

Reducing intraocular pressure: is surgery better than drugs?

T Shaarawy^{1,2}, J Flammer² and IO Haefliger²

REVIEW

Abstract

Reducing IOP is presently the evidence based, most accepted and most practised therapeutical approach for glaucoma patients. Currently topical ocular hypotensive medications, with its different classes, as well as filtering surgery (trabeculectomy and non-penetrating glaucoma surgery) are in the forefront of therapeutic modalities for IOP reduction. This article looks at the potential advantages and disadvantages of topical medications *versus* filtering surgery. It does not directly address the question of initial treatment of glaucoma, or what is the better treatment of glaucoma, as other review articles had, but rather looks in a more specific on the pros and the cons of each in relation to IOP reduction. In other words this article deals with the situation once the decision has been made to reduce IOP.

Eye (2004) 18, 1215–1224. doi:10.1038/sj.eye.6701374
Published online 16 April 2004

Keywords: glaucoma; non-penetrating; trabeculectomy; intraocular pressure; deep sclerectomy; viscocanalostomy

Introduction

Glaucoma is a progressive optic neuropathy involving characteristic structural pathological changes in the optic nerve head.^{1–3} Estimates of the number of patients bilaterally blind because of glaucoma ranges between 7 and 8 million people.^{4–6} Glaucoma is an increasingly important public health concern due to our ageing population demographics, and has been identified as the second leading cause of blindness world-wide and the first cause of irreversible blindness.

It is irreversible because it results from the degeneration of retinal ganglion cells, and to date there is no cure for neuronal central

nervous system degeneration, or means of regenerating lost neurones.

After more than a century of active research in the management of glaucoma, the 'Holy Grail' of glaucoma treatment is still elusive, and we have to be pragmatically content with our attempts to prevent further progression of glaucomatous damage, rather than curing the disease.

Glaucoma progression is strongly associated with a number of risk factors.^{7–14} Some of these factors are unmanageable like ethnicity and age, while others can be manipulated, with varying degrees of success, in an attempt to slow or arrest progression, like intraocular pressure (IOP) and possibly vascular dysregulation.

Reducing IOP is presently the evidence-based, most accepted, and most practised therapeutical approach of glaucoma patients.^{12,15,16}

Currently, topical ocular hypotensive medications, with its different classes, as well as filtering surgery (trabeculectomy and non-penetrating surgery) are in the forefront of therapeutic modalities to reduce IOP.^{15,17–23}

This review article looks at the potential advantages and disadvantages of topical medications *vs* filtering surgery and *vice versa*. It does not directly address the question of initial treatment of glaucoma,^{20,21,24–29} or what is the better treatment³⁰ of glaucoma, as other review articles had, but rather looks in a more specific fashion on the pros and cons of each in relation to IOP reduction. In other words, this review article deals with the situation once the decision has been made to reduce IOP.

What is the ideal treatment to reduce IOP?

Based on available knowledge,^{12,15,18,23,24,28,30} an ideal treatment to reduce IOP should achieve different objectives. It should offer sufficient reduction in IOP, possibly in the low teens. It

¹Glaucoma Unit Memorial Research Institute of Ophthalmology, Giza, Egypt

²Basel University Eye Clinic Basel, Switzerland

Correspondence:
T Shaarawy, MD
Glaucoma Surgery Research Group
University Eye Hospital
Mittlere St. 91 Basel 4012
Switzerland
Tel: +41 61 2658781
Fax +41 61 265 8652
E-mail: shaarawy@
glaucoma-surgery.com

Received: 10 April 2003
Accepted: 5 November 2003
Published online: 16 April 2004

should provide this reduction on a long-term bases and not just momentarily or sporadically. It should be associated with minimal IOP fluctuation, IOP fluctuation being identified as a significant and independent risk factor.

It should, if possible, encourage patient compliance or, better still, be totally independent from the compliance factor. On top of all that the ideal treatment should offer tolerable systemic and local side effects, or again better still be devoid of side effects.

Last but by any means not least, in a world exceedingly aware of the heavy medical care expenses,³¹ an ideal treatment to reduce IOP should be economically sound.

