To facilitate the scleral dissection, all Tenon’s capsule residue should be removed with a hockey stick. Sites with large aqueous drainage veins have to be avoided, to preserve as much as possible of the aqueous humour physiological outflow pathways.

A superficial scleral flap measuring 5×5 mm is dissected including one-third of the scleral thickness (about 300 μm). The initial incision is made with a No. 11 stainless steel blade. The horizontal dissection is made with a crescent ruby blade. In order to be able to dissect the corneal stroma down to Descemet’s membrane later, the scleral flap is dissected 1–1.5 mm into clear cornea.

In patients with a high risk of scleroconjunctival scar formation (young, secondary
Figure 19.1 Schematic representation of deep sclerectomy with four hypothetical mechanisms of aqueous humour resorption after passage through the trabeculo-Descemet’s membrane. (A) The subconjunctival filtering bleb; (B) the intrascleral filtering bleb; (C) the subchoroidal passage; (D) the episcleral drainage via Schlemm’s canal ostia. Reproduced with permission. Mermoud A, Shaarawy T. Non-penetrating Glaucoma Surgery. Martin Dunitz 2003; 60.

glaucoma and black people), a sponge soaked in mitomycin-C 0.02% may be placed for 45 seconds in the scleral bed and between the sclera and Tenon’s capsule.

Deep sclero-keratectomy is performed by making a second deep scleral flap (4×4 mm). The two lateral and the posterior deep scleral incisions are made using a 15 ° diamond blade. The deep flap is smaller than the superficial one, leaving a step of sclera on the three sides. This will allow a tighter closure of the superficial flap in case of an intraoperative perforation of the TDM. The deep scleral flap is then dissected horizontally using the ruby blade. The remaining scleral layer should be as thin as possible (50 to 100 μm). Deep sclerectomy is preferably started first in the posterior part of the deep scleral flap. On reaching the anterior part of the dissection, Schlemm’s canal is unroofed. Schlemm’s canal is located anterior to the scleral spur where the scleral fibres are regularly oriented, parallel to the limbus. In patients with congenital glaucoma, Schlemm’s canal localization is more difficult, because it is often more posteriorly situated. Schlemm’s canal is opened and the sclero-corneal
dissection is prolonged anteriorly for 1–1.5 mm in order to remove the sclerocorneal tissue behind the anterior trabeculum and Descemet’s membrane. This step of the surgery is quite challenging because there is a high risk of perforation of the anterior chamber. The best way to perform this last dissection is to do
two radial corneal cuts without touching the anterior trabeculum or Descemet’s membrane. This is performed with the 15° diamond knife or with a No. 11 steel blade with the bevel side up. When the anterior dissection between the corneal stroma and Descemet’s membrane is completed, the deep scleral flap is cut anteriorly using the diamond knife. At this stage, there should be a diffuse percolation of aqueous through the remaining TDM.

The juxtacanalicular trabeculum and Schlemm’s endothelium are then removed using a small blunt forceps. The superficial scleral flap is closed and secured with two loose 10/0 nylon sutures. Thus the procedure has in fact evolved into a combination of deep sclerectomy and ab-externo trabeculectomy.

**The use of implants**

To avoid a secondary collapse of the superficial flap over the TDM and the remaining scleral layer, a collagen implant is placed in the scleral bed and secured with a single 10/0 nylon suture. The implant is processed from porcine scleral collagen. It increases in volume after contact with aqueous and is slowly resorbed within 6 to 9 months leaving a scleral space for aqueous filtration. Other implants may be used to fill the sclerocorneal space left after DS dissection: reticulated hyaluronic acid implant, which resorbs in about 3 months, or a T-shaped hydrophilic acrylic implant, which is non-absorbable. The role of implants in non-penetrating surgery is still controversial, but the bulk of studies comparing deep sclerectomy with an implant versus without seems to show higher success rates with the use of an implant.

**Viscocanalostomy**

In the case of viscocanalostomy, high viscosity hyaluronic acid is injected into the two surgically created ostia of Schlemm’s canal, aiming at dilating both the ostia and the canal. It is also placed in the scleral bed. The material is resorbed in 4 to 5 days. The superficial scleral flap has to be tightly sutured in order keep the viscoelastic substance in situ and to force the aqueous percolating through the TDM into the two ostia.

**Nd-YAG goniopuncture after DS (Figure 19.2)**

When filtration through TDM is considered to be insufficient because of elevated IOP, Nd:YAG goniopuncture can be performed. Using a gonioscopy contact lens, the aiming beam is focused on the semi-transparent TDM. Using the free running Q switched mode,
with a power of 4–5 mJ, 2–15 shots are applied. This should result in the formation of microscopic holes through the TDM allowing a direct passage of aqueous from the anterior chamber to the subconjunctival space. The success rate of Nd: YAG laser goniopuncture is satisfactory, with an immediate reduction in IOP of about 50%. The success of goniopuncture depends mainly on the thickness of the TDM, hence the importance of sufficiently deep intraoperative dissection. By opening the TDM, however, goniopuncture transformed a non-perforating filtration procedure into a perforating one. Although the potential risk of late bleb-related endophthalmitis may be increased after goniopuncture, no such case has ever been reported.

Figure 19.2 Deep sclerectomy with ab-externo trabeculectomy.
There are two sites of interest when the mechanisms of function of non-penetrating surgeries are studied: the aqueous humour flow through the TDM and the aqueous resorption after its passage through the TDM.
Flow through the TDM

The TDM offers a resistance to aqueous outflow. This resistance will provide a slow decrease in IOP during surgery and will account for the reliable and reproducible IOP on the first postoperative day. Thus the main advantage of the TDM is to reduce the immediate postoperative complications such as hypotony, flat anterior chamber choroidal detachments and induced cataract.

In an experimental model, the gradual decrease in IOP was studied and the resistance of the TDM calculated.\textsuperscript{31} Experiments were performed on enucleated human eyes unsuitable for keratoplasty. The mean IOP decrease in speed was 2.7±0.6 mm Hg/min. The TDM resistance dropped from a mean of 5.34±0.19 ml/min per mm Hg to a mean of 0.41±0.16 ml/min per mm Hg.
The TDM resistance is apparently low enough to ensure a low IOP and high enough to maintain the anterior chamber depth and avoid the postoperative complications in relation with hypotony.

In the same study, the authors examined the surgical site histologically using ocular perfusion with ferritine. They were able to demonstrate that the main outflow through the TDM occurred at the level of the anterior trabeculum. There was, however, some degree of outflow through the posterior trabeculum and Descemet’s membrane.

**Aqueous humour resorption**

After aqueous humour passage through the TDM, four hypothetical mechanisms of aqueous resorption may occur.

*Subconjunctival bleb*

As after trabeculectomy, patients undergoing non-penetrating filtering surgeries have, in almost 100% of the cases, a diffuse, subconjunctival bleb on the first postoperative day. Years after the operation, using a UBM assessment, all successful cases still showed a low profile and diffused subconjunctival filtering bleb. However, this bleb is usually smaller than the one seen after trabeculectomy.

*Intrascleral bleb*

When the deep sclerectomy is performed a certain volume of sclera is removed, ranging from 5 to 8 mm\(^3\). If the superficial scleral flap does not collapse, this scleral volume may be transformed into an intrascleral filtering bleb. In order to keep this intrascleral volume, different implants may be used, such as the collagen implant. Hyaluronic acid or non-resorbable Hema implants have also been used. Using the UBM method, an intrascleral bleb was observed in more than 90% of the cases. The mean volume of the intrascleral bleb was 1.8 mm\(^3\) (Kazakova D et al. Ultrasound biomicroscopic study: long term results after deep sclerectomy, unpublished data). In the intrascleral filtering bleb the aqueous resorption may be different to that occurring in the subconjunctival bleb. The aqueous is probably resorbed by new aqueous drainage vessels, as demonstrated in the study of Delarive et al (Delarive T, Rossier A, Uffer S, Ravinet E, Mermod A. Deep sclerectomy with collagen implant: an animal model, unpublished data). In this study performed on rabbits, Delarive et al showed that in the scleral space created after the deep sclerectomy, regardless of the use of a collagen implant, new aqueous humour drainage vessels were growing and resorbing the aqueous flowing through the TDM. Similar results were obtained by Nguyen and coworkers using the same model and performing anterior segment fluorescein and indocianin green angiography (Nguyen C, Roy S, Shaarawy T, Boldea R, Mermod A. Aqueous drainage veins formation after deep sclerectomy with and without collagen implant using fluorescein and indocianin green anterior segment angiography, unpublished data).

*Subchoroidal space*
Since the remaining layer of sclera over the ciliary body and peripheral choroid after deep sclerectomy is very thin, there may be drainage of aqueous humour into the suprachoroidal
space. Using a UBM, it is possible to observe fluid between the ciliary body and the remaining sclera in 45% of the patients studied years after the deep sclerectomy (Kazakova D et al, unpublished data). Aqueous in the choroidal space may reach the uveoscleral outflow and increase this outflow pathway. It could also induce a chronic ciliary body detachment and reduce the aqueous production. It might be profitable to use an aqueous dynamics study in patients who underwent non-penetrating filtering surgery, in order to understand better the mechanism of action of this operation.

**Schlemm’s canal**

When the deep sclerectomy dissection is performed, Schlemm’s canal is opened and unroofed. On either side of the deep sclerectomy the two ostia of Schlemm’s canal may drain the aqueous humour into the episcleral veins. This mechanism may be more important after viscocanalostomy since the Schlemm’s canal is dilated with high viscosity hyluronic acid during surgery. It may also play a role when a Hema implant is used, since this implant has two arms inserted into the two ostia of Schlemm’s canal. Research has yet to establish the importance of this mechanism.

**Do non-penetrating glaucoma surgeries lower IOP?**

In a prospective non-randomized trial comparing 44 patients with medically uncontrolled primary open-angle glaucoma, who underwent deep sclerectomy with collagen implant, with a matched group of 44 patients who underwent trabeculectomy, complete success rate, defined as an IOP lower than 21 mm Hg without medication, was 69% 24 months postoperatively in the deep sclerectomy group versus 57% in the trabeculectomy group. When the patients needing laser goniopuncture were considered to be failed cases, the complete success rate of deep sclerectomy with collagen implant was 66% at 24 months.

In another non-randomized prospective trial, 100 eyes of 100 consecutive patients with medically uncontrolled primary and secondary open-angle glaucoma underwent deep sclerectomy with collagen implant. The complete success rate, defined as an IOP lower than 21 mm Hg without medication, was 44.6% at 36 months. The qualified success rate, defined as an IOP lower than 21 mm Hg with and without medication, was 97.7% at 36 months. When the different types of open-angle glaucoma were compared, no difference was found in terms of reduction in IOP, number of patients requiring antiglaucoma medications or success rate. There was, however, a tendency for lower success rate in patients with pseudoexfoliative and pseudophakic glaucoma. Shaarawy et al reported that, after 5 years, the mean IOP of 105 patients who underwent deep sclerectomy with collagen implant was 11.8 mm Hg. The complete success rate was 63% and qualified success was 95.1%.

Other authors reported favourable results of non-penetrating filtering surgery. Zimmerman et al reported good results of non-penetrating trabeculectomy in phakic and aphakic patients.
Stegmann et al\textsuperscript{18} described a similar technique, in which the scleral space was filled with a viscoelastic substance, and reported complete success in 61\% of patients and qualified success in 77\% at 26 months follow-up.

Kozlov et al\textsuperscript{25} performed deep sclerectomy with collagen implant, and reported an 85\% success rate, but no information regarding success criteria or follow-up is available. Demailly et al\textsuperscript{33} reported a mean decrease in IOP of $9.1 \pm 7.1$ mm Hg after 219 procedures using deep sclerectomy with collagen implant. Using Kaplan—Meier survival analysis, they reported a success rate without glaucoma medication of 89\% at 6 months and 75.6\% at 16 months; with glaucoma medication, their success rate increased to 97\% at 6 months and 79\% at 16 months.

The long-learning curve effect

Non-penetrating glaucoma surgery is demanding and a surgeon should invest time and effort to overcome the relatively long learning curve associated with it. One group\textsuperscript{34} compared viscocanalostomy with trabeculectomy in a randomized prospective study and came out with a 50\% success rate for trabeculectomy versus 0\% (total failure) of visco-canalostomy. The same group, a year later, presented a second study\textsuperscript{35} of their second group of patients and reported a 57\% success rate for trabeculectomy versus 30\% for viscocanalostomy. This clearly demonstrates a learning curve.

The same group analysed their dissection depth only to find that they dissected too high in 35\% and too deep in 30\% of their cases, meaning that more than half of their cases were not properly performed.\textsuperscript{36}

Summary and conclusion

From the weight of current evidence, the following conclusions may be drawn.
Non-penetrating glaucoma surgery is certainly more safe than trabeculectomy.
Non-penetrating glaucoma surgery may offer comparable IOP control to trabeculectomy. The use of implants in non-penetrating glaucoma surgery offers better IOP control for longer durations, thus enhancing success rates. The major controversies that arise from a review of the literature are the issue of IOP control and the success rates of non-penetrating glaucoma surgery compared to trabeculectomy. When these issues were examined, the learning curve of this surgery could not be overstated. The fact also remains that there are different types of non-penetrating glaucoma surgery that differ fundamentally and thus provide different results.

Another issue that merits consideration is that, although we now have an abundance of studies providing clinical results, there is a lack of studies examining the mechanisms of function of this type of surgery. Thus non-penetrating glaucoma surgery becomes a fashion or a phenomenon, with very few people asking how it works.
There remains the absolute need for a prospective randomized multicentre study in order to facilitate final conclusions on how non-penetrating surgery fares as compared to trabeculectomy, and to examine the different variations of the techniques. Once this is achieved, a quest for the ideal implant might ensue. When trabeculectomy, the golden standard, is compared with non-penetrating filtering surgery, the newcomer, it is perhaps desirable to remember the words of Heraclitus, uttered thousands of years ago: ‘Nothing endures but change’.

References

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20.
DEEP SCLERECTOMY VERSUS TRABECULECTOMY: AN ‘UNHOLY’ WAR
Stefano A. Gandolfi and Luca Cimino

Introduction

Non-penetrating procedures for glaucoma treatment are currently of great interest to the scientific community. A sometimes fierce debate, concerning their role as a successor to the gold standard trabeculectomy, has revolved around its relative effectiveness in short-to medium-term intraocular pressure (IOP) control. Several controlled clinical trials, comparing both surgical procedures in terms of long-term IOP control, safety and visual outcome are under way and some short-to-medium-term results are already available. However, it must be remembered that the mission of any glaucoma surgery is to reach the ‘guesstimated’ target IOP in the individual patient, without threatening the patient’s visual function and at a sustainable cost for the community. This chapter will consider what trabeculectomy and deep sclerectomy can offer.

Reaching the ‘guesstimated’ target IOP in the individual patient

Recent reports suggest that the progression of glaucomatous damage can be significantly reduced if the recorded IOP is consistently low. In particular, the AGIS study is providing evidence that, in clearly manifest glaucoma, the best outcome is reached when IOP never exceeds 18 mm Hg. Incidentally, the mean IOP, measured in the study cohort fulfilling the above-mentioned criteria proved to be 12.7 mm Hg. The glaucomas enrolled in the AGIS study are likely to be representative of the patient population requiring surgery in everyday life. Therefore, any effective glaucoma surgery must be able to keep the IOP in the low-teens range.

Trabeculectomy can facilitate good long-term IOP control. In particular, the CIGTS interim analysis showed that the mean untreated IOP in the surgical group proved to be 14 mm Hg through a 5-year follow-up. Further controlled clinical trials are reporting an
untreated IOP of 16 mm Hg or less in 45% to 70% of eyes undergoing trabeculectomy supplemented with postoperative injections of 5-fluorouracil.\textsuperscript{3,6,7} In fact, the success rate of conventional filtration surgery can vary according to possible intra—and postoperative supplementation with antimetabolites (mytomycin C or 5-fluorouracil). Failure of trabeculectomy occurs at a variable rate, the most frequent cause being the formation of a fibrovascular tissue at the episcleral level surrounding the flap. The use of antimetabolites has become increasingly popular among glaucoma surgeons. Therefore, any careful and realistic evaluation of the success rate of trabeculectomy must take into account the need for surgery supplementation with antimetabolites.

Non-penetrating deep sclerectomy seems less effective. As reported in one review,\textsuperscript{8} the untreated mean IOP level, observed in non-penetrating procedures, is at best in the high teens. In particular, prospective randomized controlled trials (including postoperative injection of 5-fluorouracil) are reporting that <15% of the study population show an untreated IOP of 16 mm Hg or less 2 years after surgery.\textsuperscript{3} Concurrent intraoperative application of mytomycin C has been suggested to offer slightly better IOP control.\textsuperscript{9} However, the IOP outcome of deep sclerectomy can be greatly improved if the procedure is transformed into a penetrating one by means of an opening of the filtering membrane via YAG-laser goniopuncture. Two long-term case series have been reported by Mermoud’s group in Lausanne. The first case series\textsuperscript{10} reports results collected in 105 glaucomatous eyes offered a deep sclerectomy with collagen implant (DSCI). The cohort was followed for up to 5 years. At the end of follow-up, 65 eyes (61%) showed an untreated IOP <21 mm Hg. Out of these 65, 29 had YAG-laser goniopuncture performed during follow-up because of an uncontrolled IOP. Therefore, the percentage of the study population ending with an IOP <21 mm Hg due to an actual non-penetrating procedure, dropped to 34%. However, it is noteworthy to point out that 45.7% of the overall population (including both the goniopunctured and the nongoniopunctured eyes) ended the study with an untreated IOP <16 mm Hg. The authors do not provide information allowing us to identify among this subgroup those eyes which had the non-penetrating surgery transformed by laser into a penetrating one. Nevertheless, a 5-year 45.7% success rate, with <16 mm Hg as a cut-off, is a figure comparable to that reported for trabeculectomy.

The second case series\textsuperscript{11} reports results of DSCI performed on myopic eyes (refractive error between $-6.0$ and $-23.0$ D, mean $-11.8\pm5.8$ D). Twenty-one eyes were followed for up to 4 years. At the end of the follow-up, 7 eyes (33%) reached an IOP <16 mm Hg without medication, 15 eyes (71%) had YAG laser goniopuncture. Therefore, the vast majority of the non-penetrating procedures were transformed into ‘penetrating’ procedure through follow-up.

\textbf{Summary}

In summary, early randomized control trials are unanimous in showing that standard trabeculectomy (supplemented with antimetabolites) produces lower and better sustained IOP control than non-penetrating deep sclerectomy (supplemented with 5-fluorouracil). While IOP control diminishes over time in non-penetrating surgery, this seems to be
better maintained in trabeculectomy and is in agreement with previously published data. Transformation of the non-penetrating deep sclerectomy into a penetrating procedure, by means of laser goniopuncture, leads to improved IOP control with time.

*Sparing vision*

Generically speaking, the ultimate goal of glaucoma therapy is to maintain the quality of vision of the affected patient. Glaucoma filtration surgery can be followed by sightthreatening complications. Postoperative management of the trabeculectomy patient can sometimes be more difficult than the procedure itself. The adoption of releasable sutures and the availability of viscoelastics have made flat anterior chamber and delayed post-operative suprachoroidal haemorrhage less common. However, the extensive use of potent antimetabolites led to a dramatic increase in chronic hypotony, late bleb leaks and late endophthalmitis. Furthermore, a commonly voiced concern about trabeculectomy surgery is the risk of late postoperative cataract development. The Collaborative Normal Tension Glaucoma Study showed that cataract developed in 26% of the treatment group (of which 16% occurred in operated eyes), compared with 11% of the non-treated group. A 78% increased risk of developing a cataract was reported by the investigators of the AGIS, the risk, not surprisingly, being higher in the case of postoperative complications. The development of a clinically relevant cataract is not irrelevant to the ultimate success rate of a filtration procedure. In fact, a planned cataract extraction in a previously filtered eye may be paralleled by malfunction of the filtration bleb.

As far as an uneventful non-penetrating deep sclerectomy is concerned, the avoidance of ocular entry obviates the need for an iridectomy and theoretically limits early post-operative hypotony. This in turn minimizes the attendant sequelae of hyphaema, choroidal effusions, shallow anterior chambers and cataract. However, as pointed out correctly by Tan and Hitchings, ‘concern has repeatedly been expressed about the steep learning curve associated with this type of surgery’. In fact, one report found that inadvertent perforation of the trabecular meshwork occurred in approximately one third of initial cases. Should an inadvertent perforation occur during surgery, the unavoidable conversion to a penetrating filtering procedure will result in suboptimal flap construction, leading to overdrainage. Following such conversion, the incidence of postoperative hypotony is reported to be 90% while hyphaema is 68%. As far as cataract formation is concerned, proper monitoring of lens transparency, via a slit-lamp evaluation according to the LOCSII grading system, confirmed the postulated low incidence of newly onset cataracts. Interestingly, in the same study cohort, trabeculectomy was paralleled by a much higher rate of newly onset lens nuclear opacities. However, no data are so far available to evaluate the impact of deep sclerectomy (compared with trabeculectomy) in eyes already having a significant lens opacity. In a case series, Karlen et al showed a 17% progression rate of pre-existing cataract in a 36-month follow-up in eyes subjected to non-penetrating deep
In another case series, the same group reported a 21% progression rate in 5 years of a pre-existing cataract after non-penetrating deep sclerectomy. Finally, it is noteworthy to remember that non-penetrating procedures have been associated with some ‘new’ late complications such as detachment of the Descemet membrane and iris incarceration on YAG-laser goniopuncture. Both complications seem manageable, but might necessitate further surgery in the affected eye.

Summary

Complications of trabeculectomy (supplemented with antimetabolites), while not negligible, can be managed successfully in most cases, but may occur late in the course of the disease and can have a detrimental impact on the patient’s visual function. Non-penetrating deep sclerectomy seems safer both in the short and in the long term. However, the surgeons must be aware of some types of complications that a planned trabeculectomy is associated with.

At a reasonable cost

There is a growing requirement for the health benefits of new interventions to be verified in randomized controlled trials in order that their costs may be justified. Non-penetrating deep sclerectomy is more time-consuming than the conventional trabeculectomy; the learning curve is longer; it may require the intraoperative application of devices to keep the intrascleral lake patent; surgeons must consider the need for postoperative YAG-laser goniopuncture and the application of antimetabolites is required in any case. Conversely, uneventful non-penetrating deep sclerectomy can be routinely performed on an outpatient basis; is likely to be followed by less requirement for cataract surgery and is likely to be affected by a lower incidence of surgery-related blindness.

Summary

In summary, the cost-efficacy profile of non-penetrating deep sclerectomy requires the completion of appropriate long-term clinical trials to be accurately traced.

Conclusions

The ultimate outcome of a glaucoma treatment has so far been ‘to spare vision by decreasing the IOP’. Trabeculectomy, in spite of being an effective means to achieve, by itself, low target IOPs, ends in a high rate of lens opacification. A cataract extraction in a previously filtered eye often leads to an eventual failure of the filtration bleb and can be affected by a higher rate of complications. Again, a penetrating procedure is affected by a high rate of vision-threatening complications in selected phenotypes, high myopia included. Deep
sclerectomy, if followed by a timely YAG-laser goniopuncture, can achieve a success rate comparable to a planned trabeculectomy. This is by no means unexpected, since non-penetrating deep sclerectomy becomes a penetrating procedure thereafter. However, once the procedure becomes penetrating, the efficacy improves but the traditional trabeculectomy-like complication rate does not seem to increase.