Sufficient reduction of IOP

Although it has been suggested that IOP reduction should be individualised to specific target pressure³² for each specific patient, in the majority of our patients, we are mostly aiming at pressures in the low teens.³³

In the Advanced Glaucoma Intervention Study (AGIS),³³ eyes were randomised to laser trabeculoplasty or filtering surgery when medical therapy failed. In the roughly one quarter of eyes in the study in which the IOP was always lower than 18 mmHg (mean IOP, 12.3 mmHg) during 6 years of follow-up, there was no net change in the mean visual field score. While 15% of such eyes were said to have worsened by four AGIS visual field units, an equal percentage 'improved' by the same criterion, perhaps providing an estimate of the false-positive rate of progression. In contrast, in those eyes in which the IOP was greater than 17 mmHg more than half the time (average IOP, 20.2 mmHg), eyes lost an average of approximately three AGIS units during 8 years of follow-up. A clear dose-response relationship between IOP and risk of progressive field loss was evidenced for intermediate categories.

With surgery, levels of IOP in the low teens, or even lower, are technically achievable,^{20,21,34-37} and that is independent of the IOP values prior to surgery. What determines IOP levels postoperatively are mainly the degree of surgical precision intraoperatively, the resistance to outflow posed by the scleral flap in trabeculectomy, at least initially. In the long run, the degree of wound scarring³⁰ postoperatively and whether this has been manipulated by antimetabolites,^{21,35} plays a role of paramount importance.

In topical medications, IOP in the low teens is less likely to be achieved,³⁸ but nevertheless possible specially with newer classes of medications¹⁹ and with the use of combination topical medical therapies, while the level of IOP is largely dependent on IOP values before commencing therapy. Topical medications

depending on their mechanisms of action, whether reducing production or increasing outflow, tend to knock down percentages of prior levels.

It is fair though to acknowledge that not every patient requires an IOP in the low teens in order to halt his glaucoma progression. In the collaborative initial glaucoma treatment study,²⁴ it would seem that patients with mild, initial damage can do well at pressures in the mid-to-upper teens, while those with more advanced damage indeed do better when pressure is reduced to the lower teens.

Long-term IOP reduction

In spite of initial IOP reduction of some medications, the effect seems to wear off in many cases. Watson *et al*³⁹ examined the long-term efficacy of monotherapy with topically applied beta-blocking agents. Analysis showed that less than half the eyes initially treated with topical beta blockers might be expected to still be being treated with their original medication after 5 years. The rest required either additional medication or trabeculectomy.

Long-term IOP reduction capabilities of other newer classes of medications are still not fully determined.^{40,41} One study¹⁹ with a 2-year follow-up found that Latanoprost significantly reduced IOP from pre-treatment values, and this reduction was maintained over the 24-month treatment period with no sign of upward drift.

Surgery also shows deterioration of its results with time. Chen *et al*⁴² studied the long-term outcomes of primary trabeculectomies that were successful at 1 year. This was a retrospective study of patients with various types of glaucoma who had trabeculectomies that were successful at 1 year and who had a follow-up of at least 10 years. In all, 40 patients (40 eyes) were enrolled, who had primary trabeculectomies that were successful at 1 year and who had a follow-up range of 10-21 years. Control of IOP was evaluated at 5, 10, and 15 years and at the last obtainable follow-up. Successful control of IOP was defined as IOP less than 21 mmHg or a reduction of 33% if preoperative IOP was less than 21 mmHg. Their results show that, if an eye was considered successful by IOP at 1 year, the probability of successful control of IOP was 82% at 5 years and 67% at 10 and 15 years. If an eye did not require further glaucoma surgery at 1 year, the probability that it would not still need further surgery at 5 years was 90%, at 10 years 75%, and at 15 years 67%. They concluded that loss of IOP control and progression of glaucomatous damage occurs over time despite initial success at 1 year.

Another study⁴³ examined the long-term results (1-14 years) of trabeculectomies with 5-fluorouracil injections that were successful at 1 year. In a retrospective

noncomparative case series. The authors identified 87 patients (87 eyes) who had trabeculectomies with 5-fluorouracil injections that were successful at 1 year and had a follow-up range of 1.0–14.7 years (mean 8.1, standard deviation of 4.4 years). All patients had previously failed glaucoma surgery (66.7%), cataract surgery (47.1%), or other diagnoses making them at high risk for failure. Successful control of IOP was defined as IOP less than 21 mmHg or a reduction of 33% if preoperative pressure was less than 21 mmHg. Statistical analysis was performed using Kaplan–Meier life table analysis. If an eye is considered successful by IOP at 1 year, the probability of successful control is 61% at 5 years, 44% at 10 years, and 41% at 14 years. They concluded that, despite successful IOP control at 1 year, trabeculectomies with 5-fluorouracil injections show a continual loss of IOP control over time.