Therefore, if trabeculectomy remains the gold standard for glaucoma surgery (until proven otherwise by very-long-term randomized prospective clinical trials), the time has come to stop considering deep sclerectomy as a purely non-penetrating procedure. Deep sclerectomy might find its convenient place in the glaucoma treatment algorithm as a ‘stepwise’ penetrating procedure with an interesting cost-utility profile.

References

21. GLAUCOMA DRAINAGE IMPLANTS

J Välimäki, Tarek Shaarawy and PJ Airaksinen

Introduction

Glaucoma implants are not new. In fact, the idea of controlling intraocular pressure (IOP) with an external tube has been tested for almost 100 years. Some of the materials that have been tried include horse hair, silk and tubes of solid pure gold. The long-term success in the early days was poor and the complication rate was quite high. However, with improved surgical techniques and the use of plastics, glaucoma drainage implants have, rightfully, come to occupy a special place in the armamentarium of glaucoma surgery.

Overview of modern-day drainage implants

Glaucoma drainage implants have become the standard procedure in various forms of refractory glaucomas. These modern-day implants are members of a large family of devices known as setons. A seton is a fibre or implant used to promote aqueous humour drainage from intraocular to extraocular spaces or to shunt aqueous humour through normal anatomical barriers into accessory intraocular spaces. Aqueous humour flow in the glaucoma drainage implant has the general characteristics of a simple pipe generally adhering to Poiseuille’s equation:

\[
\text{flow} = q = \frac{\Delta p}{R}
\]

where \( p \) is pressure and \( R \) is resistance to flow offered by the bleb wall.

Various types of drainage implants have been used successfully to control IOP in eyes with refractory glaucoma. Most of the currently used glaucoma drainage implants share many characteristics generally modified from the Molteno implant. The Molteno implant (Optomat Supplies, Dunedin, New Zealand) was the first so-called posterior tube shunt implant which achieved drainage of aqueous humour via a tube to an equatorial plate.

Currently used posterior tube shunt implants differ according to the presence or absence of a pressure-sensitive valve and the type of episcleral explant. Non-valved implants such as the single—and double-plate Molteno implant, the Anterior Chamber
Tube Shunt to an Encircling Band\textsuperscript{18–21} (ACTSEB or Schocket procedure), the von Denffer implant\textsuperscript{22,23} and the Baerveldt implant\textsuperscript{24} require some type of temporary ligature or occlusion to prevent excessive flow of aqueous humour through the open tube until a fibrous capsule (bleb) around the explant is completed.

\textit{Indications for glaucoma drainage implant surgery}

Postoperative scarring at the extraocular level is the major cause of filtering surgery failure\textsuperscript{25,26} The adjunctive use of the antimetabolites remarkably improves the success rate of trabeculectomy in glaucomatous eyes with a poor surgical prognosis\textsuperscript{27} However, surgical failure still occurs despite adjunctive antimetabolite therapy as a result of scar tissue formation. Glaucoma drainage implantation offers an alternative to trabeculectomy with antimetabolites in patients with refractory glaucoma (Table 21.1). Glaucomatologists differ on the exact criteria that must be fulfilled before a drainage implant is advised for glaucoma treatment. The following guidelines for characteristics of a candidate for glaucoma drainage implantation have been presented:\textsuperscript{28,29} refractory glaucoma, uncontrolled with maximum tolerated medical management and laser trabeculoplasty, if indicated, whose visual function in one or both eyes is failing or likely to fail at the current level of IOP control, and considered to be at high risk for failure of conventional glaucoma surgery with or without adjunctive antimetabolite. Glaucoma drainage implantation is recommended in glaucomas with a good filtration prognosis, that is primary open-angle glaucoma (POAG), exfoliative glaucoma and pigmentary glaucoma, after two failures of conventional filtration surgery; preferably one procedure with adjunctive antimetabolite.

Opinions on the indications for glaucoma drainage implant surgery as a primary procedure vary. On the one hand, trabeculectomy with use of antimetabolites, i.e. 5-fluorouracil (5-FU) and mitomycin C (MMC), is recommended to be attempted before

\textbf{Table 21.1 Specific refractory glucomas with a high surgical failuar rate after trabeculectomy}

\begin{tabular}{|l|
\hline
\textbf{Glaucoma} \\
Neovascular \\
Congenital/infantile/juvenile/developmental \\
In uveitis especially with juvenile rheumatoid arthritis \\
In aphakia or pseudophakia \\
After epithelial downgrowth \\
After penetrating keratoplasty \\
After previously failed filtering surgery \\
After trauma \\
\hline
\end{tabular}
glaucoma drainage implants in high-risk glaucoma patients because of the lower complication rate. On the other hand, prior conjunctival injury and scarring, following trauma or chemical injury, make the performance of trabeculectomy technically difficult because of the inability to dissect a conjunctival flap safely. Sidoti and Baerveldt reported a list of pre-existing conjunctival or external diseases which may act as long-term risks of trabeculectomy: ocular cicatricial pemphigoid, Stevens—Johnson syndrome, keratoconjunctivitis sicca or vernal conjunctivitis, or the need for contact lens use postoperatively. They recommended the use of drainage implant as the primary surgical treatment in these situations. Välimäki et al reported very good long-term results with a single-plate Molteno implant as a primary treatment in children with juvenile rheumatoid arthritis associated chronic uveitis causing severe secondary glaucoma.

**Molteno implant**

The Molteno implant, first reported in 1969 in a human cohort, is one of the most frequently used drainage implants. The prototype consisted of an episcleral plate (8 mm in diameter and approximately circular in outline) which was sutured to the sclera only a few millimetres posterior to the limbus. To overcome the possibility of conjunctival erosion of the anterior plate and other problems including discomfort, formation of corneal dellen and excessive scarring, Molteno redesigned the implant by enlarging the plate and relocating it posterior to the equator. In 1976, this implant became known as the single-plate long-tube Molteno implant.

The single-plate Molteno implant consists of a 16-mm long silicone rubber tube, with an external diameter of 0.63 mm and an internal bore of 0.3 mm, that is attached to and opens onto the upper surface of a circular, convex, polymethylmethacrylate (PMMA) plate, 13 mm in diameter. Polymers of silicone are frequently used in the drainage implants because of their relative non-toxicity and biological inertness. The plate has a 2 mm high edge. The edge of the plate has a thickened rim 0.7 mm high which is perforated to permit suturing of the plate to the sclera.

Molteno15designed the double-plate version to increase the drainage surface area. The double-plate version has an additional 12.8 mm diameter circular plate that is connected to the first plate by a 10 mm silicone tube. The double-plate systems come labelled as ‘right’ or ‘left’ eye implants, a nomenclature which assumes placement of the primary drain tube superior-nasally and the secondary plate superior-temporally.

The surface area of both sides of the single-plate Molteno implant is approximately 270 mm² and a double-plate implant is approximately 540 mm². A miniaturized single-plate implant (9.7 mm in diameter) is available for paediatric use, with a total surface area of approximately 147 mm².

A dual chamber Molteno implant has become available. This implant has an internal pressure ridge on the upper surface of the plate to form a dual chamber. The dual chamber
is intended to compartmentalize the developing filtering bleb over the plate and the swelling of Tenon’s capsule produces a temporary seal over the smaller front chamber (with as a surface area of 10.5 mm²), creating resistance to aqueous humour flow. The pressure ridge, together with smooth flexible tissue of Tenon’s capsule, acts as a pressure-sensitive valve which regulates the escape of aqueous humour into the main bleb cavity during the early postoperative period.

Susanna modified the Molteno implant by placing 10 holes in the platform of the implant to increase drainage. He stated that linking the superior and inferior space of the implant allows drainage below the implant. He also placed three 0.7 mm diameter holes in each side of the upper portions of the Molteno plate, perpendicular to the tube and at the same level. These holes allow a one-plate to be converted into a two-plate Molteno implant, which reduces the risk of complications and makes reoperation easier and safer. The tube of the second implant is inserted in the middle hole and fixed, and the implants are connected by passing the tube with a 9–0 suture through the two adjacent holes.

Molteno presented general indications for determining which size of drain system, single- or double-plate, to use. He recommended selecting a smaller drain size in eyes where the ciliary body function is severely damaged, as in most cases of neovascular glaucoma or in cases of uveitis involving the ciliary body. In such cases, the two-plate implant may drain too freely for the reduced aqueous humour production and precipitate the eye into phthisis.

Technique of implantation

In the classic implantation, Molteno et alinserted the long tube implant in one stage and the tube was left open. This technique produced excessive complications that were associated with overfiltration in the early postoperative period. In 1979, Molteno et al recommended a two-stage operation to avoid hypotony postoperatively. In the first stage, a fornix-based conjunctival flap is performed. If a single-plate implant is used, the incision through the conjunctiva and Tenon’s capsule is limited to one quadrant, while an incision of 160–180° is required for a double-plate implant. The conjunctiva is dissected to expose the equator of the globe between the adjacent rectus muscle. The plate or plates are inserted beneath Tenon’s capsule and fixed to the episclera by two non-absorbable 5–0 polyester sutures passed through the anterior suture holes in the rim of the plate(s). These sutures are positioned so that the anterior edge of the plate is at least 8 mm (and preferably 10 mm) posterior to the limbus. In the double-plate model, the connecting tube between the two plates can be placed under or over a rectus muscle. The silicone tube is partially buried in sclera and its free end tucked beneath one of the rectus muscles. Because the first stage does not reduce IOP, Molteno et al recommend that the IOP is controlled by medical antiglaucoma therapy.

Molteno et al prefer to insert the plate in the superonasal quadrant. However, the quadrant is modified as necessary, depending on the location of conjunctival scarring and previous trabeculectomy sites. On the other hand, Prata et al reported that, if possible, the superonasal quadrant should be avoided to prevent strabismus in patients with binocular
vision.
In the second stage, the goal of the procedure is to insert the silicone tube into the anterior chamber. The 6–8 week time interval between stages allows the episcleral plate to become enclosed in a layer of dense connective tissue 8–12 μm thick. This layer offers sufficient resistance to the passage of aqueous humour to maintain a normal IOP after the connection of the tube to the anterior chamber. During the second stage, the conjunctiva is reopened and lamellar scleral flap is developed. Originally, Molteno dissected two triangular scleral flaps, anterior and posterior. In 1986 he changed the technique and performed only one rectangular, two-third thickness scleral flap, which was 6 to 7 mm wide and extended as far back as the insertion of medial and superior rectus muscle\(^{47}\) (Figure 21.1). The dissection of this flap is continued forwards until the limbal region is reached.

After preparation of the scleral flap, the translimbal tract into the anterior chamber is performed using a No. 11 Bard Parker blade or a 22 or 23 gauge needle. A water-tight seal between the tube and the sclera is important and more likely if a 23 gauge or smaller needle is used. The end of the silicone tube is cut and bevelled at a point overlapping the cornea by approximately 3 mm. The tube is inserted through the tract into the anterior chamber.