Minimal IOP diurnal fluctuations

Large diurnal fluctuations in IOP have been identified as an independent risk factor in patients with glaucoma. In a retrospective study of 114 patients under treatment for primary open-angle glaucoma (POAG) and ocular hypertension OHT over an 11-year period of observation, Niesel and Flammer⁴⁴ described, more than a quarter of a century ago, a highly significant correlation between IOP and progression of visual field defects. This correlation could be shown for the visual field outer boundary in 81 eyes with OHT and for typical visual field defects in 33 eyes with chronic glaucoma. The relationship was, however, only significant when both the standard deviation of the annual IOP and the influence of cataract development upon visual acuity were considered. If only the mean IOP, not considering the standard deviation, is considered, this correlation is rendered insignificant. In another retrospective study⁴⁵ by the same group they described clearly a significant correlation between concentric constriction during 11 years of observation and the IOP fluctuation.

Asrani *et al*⁴⁶ have demonstrated that the diurnal IOP range and the IOP range over multiple days were significant risk factors for glaucomatous progression, even after adjusting for office IOP, age, race, gender, and visual field damage at baseline. This implies that we can no longer rely on an IOP in the statistically normal levels under treatment in office visits. Patients could still suffer from glaucomatous progression because of high fluctuations. What remains to be identified is the risk of this progression in large ‘within statistically normal’ fluctuations compared to fluctuations outside of what is statistically normal.

Migdal *et al*³⁸ compared the long-term functional outcome in POAG in medically treated patients *vs*

surgically treated patients. Among many results from this study, they observed that patients in the surgery-treated group had the lowest mean IOPs and with fewer peaks and troughs. The maximum mean IOP was 15.5 mmHg and the minimum mean IOP was 13.1 mmHg for surgery, compared with 22.1 and 15.9 mmHg for medicine.

Another study⁴⁷ was designed specifically to compare the IOP fluctuations in glaucoma patients under ocular hypotensive therapy with those of patients previously submitted to trabeculectomy. IOP peaks and fluctuations for the same patients in response to the water-drinking test (WDT) were also examined. The study included 30 POAG patients using ocular hypotensive medications and with no history of previous intraocular surgery (medical group), and 30 POAG patients previously submitted to one or more trabeculectomies though taking no medication at the time of the study (surgical group). All patients were submitted to a diurnal tension curve-DTC followed by the WDT. The IOP peak and IOP fluctuation during the diurnal tension curve were significantly greater in the medical group than in the surgical group. The same was observed following the WDT. From an overall baseline IOP of 10.6 mmHg, the mean IOP change following the WDT was 13% in the surgical group and 40% in the medical group. The study concluded that patients submitted to trabeculectomy have less IOP fluctuations during the diurnal tension curve and following a water-drinking provocative test.

This observation does constitute a definite advantage of surgery over medical treatment in that respect, thus potentially offering better potential chance of stabilisation or retardation of the glaucomatous disease process. One criticism to these two studies, though, was the inclusion of patients under different classes of ocular hypotensive medications under the medical group. Different classes have different effects on IOP diurnal curves, as has been demonstrated by Orzalesi *et al*⁴⁸ They compared the around-the-clock IOP reduction induced by timolol 0.5%, latanoprost 0.005%, and dorzolamide in patients with POAG or OHT. This was a crossover trial, 20 patients with POAG or OHT were treated with timolol, latanoprost, and dorzolamide for 1 month. The treatment sequence was randomised. All patients underwent measurements for four 24-h tonometric curves: at baseline and after each 1-month period of treatment. The between-group differences were tested for significance by means of parametric analysis of variance. To compare the circadian IOP rhythms in the POAG–OHT and control groups, the acrophases for each subject were calculated. All the drugs significantly reduced IOP in comparison with baseline at all times, except for timolol at 0300 h. Latanoprost was more effective in lowering IOP than timolol at 0300, 0600, and

0900 h ($P=0.03$), noon ($P=0.01$), 2100 h and midnight ($P=0.05$), and was more effective than dorzolamide at 0900 h, noon ($P=0.03$), and 1500 and 1800 h ($P=0.04$). Timolol was more effective than dorzolamide at 1500 h ($P=0.05$), whereas dorzolamide performed better than timolol at midnight and 0300 h ($P=0.05$). In this study, Latanoprost seemed to lead to a fairly uniform circadian reduction in IOP, whereas timolol seemed to be less effective during the night-time hours. Dorzolamide was less effective than latanoprost, but led to a significant reduction in nocturnal IOP. Although the study compares the IOP-lowering effect of the medications over a diurnal curve, the study lacks, or does not report, information on the differences in fluctuations in the diurnal curve between the different medications. In fact, if one compares different diurnal curves of different medications, latanoprost seems to have its curve in the lowest level, but if one examines the IOP diurnal curves presented in this study, it appears that latanoprost provides a similar range of fluctuations to timolol. Another concern is that we are judging the mean IOPs and not individual curves, theoretically single individuals might be at a higher risk of glaucomatous progression due to high fluctuations, which would not be apparent from mean IOP curves, this is of special concern in an era where individualised therapeutic decisions are stressed.