The correct position of the tube after insertion is in the middle of the anterior chamber without touching the cornea, iris or lens (Figure 21.2). Molteno\(^{47}\) used a shim of donor sclera beneath the anterior part of scleral flap at the point of entry of the tube into the anterior chamber, in the case of cornea–tube touch. This sutured shim depressed the end of the tube and kept it away from corneal endothelium.
Figure 21.1 Two-third thickness lamellar rectangular scleral flap is developed and extended as far back as the insertion of the medial and lateral rectii.
In certain cases of refractory glaucoma in which the anterior chamber anatomy has been severely disrupted, some authors recommend vitrectomy and trans-pars plana placement of tubes for glaucoma drainage implants. Freedman reported a modified technique in which the tube goes directly through the limbus into the anterior chamber and no scleral flap is performed. He used a scleral patch graft to cover the episcleral portion of the tube. Tanji et al recommend the use of a human cadaveric fascia lata patch graft over the subconjunctival portion of the tube as an alternative to eye bank sclera. Ollila et al reported a technique where the Molteno tube is placed in a long scleral tunnel, performed in the same way as a phako tunnel. This way the entire tube is covered by the patient’s own sclera.

**Modifications of the technique to prevent postoperative hypotony**

Over time, the surgical technique has changed in an attempt to avoid two operations and achieve more rapid IOP control postoperatively. As a result, many techniques of the single-stage procedure with the temporary occlusion of tube lumen have been developed to help to eliminate these problems. Price and Whitson described the use of a polypropylene ligature to occlude the intracameral portion of the tube, and postoperatively the ligature is lysed by transcorneal laser application to open the tube. Molteno et al used an absorbable 5–0 ligature (Vicryl®) around the external portion of the tube. The ligature spontaneously releases between 3 and 5 weeks after surgery. Minckler et al did not find apparent differences among various 5–0 ligature suture materials, including plain rapid-absorbing plain and chromic, with spontaneous release. Sometimes the suture dissolves incompletely and direct incisional lysis is needed. Rojanapongpun and Ritch used clear corneal graft overlying the subconjunctival portion of the tube to facilitate argon laser suture lysis. Hoare Nairne et al occluded the lumen of the tube with an intraluminal suture (stent) of 3–0 polypropylene suture (Figure 21.3), that is a rip-cord or obturator technique. The suture is inserted half way down the Molteno tube and the distal end of the suture is passed.
under the superior and horizontal rectus muscles and secured to the sclera. The stent is removed under local anaesthesia at 6 weeks, through a small conjunctival incision over the distal end of the suture. Egbert and Lieberman also used the ripcord technique, but with a 4–0 or 5–0 chromic stent which exited the conjunctiva in the inferior fornix and could be removed postoperatively by pulling the exposed suture.
Postoperative suture removal, however, may expose the patient to severe intraocular inflammation, including hypopyon.\textsuperscript{58}

An alternative modification to the use of intraluminal suture is a releasable, nylon, pullout suture tied around the subconjunctival part of the tube and exposed externally. This suture is pulled out at the appropriate postoperative time to remove tube occlusion. Care must be taken not to dislodge the tube when removing this ligature. Other investigators\textsuperscript{59} used perfluorocarbon gas injections into the anterior chamber, along with fixation of the tube with an external absorbable occluding ligature in single-stage implantations with fistulization.

The initial results with the dual-chamber, single-plate Molteno implant have been encouraging and suggest that this model may obviate the need for temporary occlusion of tube lumen or a two-stage installation.\textsuperscript{19,60–65} In contrast, Gerber et al\textsuperscript{66} reported that the ridge effect is unpredictable with the dual-chamber, double-plate Molteno implant and further modifications are necessary to prevent postoperative hypotony.

**Surgical outcome**

The results of Molteno implantation, as reported in the literature, are not directly comparable because of the lack of uniform categories for success and failure and variation in surgical technique among authors. In 1995, The Food and Drug Administration (FDA) listed the appropriate outcome measures that should be reported with clinical data of glaucoma drainage devices. These are visual acuity (pre-operative and postoperative as a function of time) and IOP (pre-operative and postoperative IOP as a function of time, including data on the number of IOP-lowering medications). Visual fields are an inappropriate outcome measure in this population with refractory glaucoma.

In most of the reports, the overall success rate is the combination of success rates in various diagnoses of glaucoma. A review from studies of a minimum 6-month follow-up of
eyes with single—or double-plate Molteno implant indicates the conventional overall success rate to be between 50% and 96%. In children aged 13 years or less, the conventional overall success rate with at least a 6-month follow-up ranged from 31% to 59%. However, success after Molteno implantation is dependent on the type of glaucoma.
Life-table success rates for neovascular glaucomas were reported to be 62% at 1 year and 53% at 2 years\(^8\) and for uveitic glaucomas 79% and 79%.\(^{81-83}\) Promising results with Molteno implantation have been reported in rare cases such as glaucomas associated with penetrating keratoplasty\(^8\) and with epithelial downgrowth.\(^\)\(^8\) However, the incidence of graft rejection is high (34%) after drainage implants.\(^8\)

Heuer et al\(^\)\(^6\) designed a prospective study comparing the single- and double-plate Molteno implant. They reported that 1- and 2-year life-table success rates, respectively, were 55% and 45% with a single-plate implant (50 patients) and 85% and 71% with a double-plate implant (51 patients). Conventional success rates at the last follow-up, success being defined as an IOP\(\geq 6\) and \(\leq 21\) mm Hg without additional glaucoma surgery or devasting complication, were 10% without antiglaucoma medication and 40% with medication in single-plate implants; the corresponding figures were 12% and 63% in double-plate implants. Smith et al\(^19\) compared the results of the double-plate Molteno implant with those of the Schocket procedure and their group\(^6\) compared the double-plate Molteno implant with the Baerveldt implant. Both studies reported that postoperative IOP control appears to be similar regardless of which implant is used. However, early stent removal was not recommended in eyes with the Baerveldt implant because of a tendency to flat anterior chamber.

A review of the visual outcomes indicates the rate of reduced visual acuity at the final follow-up to be between 11% and 37%.\(^21,68,70,80\) However, the criteria for worsening visual acuity are not uniform, ranging from one line to at least two lines worsened post-operatively than preoperatively. The visual outcome of Molteno implantation is reported to be disappointing in aphakic/pseudophakic eyes, in eyes with rubeosis and in eyes with a previous failed filtering procedure.\(^39\) The postoperative visual acuity was at least two lines worse than preoperative visual acuity in 53% of the aphakic/pseudophakic eyes\(^86,87\) and even in 70–83% of eyes with previous failed filtering procedures. In the study of Lloyd et al,\(^87\) overall 10% of eyes lost light perception, the highest, 17%, being in neovascular glaucoma. Visual loss in these two groups was primarily attributed to the following: corneal oedema, cataract, retinal detachment, epiretinal membrane, progressive glaucomatous optic neuropathy and hypotony. Much of the visual deterioration could be attributed to complications, rather than a lack of IOP control. Airaksinen et al\(^73\) used visual acuity at the last follow-up visit as a criterion for the success of Molteno implantation. Success was achieved if the visual acuity was not reduced by \(>2\) Snellen lines. The best success rate was in patients with neovascular glaucoma (100%) and glaucoma associated with trauma (100%) and the lowest in patients with chronic open angle glaucoma (33%).

### Complications

The Molteno implant has an associated rate of complications that is generally commensurate with other forms of surgery for these refractory glaucomas. However, the severity of glaucoma and many prior surgical procedures increase the rate of complications. \(\text{Table 21.2}\) lists the complications of Molteno implant surgery. Some intraoperative and post-operative complications of Molteno surgery are similar to other forms of intraocular surgery. Since the
Molteno implant is used in the most severe cases of glaucoma, the
reported complication rates have been higher in patients undergoing Molteno surgery than in trabeculectomy. The main reason for Molteno implant surgery failure is an excessive fibrotic response around the plate which leads to the encapsulated bleb, that is Tenon’s cyst formation (Table 21.2).

Table 21.2 Complications of Molteno implant surgery

<table>
<thead>
<tr>
<th>Complications</th>
<th>Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Device-related</strong></td>
<td></td>
</tr>
<tr>
<td>Tube behind iris</td>
<td>10</td>
</tr>
<tr>
<td>Tube-iris touch</td>
<td>3</td>
</tr>
<tr>
<td>Tube-cornea touch</td>
<td>1–20</td>
</tr>
<tr>
<td>Tube retraction from anterior chamber</td>
<td>1–4</td>
</tr>
<tr>
<td>Plate extrusion/erosion through conjunctiva</td>
<td>1–5</td>
</tr>
<tr>
<td>Tube erosion through conjunctiva</td>
<td>1–5</td>
</tr>
<tr>
<td>Strabismus</td>
<td>1–3</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
</tr>
<tr>
<td>Encapsulated bleb</td>
<td>10–17</td>
</tr>
<tr>
<td>Hyphaema</td>
<td>6–30</td>
</tr>
<tr>
<td>Phthisis bulbi</td>
<td>5–18</td>
</tr>
<tr>
<td>Tube ostium obstruction</td>
<td>5–17</td>
</tr>
<tr>
<td>Suprachoroidal haemorrhage</td>
<td>5–8</td>
</tr>
<tr>
<td>Cataract</td>
<td>4–9</td>
</tr>
<tr>
<td>Corneal graft decompensation/failure</td>
<td>4–13</td>
</tr>
<tr>
<td>Epiretinal membrane</td>
<td>2–12</td>
</tr>
<tr>
<td>Uveitis</td>
<td>2–7</td>
</tr>
<tr>
<td>Choroidal detachment</td>
<td>1–6</td>
</tr>
<tr>
<td>Retrocorneal membrane</td>
<td>2</td>
</tr>
<tr>
<td>Corneal abrasion</td>
<td>2</td>
</tr>
<tr>
<td>Flat anterior chamber</td>
<td>1–23</td>
</tr>
<tr>
<td>Corneal oedema</td>
<td>1–19</td>
</tr>
<tr>
<td>Retinal detachment</td>
<td>1–16</td>
</tr>
<tr>
<td>Prolonged hypotony</td>
<td>2–10</td>
</tr>
<tr>
<td>Pupillary membrane</td>
<td>1–9</td>
</tr>
<tr>
<td>Vitreous haemorrhage</td>
<td>1–7</td>
</tr>
<tr>
<td>Endophthalmitis</td>
<td>1–2</td>
</tr>
<tr>
<td>Corneal ulcer</td>
<td>1–2</td>
</tr>
<tr>
<td>Malignant glaucoma</td>
<td>1</td>
</tr>
</tbody>
</table>
Epithelial ingrowth 1
Corneal epitheliopathy 1
Focal non-necrotizing seleritis 1
Branch retinal vein occlusion 1
The most serious complications of Molteno implantations are suprachoroidal haemorrhage (SCH), prolonged hypotony or endophthalmitis. SCH occurred in 5–8% of the patients after Molteno implantation.\textsuperscript{39,88,89} In all studies, SCH was delayed, except in the study of Hill et al\textsuperscript{88} where two eyes had intraoperative SCH and two eyes had delayed SCH. Delayed SCH has been associated with prolonged hypotony.\textsuperscript{89} The hypotony is usually transient and due to overfiltration. Overfiltration and/or decreased aqueous production secondary to ciliary body dysfunction may lead to chronic, prolonged hypotony (IOP ≤5 mm Hg) after tube implant surgery (Table 21.2). Implant failure, visual loss and phthisis bulbi are more likely in severely compromised eyes.\textsuperscript{80} Endophthalmitis is a quite uncommon complication of Molteno surgery (1–2%) (Table 21.2). It is unclear whether the Molteno implant should be removed as part of the management of the endophthalmitis. Excellent results were obtained both with\textsuperscript{90} and without removal of the implant.\textsuperscript{91} Tube ostium obstruction may occur with vitreous, fibrous tissue, the sequelae of post-operative inflammation and/or hyphaemas (Table 21.2). Pastor et al\textsuperscript{92} successfully dissolved a fibrin clot tube obstruction with intracameral tissue plasminogen activator. In their study, the only complication was a small, layering hyphaema. It is also possible to relocate the Molteno implant tube if the end of the tube in the anterior chamber is blocked and cannot be managed non-invasively with either the argon or the neodymium:yttrium—aluminum—garnet (Nd: YAG) laser.\textsuperscript{93}

\textit{Future horizons}

It is quite likely that we have not yet seen the last chapter in the saga of glaucoma drainage implants that started almost a century ago. So far, available implants have been fairly simple in design and principle. With the encouraging clinical results that have been reported, and the advances in tissue manipulation and wound healing, together with the technological revolution in microsensors, superconductors and microprocessors, it is possible that it will not be long before we witness the dawn of a new epoch.