Medication class-specific or even medication-specific studies comparing IOP fluctuations in surgically *vs* medically controlled glaucomatous patients are in dire need, if this point is to be resolved. Though, the bulk of evidence, for the time being, seems to point to a relative advantage of surgery over medications in that respect.

The issue of compliance and persistence

Though compliance is not a real issue in surgically treated patients, it does pose a serious challenge to the efficiency of medical treatment.^{49–55}

Clinically significant noncompliance with glaucoma medications has been well documented. One study⁵⁶ documented the prevalence of noncompliance in a Greek cohort. Clinically significant noncompliance (more than two doses missed per week) was established in 44% of patients examined. Men and those using eye drops more than four times a day were more likely to default. Noncompliant patients exhibited higher mean IOP (22.9 *vs* 18.5 mmHg; $P>0.001$) and worse visual field loss (10.8 *vs* 7.0 dB; $P=0.008$) compared with compliant patients. Involuntary non-compliance was also common in this group, with only 53% instilling their eye drops accurately.

Another study⁵² was designed to assess the levels of compliance in elderly glaucoma patients on timolol eye

drops. In all, 24% of patients were admitted to omitting eye drops either occasionally or frequently. A total of 51% were found to have had insufficient drops dispensed to comply with treatment as prescribed. In noncompliant patients, the mean period without drops was 85 days of the year, with a maximum of 165 days.

Compliance could theoretically, but safely, be assumed to be much worse in developing countries compared to developed countries, for obvious reasons. It could be assumed to improve with fewer medications and fewer doses per day, more easily tolerated side effects, as well as with better understanding of the nature and gravity of the disease process.

One study⁵⁷ examined the causes of noncompliance with drug regimens in glaucoma patients. The results showed that forgetfulness was the number one reported reason for noncompliance.

In the literature,^{49–57} rates of noncompliance range between 23 and 51%; whatever the rate may be in different communities and age groups, surgery has a clear advantage over medications in this respect.

One useful way in assessing compliance with eyedrop medications is the miniature compliance monitor, as purposed by Kass *et al.*⁵⁸ The medication monitor resembles commercially available 30-ml eyedrop bottles in size, shape, and weight. It electronically records the date and time of each medication administration over a 6-week period.

Glaucoma patients' persistence with long-term pharmacotherapy is also an issue of concern when discussing ocular hypotensive medications. Two studies^{59,60} have identified persistency as a significant factor that may influence not only health outcomes, but also long-term costs and health planning. One study compared the persistency (time on initial therapy) of latanoprost *vs* beta-blocker monotherapy. The authors reported that patients receiving a beta-blocker as initial therapy were 3.8 times more likely to change therapy than those initially treated with latanoprost.

Ocular side effects and complications

Surgery carries with it a set of serious ocular side effects and complications, most notably endophthalmitis.^{61–64} The use of antimetabolites^{35,36,43,64–66} with trabeculectomy ups the stakes, on the one hand, better success rates are achieved, on the other higher complication rates are usually reported. Incidence of endophthalmitis is 0.2–1.5%^{67,68} in trabeculectomies without antimetabolites (this should be compared to the incidence of endophthalmitis after cataract extraction, which ranges between 0.07 and 0.12%⁶⁹); in trabeculectomies with 5-FU it is 3.0%⁷⁰ and in trabeculectomies with MMC it is 2.1%.⁷¹

Another much dreaded, but fortunately a rare complication is expulsive haemorrhage. One study⁷² reported an incidence of 0.57% after trabeculectomy. Another study⁷³ examined delayed suprachoroidal haemorrhage (DSCH) after glaucoma filtration procedures. Of a total of 1863 trabeculectomy procedures, DSCH developed in nine of 615 (1.5%) trabeculectomies without antimetabolite, 30 of 1248 (2.4%) trabeculectomies with antimetabolite.

Other complications that do occur more commonly include hypotonic maculopathy (8.9%), bleb leaks (8–14.6%), hyphaema (24.6%), and choroidal detachment (14.1%).⁷⁴

Of special interest is cataract incidence after trabeculectomy. This complication, aside from its deleterious effect on vision, often necessitates another intraoperative surgery, which could adversely affect the initial trabeculectomy results. The cataractogenic effect of surgery has been well documented.^{24,75} Cataract incidence post trabeculectomy has been reported to be as high as 20.2% in a follow-up of 12 months.⁷⁴

It is worth mentioning that such complication rates are not reported with nonpenetrating surgery.^{76–83} The vast majority of studies in the literature report significantly lower early postoperative complications compared to trabeculectomy. It also reports lower incidence of postoperative cataract formation. It is necessary though to acknowledge that the randomised controlled trials reporting on cataract incidence after nonpenetrating surgery do not have the same long-term follow-ups as in the case of trabeculectomy.

Ocular hypotensive medications are not devoid of ocular side effects and complications. For one, the early manifest glaucoma trial¹⁵ reported increases in clinical nuclear lens opacity gradings with medical treatment ($P=0.002$). Similar observation, but not statistically significant, was observed in the ocular hypertensive treatment study,⁸⁴ where 6.4% of the treatment group had cataract surgeries compared to 4.3% of the observation group ($P=0.06$).

It is worth mentioning that the last two studies' medication groups were under different medications. We have no information about which ocular hypotensive medication would put a patient under a higher risk of cataract occurrence.

The noxious effect of ocular hypotensive medications on the ocular surface has been long identified. One study⁸⁵ reported that administration of a single topical medication preserved with benzalkonium chloride, irrespective of type, for 3 months or more induced a significant degree of subclinical inflammation, detected as increased expression of HLA-DR on conjunctival epithelial cells. Another study⁸⁶ reported that latanoprost treatment induces ocular surface changes which are more

evident in POAG patients who are also affected by allergic conjunctivitis. The authors hypothesised that these findings are probably related to the very high latanoprost concentration of benzalkonium chloride and to its bedtime administration, which further amplifies the toxicity.

An increasing number of studies,^{24,38,87,88} both experimental and epidemiological, have provided evidence that filtering glaucoma surgery may be less effective than initially described. Of a number of risk factors for failure, duration and number of antiglaucoma drugs prior to surgery seem to play a critical role and highly accumulated antiglaucoma topical treatments significantly reduce the success rates.⁸⁹ Inversely, trabeculectomies performed as a primary procedure do offer higher success rates than trabeculectomies performed after a history of ocular hypotensive medications.

Again, very little is known about which medication, in which patient is associated with which adverse effects, and if that is clinically relevant.

Systemic side effects and complications

Aside from the systemic side effects of general anaesthesia, which is rarely resorted to in glaucoma surgery^{90–92} nowadays, surgery appears to be at a clear advantage in this respect. Ocular hypotensive medications have a long list of potential systemic side effects^{93–96} (Table 1).

Among others, pulmonary effects of beta-blockers are exceptionally worrisome. Two drops of 0.5% timolol equates to a 10 mg oral dose. This is not enough to cause symptoms in many patients, but unfortunately glaucoma and airways disease frequently coexist. Glaucoma affects 5% of people over 65 years⁹⁷ and incidence⁹⁸ of asthma in elderly patients (above 65 years old) is 4% in males and 7% in females. This should not be understood in the sense that beta-blockers are contraindicated in patients above 65 years, only patients with a clinically relevant bronchial asthma does run a risk with beta-blockers.

Attempts have been made though to offer better safety profile ocular hypotensive medications. Betaxolol (Betoptic) is a cardioselective beta-blocker, but is associated with poorer IOP control.⁹⁹ Carbonic anhydrase inhibitors^{31,48,100–106} applied topically are associated with less serious systemic side effects, but are also less potent than if orally administered. Prostaglandins^{19,41,48,96} are, however, very effective at lowering the IOP with, as far as we know, minimal systemic side effects, and have become the treatment of first choice in many cases.