\textit{References}

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Introduction

The ability to modulate wound healing fully is the key to setting the intraocular pressure (IOP) in the low teens for all patients undergoing glaucoma filtration surgery. Recent large clinical trials have all shown that long-term IOP lowering down to the low teens minimizes the risk of glaucomatous progression. The repair and regeneration process after glaucoma filtration is the main determinant of long-term IOP. In this chapter we review recent new techniques which have increased the safety of antimetabolites, and many of the new areas of advance including growth factor neutralization and future molecular strategies to control tissue repair and healing.

Background

An IOP in the low teens best preserves vision in glaucoma, even when the IOP is within the ‘normal’ range.\textsuperscript{1-3} The most important determinant of the final IOP after glaucoma surgery is the healing response of the eye. If the healing could be accurately modulated then most patients could achieve an IOP of 10 mm Hg after surgery. At present this level of IOP control is most consistently achieved by filtration surgery combined with antimetabolites, usually mitomycin-c (MMC).

Antimetabolites have revolutionized glaucoma surgery, particularly in patient groups with a high risk of surgical failure due to scarring. However, there are still blinding complications associated with the use of these agents, especially if antimetabolites are to be used in all patients undergoing surgery,\textsuperscript{4} where the risk of complications such as endophthalmitis appears to be increased. There are still patients who fail surgery despite the
use of strong antimetabolites. As such, further understanding of the biology of healing is essential, together with the development of new treatments combined with improvements in surgical techniques. This will ultimately lead to optimal outcomes for patients after glaucoma surgery.

There are many complex overlapping biological events which occur after surgical trauma; these are summarized in Table 22.1 Modulation of various components of the healing response can reduce the scarring response and these are shown in the table.

**Pre-existing cellular activation**

Pre-operative cellular ‘activation’ in the conjunctiva may occur with long-term topical medical therapy, particularly therapies that cause a chronic red eye. This therapy may be associated with a poor glaucoma surgery outcome. Studies have confirmed increased pre-operative conjunctival cells in patients with higher IOPs after surgery. Several mechanisms alter fibroblast phenotype lead to activation of a fibrotic response. The authors have observed that the state of cellular activation can dramatically reduce the response to antimetabolites such as 5-fluouracil (5FU) and MMC.

The authors’ group has previously shown that, although antimetabolites can cause cellular growth arrest, these growth-arrested cells are still able to stimulate neighbouring cells to scar via growth factors. This helps explain some of the scarring after filtration surgery that occurs despite antimetabolite treatment, especially in focal avascular blebs, where a central acellular area may be surrounded by a ring of growth-arrested cells still able to stimulate fibrosis, the so-called ‘ring of steel’ (Figure 22.1).

**Tissue injury**

Minimizing tissue injury, especially the reduction of bleeding which is very stimulatory to healing, is important. At present there is no surgical procedure that is free of the scarring response that occurs after tissue injury, with a gradual fall in success rate. Injury to tissues is associated with the release of various cytokines. An often overlooked component of this injury in the eye is breakdown in the blood—aqueous barrier, which may not be clinically visible.

**Inflammation**

Persistent conjunctival inflammation is associated with a pronounced scarring response. Conjunctival epithelial cells may continue to express HLA-DR several months after surgery,
Table 22.1Sequence of events in tissue repair and possible types of modulation after glaucoma filtering surgery (events and agents have overlapping time duration and action).
(Modified from Khaw and Chang.14)

<table>
<thead>
<tr>
<th>Event</th>
<th>Possible modulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activated conjunctiva ‘Pre-activated’ cells</td>
<td>Stop medical therapy (especially drops causing red eye)</td>
</tr>
<tr>
<td></td>
<td>Pre-operative steroids</td>
</tr>
<tr>
<td>Conjunctival/episcleral/scleral incisions</td>
<td>Minimal trauma Less invasive surgical techniques</td>
</tr>
<tr>
<td>Damage to connective tissue Release of plasma proteins and blood cells</td>
<td>Haemostasis (blood can reverse MMC)</td>
</tr>
<tr>
<td>Activation of clotting and complement Fibrin/fibronectin/blood cell clot</td>
<td>Agents preventing/removing fibrin, e.g. heparin, tissue plasminogen activator, hirudin</td>
</tr>
<tr>
<td>Release of growth factors from blood</td>
<td>Antagonists to growth factor production, e.g. antibodies to growth factors, humanized anti-TGF-β2 antibody (CAT 152 Trabio®) or receptors Anti-sense oligonucleotides, ribozymes Less specific antagonists, e.g. tranilast, genistein,</td>
</tr>
<tr>
<td>Aqueous released from eye Some breakdown of blood-aqueous barrier</td>
<td>Blood-aqueous barrier stabilizing agents, e.g. steroids</td>
</tr>
<tr>
<td>Release of growth factors into aqueous</td>
<td>Non-steroidal anti-inflammatory agents</td>
</tr>
<tr>
<td>Aqueous begins to flow through wound</td>
<td></td>
</tr>
<tr>
<td>Migration and proliferation of polymorphonuclear neutrophil cells, macrophages and lymphocytes</td>
<td>Anti-inflammatory agents, e.g. steroids/ cyclosporine Anti-metabolites e.g. 5FU/MMC, Antibodies to inflammatory mediators Angiotensin-converting enzyme or chymase inhibitors</td>
</tr>
<tr>
<td>Activation, migration and proliferation of fibroblasts</td>
<td>Pre-operative steroids to reduce activation Antinrotabolites MMC 5FU Methylxanthine derivatives, mushroom lectins Antiproliferative gene p21(WAF-1/Cip-1) Photodynamic therapy</td>
</tr>
<tr>
<td>Wound contraction</td>
<td>Anti-contraction agents e.g. colchicine, taxol, lectins, MMP inhibitors</td>
</tr>
<tr>
<td>Fibroblast synthesis of tropocollagen, glycosaminoglycans and fibronectin</td>
<td>Interferon alpha MMP inhibitors, fibrostatin-c</td>
</tr>
<tr>
<td>Collagen cross-linking and modification</td>
<td>Anti-cross-linking agents, e.g. beta-aminopropionitrile/penicillamine</td>
</tr>
<tr>
<td>Blood vessel endothelial migration and proliferation</td>
<td>Inhibitors of angiogenesis, e.g. fumagillin analogues, heparin analogues</td>
</tr>
</tbody>
</table>
Event                  possible modulation
Resolution of healing  Resolution MMC 5FU
Apoptosis              Death receptor ligands
Disappearance of fibroblasts Fibrous subconjunctival scar Stimulants of apoptosis pathways

Figure 22.1 The hypothesis for cystic blebs—anterior aqueous drainage and ring of scar tissue, the so-called ‘ring of steel’. Antimetabolites merely exacerbate pre-existing conditions for a cystic bleb.

which may increase the ability of these cells to induce immune inflammation and fibrosis. Cataract surgery can raise the pressure in eyes hypotonous after MMC use in glaucoma filtration surgery. Subclinical anterior chamber inflammation, such as that seen in combined cataract and glaucoma surgery, has a worse prognosis than glaucoma surgery alone. Laser flare readings are persistently higher after cataract surgery compared with trabeculectomy, even in clinically quiet eyes, which helps to explain the effect of cataract surgery on healing (Figure 22.2).

Topical corticosteroids have been shown to suppress the local inflammatory response experimentally. This has been confirmed clinically where topical corticosteroid treatment after trabeculectomy is associated with a significant reduction in final intraocular pressure.
The role of non-steroidal anti-inflammatory drugs (NSAIDs) is still uncertain. Newer agents affecting aspects of the inflammation pathway include cyclosporine and cyclooxygenase-2 inhibitors.
Figure 22.2 Graph showing the prolonged increased flare after cataract surgery compared with trabeculectomy. This clinically imperceptible flare predisposes to increased failure due to scarring, even though the eye appears quiet.

**Clotting**

Clotting and fibrin formation in itself may enhance surgical failure by blocking outflow and sequestering growth factors and stimulating scarring in its own right. Fibrinolytic agents such as tissue plasminogen activator and urokinase have been used to lyse blood clots after surgery. In the short term, fibrinolytic agents may lower IOP by lysing clots but there is a risk of further extra- and intraocular haemorrhage. In addition, the breakdown molecules may have a longer-term stimulatory effect on wound healing. Prevention of clotting may be a more promising avenue, with agents such as heparin. The authors have shown for the first time that clinical proliferative vitreoretinopathy (PVR) can be prevented, if a regimen of intraoperative 5FU is combined with heparin.

**Growth factors**

Within the bleb tissues and flowing through the bleb in the aqueous are a large number of small protein molecules which stimulate cells known as growth factors or cytokines. One growth factor, transforming growth factor beta (TGF-β), stimulates more activity than the other growth factors found in the aqueous. It may also be the most important growth factor stimulating the production of further TGF-β through its autoinductive action. TGF-β may even neutralize the effect of MMC in vivo.
A variety of agents may act on growth factors including TGF-β. Tranilast ((N-(3',4'—dimethoxycinnamoyl) anthranilic acid) inhibits TGF-β activity and has anti-scarring effects in the body and the eye. In experimental models, it has been shown to inhibit scarring effectively in experimental PVR, and photorefractive keratectomy. It also decreases conjunctival scarring following application in glaucoma filtration surgery. Genistein and suramin also suppress TGF-beta activity. One study has shown that suramin reduces post-operative scarring in an experimental model of filtration surgery, and an early pilot study appears to be promising. Interferon-α, an antifibrotic cytokine, has been shown to reduce the scarring activity of fibroblasts, although a clinical trial did not show it to be significantly better than current antimetabolites.

After the authors established the important role of TGF-β relative to other growth factors in the eye, our group has used different methods of targeting TGF-β activity, including a novel antibody and antisense oligonucleotides. CAT-152 (TrabioR) (Cambridge Antibody Technology, Cambridge, UK) is a fully human monoclonal antibody specific to the active form of human TGF-β2, which is the predominant form in the aqueous. One of the theoretical advantages of the antibody is that, unlike an antimetabolite, it only acts if there is TGF-β2 in the wound. We have shown its efficacy in vitro and in vivo. In an animal model of aggressive conjunctival scarring, it significantly improved glaucoma filtration surgery outcome compared to control. Compared to the effects of MMC treatment histologically, it appeared much less destructive to local tissue.

We have now taken this antibody through to clinical use. A pilot clinical study at Moorfields Eye Hospital and the Western Eye Hospital of this antibody in glaucoma filtration surgery has shown neither significant side-effects nor inflammatory reaction and an IOP reduction of 4.6 mm Hg in the placebo group and 10.4 mm Hg in the antibody-treated group at 1 year, with fewer interventions in the antibody-treated group without the very cystic blebs seen with antimetabolites. A similar trial of the antibody in phacotrabecelectomy has shown similarly encouraging results and several
Figure 22.3 Computer model reconstruction of human antibody to TGF-β₂ (Trabio®, also known as CAT-152).
Figure 22.4 Simulation of antibody in bleb. If minimal TGF-β₂ is present then there is a minimal effect. Only if TGF-β₂ is present in the wound does the antibody work. This theoretically minimizes side-effects such as hypotony.
Figure 22.5 Bleb from patient treated with TGF-β2 antibody (Trabio®, also known as CAT-152). After 3 years the bleb is diffuse and non-cystic.
multicentre studies are currently under way. Further studies have also shown that prolonged injections of the antibody to TGF-β₂ (CAT-152 Trabio®) may extend the length of bleb survival and are superior to injections of 5-FU.⁴⁷

**Fibroblast proliferation (and other cellular activity)**

The drugs MMC and 5FU are the main anti-scarring agents in use at present, although we are still carrying out trials with single applications of beta-radiation, which has the advantage of good bleb morphology.⁴⁸ Subconjunctival 5FU was the first established antimetabolite regimen based on the work of Parrish and his colleagues in Miami.⁴⁹ Since then, the intraoperative regimens for MMC⁵⁰ and 5FU, which we introduced on the basis of our cell culture results showing that long-term cellular growth arrest could be achieved with short applications of antimetabolites,¹⁰,¹¹,⁵¹–⁵³ are much more popular due to their convenience, supplemented by 5FU injections. However, a meta-analysis has suggested that fewer than four injections of 5FU may have little effect.⁵⁴ Both treatments were generally associated with relatively small treatment areas combined with limbus-based surgery and a posterior incision resulting in the production of thin avascular blebs with complications including leakage, hypotony and endophthalmitis with long-term follow-up.⁴ Although methods have been described to treat these thin leaking blebs, including compression sutures and blood⁵⁵ or Nd-YAG induced subconjunctival bleeding,⁵⁶ these methods are totally satisfactory. Furthermore, the presence of an interpalpebral or inferiorly placed bleb is associated with a very high incidence of complications (up to 10 times normal) (Figure 22.6).

**Improved techniques of antimetabolite use**

Newer techniques that have evolved to minimize the incidence of complications associated with antimetabolite use in glaucoma filtration surgery include optimizing the choice of agent, method of application and the surgical technique. This includes restricting their use

![Figure 22.6](image-url)  *Endophthalmitis associated with a focal bleb after limbus-based trabeculectomy with MMC and small treatment area placed in the interpalpebral position.*
by adopting a strategy based on different single application anti-scarring agents and concentrations ‘titrated’ against patient risk factors. This is particularly important if patients have a lower risk of scarring but still require lower target pressures, such as in normal-tension glaucoma. A study from Moorfields showed that, although intraoperative MMC lowered IOP more than intraoperative 5FU, there were many more complications with MMC, illustrating the importance of choosing the right agent and dose.57

A very important parameter that our group has shown to influence bleb morphology greatly is that of size of MMC treatment area; small treatment areas give rise to thin-walled and cystic blebs compared to the more diffuse-looking, thicker-walled blebs associated with large treatment areas. This was based on a simple clinical observation of what characterized cystic blebs. Two features are common—anteriort aqueous drainage at the limbus and a ring of scar tissue, the ‘ring of steel’58 (Figure 22.1). This hypothesis has subsequently been confirmed experimentally59 and clinically.60,61 In 1996 the authors altered the antimetabolite application technique to ensure a large MMC treatment area with much more diffuse non-cystic blebs combined with fornix-based flaps (Figure 22.7) and this has dramatically lowered the severe bleb-related complications over 3–5 years from 20% to 0%. Various systems of bleb grading have been proposed to classify the long-term effects of various agents and these classifications may become increasingly important as criteria for success move from not just IOP control to minimization of side-effects.62,63

The application of intraoperative antimetabolites under the scleral flaps (but before

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**Figure 22.7** Photograph showing patient treated with limbus-based trabeculectomy with a small area of MMC on the patient’s left. The bleb is small and cystic and the patient has had discomfort with recurrent attacks of blebitis. In the right eye the patient had a fornix-based trabeculectomy with a large area of MMC treatment and has a diffuse non-cystic bleb that is very comfortable, without any complications over 7 years.
entering the anterior chamber) as well as under the conjunctiva appears to be advantageous.\textsuperscript{64} If the anterior chamber is not entered, then earlier concerns about ciliary body toxicity do not seem to have been borne out clinically. The time of antimetabolite exposure varies among surgeons and centres. A study carried out by the authors showed that tissue uptake rises sharply then peaks at about 3 minutes, with only a small rise after that.\textsuperscript{65} Varying the concentration appears to be a more accurate way of determining tissue uptake than volume.\textsuperscript{66} Therefore we try to fix exposure times to a minimum of 3 minutes and vary agent and concentration for different risk groups. The current Moorfields regimen is shown in Table 22.2. Finally, the advent of other surgical techniques such as releasable sutures has increased pressure control, but these are still associated with hypotony some months after surgery. We have designed a new adjustable suture with special forceps (2–502, DuckworthandKent.com) allows the pressure to be gradually and gently adjusted down towards target pressure\textsuperscript{14,61} (Figure 22.8). The combination of changes that has considerably altered the safety of antimetabolites is shown in Figure 22.9.

A form of photodynamic therapy with diffuse blue light coupled with a photosensitizing agent to kill fibroblasts may also be another way to control surface area of treatment.

Table 22.2 Moorfields Eye Hospital (More Flow) intraoperative single does antiscarring regimen v2003 (continuously evolving). Lower target pressures would suggest a stronger agent was required.

| Low-risk patients (nothing or intraoperative 5-FU 50 mg/ml\textsuperscript{*})*† | Intermediate risk patients (intraoperative 5-FU 50 mg/ml\textsuperscript{*} or MMC 0.2 mg mg/ml)† |
| Low-risk patients (nothing or intraoperative 5-FU 50 mg/ml\textsuperscript{*})*† | Intermediate risk patients (intraoperative 5-FU 50 mg/ml\textsuperscript{*} or MMC 0.2 mg mg/ml)† |
| No risk factors Topical medications (beta-blockers/pilocarpine) Afro-Caribbean (elderly) Youth <40 with no other risk factors | Topical medications (adrenaline) Previous cataract surgery without conjunctival incision (capsule intact) Several low risk factors Combined glaucoma filtration surgery/cataract extraction Previous conjunctival surgery, e.g. squint surgery/detachment surgery/trabeculotomy |
| High-risk patients (intraoperative MMC 0.5 mg/ml)† | Low-risk patients (nothing or intraoperative 5-FU 50 mg/ml\textsuperscript{*})*† |
| Neovascular glaucoma Chronic persistent uveitis Previous failed trabeculectomy/tubes Chronic conjunctival inflammation Multiple risk factors Aphakic glaucoma (a tube may be more appropriate in this case) | No risk factors Topical medications (beta-blockers/pilocarpine) Afro-Caribbean (elderly) Youth <40 with no other risk factors |

* Intraoperative beta-radiation of 1000 cGy can also be used. CAT-152 (Trabio\textregistered) or humanized anti-TGFbeta2 antibody may be appropriate in the low- and intermediate-risk groups in the future based on the results of current studies. These groups account for the majority of patients undergoing glaucoma surgery.
† Postoperative 5-fluorouracil injections can be given in addition to the intraoperative applications of antimetabolite.
Figure 22.8 Transconjunctival adjustment of adjustable sutures using a special pair of smooth, non-cutting forceps. The IOP can be lowered gradually, minimizing the chance of hypotony.
and modulate healing.\textsuperscript{67} It would be important to determine the effect of these agents on the overlying epithelium, as differentiated stable epithelium may have a suppressive effect on fibroblasts in the wound.\textsuperscript{68,69} A pilot clinical trial has shown promising results.\textsuperscript{70} There are also other approaches to the control of proliferation and these include a variety of
other agents including mushroom lectins, methylxanthines and overexpressing genes inhibiting proliferation such as p21 WAF-1/CIP-1, introduced via an adenovirus system, without the bleb thinning caused by MMC, antagonizing integrins and their receptors or altering intracellular transcription.

Fibroblast migration, tissue contraction and extracellular matrix synthesis

The migration of cells is an intrinsic component of tissue contraction, which is important in filtration surgery failure. The matrix metalloproteinases (MMPs) are enzymes that degrade the extracellular matrix. The levels of MMPs in the vitreous relate to the development of retinal scarring. Their importance has been demonstrated by the fact that cell-mediated collagen contraction can be inhibited using MMP inhibitors. This applies to retinal pigment epithelium as well as Tenon’s fibroblasts. The authors have now shown a dramatic reduction in scarring in an experimental model with retention of normal tissue morphology using an MMP inhibitor (Figures 22.10 and 22.11) This action is equivalent to MMC without the deleterious side-effects. A number of agents can affect the cytoskeleton of the cell and hence inhibit migration, including taxol and etoposide (microtubule-stabilizing agents) and cytochalasin B (a microfilament inhibitor). Taxol and etoposide have been used in models of filtration surgery and prolong bleb survival, although neither have been assessed in human clinical trials to date.
Figure 22.10 Flat failed bleb 30 days after filtration surgery in a model with control injections.
Figure 22.11 Functioning diffuse bleb after filtration surgery in a model with injection of a matrix metalloproteinase inhibitor. The effect is equivalent to MMC, but without the epithelial damage and avascularity seen with MMC.

**Extracellular matrix synthesis**

Various agents primarily interfere with molecular cross-linking of collagen, such as β-aminopropionitrile and D-penicillamine. There is experimental and clinical evidence that they may work in filtration surgery. Fibrostatin-c, an inhibitor of prolyl-4-hydroxylase, has been shown to inhibit type I collagen secretion by Tenon’s capsule fibroblasts. Fibrostatin-c, an inhibitor of prolyl-4-hydroxylase, has been shown to inhibit type I collagen secretion by Tenon’s capsule fibroblasts. Methylxanthine derivatives also reduce collagen secretion. Interestingly, MMP inhibition also surprisingly results in a reduction in collagen synthesis in vitro, which may help to explain the dramatic reduction in scar tissue in vivo.

**Cessation of healing**

At present little is known about the physiological signals initiating the end of wound healing, although fibroblast apoptosis is probably an important component. MMC and high doses of
5FU not only inhibit fibroblast proliferation and cause long-term growth arrest, but also induce apoptosis.\textsuperscript{84} However, fibroblasts which are not killed but merely growth arrested by MMC can keep T-lymphocytes from apoptosing, which would result in a persistent inflammation.\textsuperscript{85,86} Apart from antimetabolites there are other strategies of inducing apoptosis, including pro-apoptotic peptides.\textsuperscript{87} Induction and regulation of
apoptotic mechanisms potentially offer a novel way of regulating and terminating excessive and unwanted healing.

**Conclusion**

The ability to modulate the healing process fully would ultimately allow us to determine the long-term final IOP in patients after glaucoma filtration surgery. Our increasing understanding of the healing and repair processes and developments in modern scientific techniques in cell and molecular biology will ultimately lead to better and safer therapies for our patients.

**Acknowledgements**

This chapter is dedicated to our dear friend Rodolfo Armas MacDonald, former Glaucoma Fellow, Moorfields Eye Hospital and Institute of Ophthalmology, who passed away on Friday 29th August 2003. Our research has been supported in part by the Medical Research Council (G9330070), Guide Dogs for the Blind, Wellcome Trust, RNIB Fight for Sight, Eranda Trust, Hayman Trust, Joan Richardson Healing Fund and AWTE and the Michael and Ilse Katz Trust.

**References**


23.
THE FUTURE OF GLAUCOMA THERAPY

E Michael Van Buskirk

Introduction

Before the 19th century, much of sickness was treated as a single entity with non-specific bleeding, purging, and blistering to drive out the unnatural or imbalanced phlogistic forces within. Descriptions of specific disease entities burgeoned in the early 19th century, glaucoma among them, with the attribution of elevated intraocular pressure (IOP) to the glaucomatous eye by Demours in 1818 and McKenzie in 1830. Following Helmholtz’s description of the ophthalmoscope in 1851, Von Graefe described the characteristic appearance of the optic nerve we now call glaucomatous optic neuropathy. The latter third of the 19th century brought instruments to measure the eye pressure with relative convenience and accuracy. By 1880, physiostyamine and pilocarpine had been shown to reduce IOP in many cases. The first two decades of the 20th century brought modern concepts of surgical management of glaucoma by creating a fistula through the eye wall. Thus, by the early 20th century, both the concept of glaucoma as a pressure-induced disorder and available therapeutic means set the stage for treating glaucoma by reduction of the eye pressure. For the most part, the strategy persists unchanged to this day. By 1950, glaucoma had been subdivided into many of the primary and secondary subtypes we now recognize, but surgical and medical modalities then available comprised the principal methods to reduce IOP in virtually all categories of glaucoma.

From the very beginning of serious investigation, many investigators proposed that glaucoma was more complex than a mechanical problem with the intraocular plumbing. Beginning in the 1950s, both technical and conceptual advances made possible new conceptual and practical approaches to glaucoma. First, it became possible to measure the IOP accurately, rapidly, and conveniently with Goldmann’s Applanation tonometer mounted on the slitlamp biomicroscope. This allowed more patients to be identified and permitted recognition and study of the wide variation of IOP among glaucoma patients. Second, the development of threshold, static, and automated perimetry from the Goldman and Tubingin manual instruments to the modern automated digitized machines made possible more reliable and earlier detection of neural damage. These new instruments have disclosed more patients with early functional loss who exhibit normal aqueous humor dynamics or even normal appearing optic nerves. Third, filtration surgery became
more controllable with the various guarded procedures and thus a more viable option for early management. Fourth, a host of new drugs (from the carbonic anhydrase inhibitors of the 1950s, the β-blockers of the 1970s, the α-agonists of the 1980s, and the prostaglandin analogs of the 1990s) give us more pharmaceutical options than we could possibly use to reduce the IOP. Fifth, the application of lasers within ophthalmology reached the routine therapeutic armamentarium by 1980. Finally, advances in epidemiologic methodology and its application to glaucoma-susceptible populations has revealed new information about associations with glaucoma and substantial differences among geographic populations. Of particular interest is the observation that a minority of glaucoma patients in Japan exhibit eye pressure above the statistical normal range.\textsuperscript{5} Recent data also suggests an enticing statistical association between the propensity to develop glaucoma and thin corneas, an association not explained solely by the tendency toward spuriously low measured eye pressure in glaucoma.

Concept of the therapeutic goal

From the latter decades of the 19th century to the present time, ophthalmologists have sought to treat glaucoma by reducing the IOP from baseline, but the degree of reduction needed for an individual patient remains obscure. Regardless of whether the IOP acts alone or in concert with other factors, there is no way to determine an individual patient’s threshold of pressure damage. If one can accept the strategy of pressure reduction for the treatment of glaucoma, the establishment of a goal, or desired outcome, for any instituted therapy makes sense. Of course, the ultimate goal must be, not pressure diminution, but preservation of the visual function. Since all forms of treatment are directed towards lowering eye pressure, it seems desirable to establish a desired pressure as a penultimate outcome of hypotensive therapy. For surgery or laser, the goal becomes self-determined by the procedure itself because the final pressure has less to do with the surgeon and more with the endogenous characteristics of the patient. The surgeon must accept the pressure outcome as both a product of the technical skill applied and the individual healing characteristics of the patient. On the other hand, the degree of pressure reduction with medical therapy is titratable within finite limits, depending upon the agents employed, their concentration, their frequency and whether or not they act alone or in conjunction with other drugs.

Most important would seem the establishment of whether or not an agent has in fact reduced the IOP. Given applanation tonometric precision only to the nearest 1 mm, any intervention must produce a documentable 2 mm change to become identifiable. With a pressure in the 20s, that amounts to a 10% change, in the absence of which one can safely conclude that a particular patient is unresponsive to that particular agent. Beyond determining whether the drug has had any effect at all, any other ‘target pressures’ are arbitrarily based upon population data, not the characteristics of the individual patient. Using
population data to predict a safe target pressure for an individual more closely resembles the casino odds maker than the prudent clinician scientist. Unfortunately, there is no more reliable method with current technology to determine the threshold of pressure damage in an individual. In the absence of an objective method to determine a legitimate target, the therapist must choose between titrating the target progressively downward as the optic neuropathy progresses or accepting the very lowest possible compatible with the health of the eye, typically in the range of 8–12 mm Hg.

**Current therapy modalities**

At the present time, lowering of IOP is the only strategy regularly employed in the therapy of glaucoma. Direct biochemical protection of optic neural (retinal ganglion) cells looms as a bright but distant beacon obscured through a self-perpetuated fog of wishful thinking and unsubstantiated claims. Clinical trials of systemically administered agents are under way. Conceptual differentiation of eyes susceptible primarily to pressure from those susceptible to other exclusive or adjunctive factors seems even more distant.

A detailed description of current therapeutic modalities lies well outside the intent and scope of this chapter, but it is worth considering some basic strategies. Intraocular pressure can be reduced either by reducing the inflow or enhancing the outflow of aqueous humor, or the two strategies may be used in combination with good effect. Combinations appear to work among some pharmaceutical agents or, in some cases, in combination with laser treatment. Indeed, our hypothesis from the earliest days of laser trabeculoplasty has been that it functions by altering the biology of the trabecular cells more akin to a drug than to a mechanical effect. On the other hand, because surgical therapy involves bypassing all or a portion of the conventional outflow pathways, neither medical nor laser enhancement of those tissues logically adds well to surgery. At least in North America, incisional surgery remains the last step in the management of glaucoma, usually following attempts with medical therapy and often with laser surgery. This sequence of therapy has persisted for many decades, primarily because medical therapy is, by and large, temporary, reversible, and additive, both to its various combinations and to the effects of laser. In practice, some medications can also be used to supplement the hypotensive effect of filtration surgery, but the institution of such a regimen must acknowledge that the surgery alone has failed to achieve a sufficiently low pressure to meet the patient’s needs. The more recently described non-penetrating procedures would leave portions of the trabeculum intact, but evidence suggests that many of these techniques, when successful, really act as modified fistulizing procedures. One could argue that agents that suppress aqueous humor inflow may make more sense in the postoperative patient with elevated IOP, and indeed these agents do typically reduce IOP, even after filtration surgery. However, the surgeon must recognize that suppressing flow reduces the flow of aqueous into an already collapsing filtration bleb and, on a theoretical basis, could hasten the bleb’s
ultimate demise. Although these considerations each can be countered with reasoned alternatives, the issue remains that it is difficult to rationalize the role of adjunctive medical therapy after filtration surgery.

Pressure-induced glaucoma derives primarily from progressive idiopathic obstruction of aqueous humor outflow. Despite extensive work in this area, we still do not have a complete understanding or consensus about how aqueous percolates out of the eye and where it becomes obstructed in glaucoma, likely a combination of processes yet incompletely described. Nevertheless, enhancement of aqueous humor outflow by direct stimulation of cholinergic receptors or blockade of cholinesterase was the first strategy used to treat glaucoma with pilocarpine and physostigmine. Both agents contract the ciliary muscle, which in turn improves outflow through its mechanical tension upon the trabecular mesh-work and Schlemm’s canal. Even in the excised dead eye, mechanical tension placed upon the outflow pathways by retrotension upon the lenticular zonules will diminish resistance to outflow.9 Conversely, the outflow-enhancing effect of a cyclotonic agent becomes lost when the insertion of the ciliary muscle into the scleral spur is disrupted.10

Suppression of aqueous humor inflow is possible with many adrenergic agents, including epinephrine (which enhances outflow as well), but did not become popular as a specific therapeutic strategy until the advent of oral carbonic anhydrase inhibitors in the 1950s. Their substantial side-effects and the reluctance of ocular therapists to invoke systemically administered agents when topical alternatives were available kept miotic/cyclotonic agents as front-line glaucoma therapy until the introduction of the β-adrenergic antagonists in the 1970s. Within months of the release of timolol in the United States, the primary strategy for treating glaucoma abruptly shifted from enhancement of aqueous humor outflow toward blockade of inflow. With the recent introduction of prostaglandin analogs that exploit and enhance outflow through the uveoscleral pathways, we now see a reversion to outflow enhancement as the primary strategy in treating glaucoma.

Compared to, for example, 1973, glaucoma therapy in 2003 employs a similar therapeutic strategy, but more effectively, safely, and conveniently. Many patients in 1973 took pilocarpine four times daily with the concomitant miotic induced dimming, blur, and headache, epinephrine with erythema and eventual allergic dermatitis and suffered the malaise of systemic carbonic anhydrase. Complex regimens brought the instillation of glaucoma medications to nearly a full-time vocation for many patients. In contrast, it is now possible, even routine, to achieve good 24-hour control of eye pressure with once-daily instillation of either a β-adrenergic antagonist or a prostaglandin analog, or in some cases a combination of the two. At worst, a patient needs to instill drops at bedtime and with their morning ablutions, leaving the daytime hours to pursue activities of normal life. In addition to the three groups of agents of 30 years ago, we have added at least a host of β-blockers, four prostaglandin analogs, two topical carbonic anhydrase inhibitors, two α-adrenergic agonists, and innumerable combinations to comprise more possibilities than could be combined in a reasonable therapeutic lifetime.

The contemporary glaucoma therapist, then, faces an embarrassment of riches that must be tempered by a selection of acceptable and effective agents for routine use. Now
we have equally efficacious and safe convenient agents for outflow enhancement in aqueous suppression. Even 30 years ago, when surgery was less refined than today, we had to gird ourselves against the temptation to find that last untried combination to stave off filtration surgery. Now, with exponentially expanded possible combinations of products, we must become even more resistant to the multiplicity of choices, lest delaying the inevitable allows the residual functional vision to dribble into the night. Given then that trying combinations of all available choices is unacceptable, it seems that patients in whom the pressure cannot be controlled by a single effective outflow enhancer in combination with a single effective aqueous suppressant should be looking toward laser or surgery. This is not to say that no patient ever needs more than two drugs. One must bear in mind that pharmaceutical enhancement of aqueous humor outflow must ultimately be constrained by the maximal conductivity of the tissue; likewise, the capacity to suppress aqueous formation is limited. In the absence of allergy, it makes little sense to change drugs within a single class, for example β-blockers or prostaglandin analogs. One exception might be that a cardio-selective β-blocker might make a more prudent choice for the patient with mild reactive airway disease. On the other hand, drugs that do not substantially reduce pressure in a given patient should be withdrawn and substituted with another class of agents.

Laser therapy for open angle glaucoma had undergone a decline in popularity in the recent past but now enjoys a mild resurgence with the interest in selective laser treatment for open angle glaucoma. Although laser trabeculoplasty was introduced with the idea that it worked as a sort of laser-pilocarpine, as a method of mechanically distorting the meshwork or the angle to enhance outflow, there were reasons from the beginning that suggested an alternative biologic mechanism. Initially, treatment was often applied deep in the angle to scleral spur or even the ciliary body band and the pressure lowering effect was good. The strategy shifted to treating either in the mid meshwork or, preferably, more anteriorly, near Schwalbe’s line to avoid peripheral anterior synechia. Our laboratory eventually developed models to demonstrate that laser treatment of the meshwork incites a cascade of biologic events that stimulate anterior meshwork cells to migrate into and around burn sites to repopulate the trabecular meshwork with active healthy cells. Early in the 1980s, it was demonstrated that IOP could be effectively lowered by laser treatment of the angle regardless of location of the spot, size of the spot, wavelength of the laser, and even of the number of clock hours treated. Wilensky and Weinreb showed good pressure lowering by treating only one quarter of the circumference. By the same token, we demonstrated early on that the procedure could be effectively repeated. In recent years, laser trabeculoplasty has been modified under the sobriquet of ‘selective laser trabeculoplasty’. This modification is based upon the hypothesis that a laser of a specific wavelength designed to be absorbed only by trabecular cells could spare the mesh-work widespread coagulation necrosis and permit multiple repeat treatments. In fact, as noted above, repeat treatment has been shown to be effective in some studies, but the idea may have some merit.
Future development

It is fair to say that in 2003 we have a better understanding of glaucoma than did our counterparts of the early years of the last century, but that many of the questions from that era remain unanswered. Sometime during the middle to latter part of the last century the idea gradually became accepted that glaucoma was more than just the IOP compressing the optic nerve head. The role of many other factors, especially those involving peripheral and ocular blood flow, began to be considered and investigated, especially by the laboratories of Stephen Drance in Vancouver, BC and of his student Josef Flammer in Basel. Largely influenced by them, we, in 1994, set out to develop a multidisciplinary laboratory that would strive to develop non-pressure models of glaucoma. At first, the group focused on the ischemia to induce a glaucoma model. This, not surprisingly, has proved difficult, perhaps because we have isolated just one factor. We have chronically diminished optic nerve blood flow in monkeys by continuous administration of low dose endothelin-1 to the peri-optic neural space, sufficient to create ischemia but insufficient to induce infarction. These monkeys have mimicked some aspects of glaucoma by selective loss of temporal retinal ganglion cells and their axons, regional activation of the optic nerve and retinal glial tissues, and localized electrophysiological deficits. Interpretation of this work and of the many other studies of ocular blood flow is hampered by the lack of good technology that directly measures the velocity of blood flow in the pertinent vessels of the prelaminar and laminar regions of optic nerve in human subjects. We are left with drawing informed conclusions from measured changes in non-human models or in other contiguous vascular systems.

As investigators identified more and more patients who suffered from glaucomatous optic neuropathy, but who lacked demonstrable elevation in IOP, clinicians have sought to characterize these so-called normal pressure glaucomas by the other factors that could have damaged their optic nerves. The answers however, to date, are not nearly so clean as we would have liked because it is impossible to separate people with normal-pressure glaucoma from those with conventional primary open-angle glaucoma, except by an arbitrary level of measured eye pressure. This is not to say that one cannot make predictions about patients by looking at their optic nerve. Indeed, several classifications of optic disk damage have been proposed. I felt like Dr Watson to Dr Jost Jonas’ Holmes when he pointed out to me that the glaucomatous cupping we exhibited on the cover of the Journal of Glaucoma derived from markedly elevated IOP probably in a young adult. Like Sherlock Holmes, it was elementary to him that the diffusely enlarged cup and the relatively pink if thinned remaining neural rim could only belong to a young adult with high pressure. Certain classic disk types can be attributed to specific clinical characteristics, but many patients are a mixed lot with only mildly elevated pressure and a polyglot of disk appearances. By the same token, there is no more reason to suppose that a normal eye pressure prevents the nerve from being susceptible to pressure damage than to expect elevated pressure to render the nerve immune to vascular or other non-hydrostatic influences. The Collaborative Normal Pressure Glaucoma Trial confirmed that glaucoma
patients without elevated IOP benefit from pressure lowering.\textsuperscript{20} On the obverse of the same coin, Schultzer et al showed that vascular disease was equally common among glaucoma patients with high as with normal pressure.\textsuperscript{21}

Now we understand that a whole host of extrinsic and intrinsic processes, from compression by the IOP and relative ischemia to neural and glial cellular excitotoxicity, all may participate in the process of ganglion cell injury and death. These processes comprise the focus of much work in laboratories around the world and we can anticipate that the coming two decades will bring us better understanding of the mechanisms of neural injury in glaucoma. At the same time, the possibilities revealed by resolution of the human genome bring into focus entirely new avenues of research into the genetic characteristics of various glaucoma clinical conditions. This work proceeds at break-neck pace in the various genetic laboratories around the world, but is hampered by clear-cut clinical definitions of the various glaucoma phenotypes. It seems likely that as more and more ‘glaucoma genes’ become described, they themselves will determine clinical subtyping as we practitioners move away from exclusive reliance upon phenotypical description toward categorization of our patients by their common genes.\textsuperscript{22}

There were three substantial advances in filtration surgery in the latter half of the 20th century that will influence glaucoma management in the foreseeable future. The most significant, in my view, was the practicality of seton-tube implants because these devices have allowed successful filtration and visual preservation, even restoration, in eyes that previously were doomed to failure and assigned to massive palliative cyclodestruction or enucleation.\textsuperscript{23} These eyes would include, for example, multiply-operated filtration failures, eyes with aphakia and extensive conjunctival scarring such as with extensive scleral bucklings and some of the severe congenital glaucomas. We can anticipate that these devices will continue to play an important role and can hope to see technological improvements in safety. New shunts to divert aqueous directly to Schlemm’s canal, to the uveoscleral pathways or to various intra- and extraocular veins are all being investigated. All of these approaches hold promise to obviate the dreaded filtration bleb and its attendant risks.

The next most significant advance was the introduction of the split-thickness scleral flap or trabeculectomy procedures that so dramatically improved outcome, safety, and convenience of filtration procedure. Until new advances can be proven to be safer and equally effective, trabeculectomy will remain the standard approach to achieve a consistently low pressure.\textsuperscript{24}

Finally, the introduction of adjunctive antimetabolites has permitted filtration in higher risk cases with scarred or scar prone conjunctiva, but their indiscriminate use has also brought the substantial postoperative complication rate nearly to the level before trabeculectomy.\textsuperscript{25} Ironically, postoperative hypotony, the benchmark of glaucoma consultation prior to 1975, has again become a mainstay of complex glaucoma management after an approximately 20-year hypotony-free interval!

The last decade has brought the reintroduction and popularity of various nonpenetrating filtration procedures that are continuing to evolve.\textsuperscript{26,27} These operations
theoretically derive from the idea that blockade of aqueous humor outflow occurs external to the corneo-scleral component of the trabecular meshwork. Thus, the internal mesh-work could be left intact while the diseased and dysfunctional layers adjacent to Schlemm’s Canal are removed. In theory, removal of the blocking tissue, the juxtacanalicular (cribiform) meshwork, and Schlemm’s canal, would make possible diversion of the aqueous humor directly from the interstices of the corneo-scleral layer into the aqueous collector channels, obviating the need for a filtration bleb and all its associated complications. A variety of these procedures continue to evolve, but the technical aspects appear to be difficult. Many subjects mimic through-and-through filtration under a scleral flap because of micro- or macroperforations of the inner trabecular layers. Most studies to date demonstrate that these non-penetrating procedures bring fewer traditional complications associated with conventional trabeculectomy, but also suffer from diminished pressure lowering compared to conventional filtration. This dilemma brings to mind the target pressure controversy alluded to previously, except that one must again consider that surgery is for many the last and only step to prevent visual loss. Thus, it would seem ideal for surgical procedures to induce the lowest pressure possible, regardless of the state of their nerve.

In these early years of a new millennium, we also can suggest that we have developed an evolving appreciation of the complexity of glaucoma. From both the clinical and research standpoints, at this stage of understanding, it would seem both sensible and practical to view glaucoma as an intrinsic progressive optic nerve disorder, glaucomatous optic neuropathy. This nomenclature absolves the clinician from the fruitless attempts to subdivide open-angle glaucoma patients by the level of their eye pressure. It seems likely that the future will bring more sophisticated methods to subtype glaucoma by their susceptibility to various extrinsic and intrinsic factors and also, perhaps, by their associated genotypes.

In the meantime, investigators seek improved methods to identify subjects with early glaucoma before vision becomes irrevocably lost. Two aspects of population growth impact the need for more efficient glaucoma detection and treatment. The average world population age gradually shifts upward as the post world war population explosion reaches old age and people live longer than before, well into their 80s, 90s and hundreds. At the same time, the prevalence of glaucoma increases with each advancing decade. Thus, over the coming decades, we will see a burgeoning both of elderly individuals and of the proportion of people who have glaucoma. In the United States alone, census figures project the population 85 years of age and over to increase from 4.2 million in 2000, to 6.8 million in 2020 and 19.4 million by 2050. This new demand will pose upon our societies challenges and opportunities to find more efficient methods to detect, to diagnose, and to manage glaucoma cases. These methods likely will involve more efficient electronic medical record keeping, electronically available proactive standardized protocols for diagnosing and treating specific glaucoma subtypes, and recruitment of non-physicians in early glaucoma management. The oncoming physician shortage in the face of an increasing susceptible population, such as is projected in the United States, likely will mandate that
technically oriented non-physicians will play an increasingly important role, with physician surgeons managing the more complex and difficult problems.

At the same time, methods to screen populations using sophisticated psychophysical testing, perhaps neural imaging, and even genetic screening, will make possible earlier detection of individuals most susceptible to glaucoma damage. Screening for glaucoma using tonometry has long been fraught with errors because of the wide variability of eye pressure. Direct detection of early glaucomatous optic neuropathy holds promise with more portable perimeters using less than 60 second screening strategies.29

Unfortunately, it appears that the immediate future holds only the strategy of lowering IOP as practical for glaucoma therapy, but direct neuroprotective agents are under investigation. We now have a broad spectrum of methods to treat glaucoma, all aimed to reduce IOP in glaucoma patients. Given half a dozen agents to enhance outflow and at least an equal number to diminish inflow, with their virtually innumerable combinations, it seems difficult to envisage the advantage of any new pharmaceutical agent that would be directed at either of these strategies, enhancement of outflow or reduction of inflow. The market seems to me to be saturated with effective, safe and convenient agents. We live in an age of vanity and convenience with our patients unwilling to tolerate the inconvenience of addressing their pesky but potentially blinding glaucoma. Thus, the exception to my statement might be the introduction of agents such as has been proposed with ethacrinic acid, a single dose of which could substantially reduce IOP with less frequent administration (Epstein D, personal communication, 2003).

Laser trabeculoplasty has been shown to have a role in the therapy of glaucoma, but not the crucial role as it was at one time hoped and envisaged.30,31 Our view of laser trabeculoplasty is that it produces a transient biologic effect upon trabecular meshwork cells, similar in the most general way to the effect of a drug on cells, and that the effect diminishes over time, in months compared to hours. This means that it either needs to be repeated or replaced with something else. Although the half-life of the laser effect is highly variable among individuals, there appears to be an approximately 10% failure rate per year. Selective laser trabeculoplasty uses a specific wavelength to effect pigmented trabecular cells without producing extensive coagulation necrosis throughout the tissue. This may allow for more successful repeat treatments, but, as mentioned above, retreatment has been successful in the past.11,14

It is likely that glaucoma and its treatment will gradually evolve over the immediate future from roots planted in the latter half of the 20th century with hypotensive drops administered once or perhaps twice daily. Laser therapy seems relegated to an auxiliary role in selected cases. Surgery seems to be evolving aggressively but haphazardly toward better procedures that obviate the filtration bleb. Meanwhile, genetic therapy for glaucoma looms in the distant future awaiting the results of intensive research. First, geneticists will need to uncover the broad spectrum of genes contributing to various forms of glaucoma. Basic and clinical scientists will need to resolve many of the nagging questions about the pathophysiology of the glaucoma entities, as clinicians will learn to match glaucoma phenotypes to the genetic anomalies. Then, geneticists will be prepared
to help us deliver appropriate genetic material to an appropriate tissue using viral or non-viral vectors.

The most challenging patients remain on the two ends of the spectrum of complexity. Although large collaborative trials lend credence to the concept of early treatment of selected individuals, the methodology for that selection remains obscure. At the other end, the endstage patient with multiple treatment failures continues to pose our most pressing challenge to enable them to retain their last island of functional vision.

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