The advantage of beta blockers, still, is that it has been tried and tested, we know a lot about beta-blockers and

Table 1 Side effects of ocular hypotensive medications

Medication	B Blockers	Carbonic Anhydrase Inhibitors (oral and topical)	Alpha Agonists	Parasympatho mimetics	Prostaglandin analogues
Side effects	Dyspnea, Bradycardia impotence confusion, depression, hypotension wrsening of peripheral vascular disease	Parasthesiae (systemic) Renal Stones (systemic) Blood dyscrasias (systemic and ? topical Rashes (either) Hypokalaemia (systemic) Polyuria (systemic) Metallic taste (topical and systemic)	Dry mouth GI upset palpitations fatigue decreased libido, hypotension rspiratory arrest in infants	Nausea Vomiting Headache Confusion	Minimal systemic side effects caution in asthma? contraincated in pregnancy

we probably do not know the same amount of information about newer classes of ocular hypotensive medications. This makes beta-blockers still a very valid option.

Economical burden of IOP-lowering strategies

The cost of surgical reduction of IOP decreases with time, where the cost of surgery can be divided by the number of years of life expectancy. The opposite is true for ocular hypotensive medications where the cost increases with time and could be multiplied by the number of years of life expectancy.

The cost of medication^{107,108} for a latanaprost-treated patient per year is 337\$, while it is 336\$ and 288\$ for betaxolol and dorzolamide, respectively. The daily cost of latanaprost is 0.87\$; this should be put in context with the fact that, according to the United Nations and the World Bank, more than one billion to 1.3 billion people live on a daily income of less than 1\$ (one dollar) a day. This makes glaucoma a surgical disease in most of the developing countries. Developing countries have the majority of glaucoma patents, and thus surgery is the treatment of choice to the majority of glaucoma patients. Unfortunately, very little industry research funding is being allocated for research in glaucoma surgery, which the majority of glaucoma patients are poised to benefit from.

There is evident lack of studies related to economic evaluation in glaucoma. Kobelt¹⁰⁹ states that the genuine lack of a useful outcome measure, and the impossibility to calculate the absolute annual risk of vision loss at given levels of the one parameter that is being treated, IOP, has essentially limited the research to resource utilisation. Another limitation is that economical studies usually take in consideration data from industrialised countries, which could be misleading if applied to developing countries' circumstances.

Conclusions

In essence, surgery has the potential to fulfil many features of an ideal approach to reduce IOP over drugs. It can lower the IOP to low teens, achieve long-term IOP reduction, minimise IOP fluctuations, lower the cost, and minimise systemic side effects. The major drawback, though, is the potentially devastating, but rare, ocular side effects.

Although surgery is usually the first-line treatment in developing countries, it is still resorted to as a final attempt to reduce IOP in developed countries. The possibility of employing surgery as a first-line treatment is limited by the high incidence of potential ocular complications.

Beta-blockers are effective and relatively safe ocular hypotensive medications, but have a well-established list of side effects; it has been tried and tested over long-term follow-ups. The real advantage lies in the fact that the amount of information that we possess about beta-blockers is relatively large. Prostaglandins may offer certain advantages of limited side effects and effective IOP reduction, but longer follow-ups are in dire need to provide evidence of efficacy and safety.

There is evidence that nonpenetrating surgery could offer a safer option to trabeculectomy, but the widespread practice is hindered by its surgical complexity, which results in long learning curves. Being technically demanding, it is very difficult to employ in mass surgical treatment, specially in developing countries. The use of implants with nonpenetrating surgery is an extra considerable cost. Another disadvantage is that nonpenetrating surgery does not seem to achieve its previously defined target IOP, in a significant percentage, without the postoperative use of goniopuncturing, which necessitates the access to laser equipment.¹¹⁰

There is an urgent need to improve our surgical options in order to reduce the related ocular

complications. If possible, safer and simpler surgical procedures should be developed to tackle the bulk of our glaucoma problem in developing countries.

Reducing IOP, is surgery better than drugs? As is the case in many aspects of glaucoma, indeed as in life itself, there are no easy answers to such questions. What could be at a clear advantage for one patient could be an absolute contraindication for another. In fact, many patients, specially in the developing world, do not have the luxury of an option.

We look forward to the day when effectively reducing IOP would not be such an important matter, when we can manipulate other risk factors, such as vascular autoregulation and neuronal damage, to the advantage of our glaucoma patients.

References

- Anderson DR. Glaucoma: the damage caused by pressure. XLVI Edward Jackson memorial lecture. *Am J Ophthalmol* 1989; **108**: 485–495.
- Bathija R, Gupta N, Zangwill L, Weinreb RN. Changing definition of glaucoma. *J Glaucoma* 1998; **7**: 165–169.
- Foster PJ, Buhrmann R, Quigley HA, Johnson GJ. The definition and classification of glaucoma in prevalence surveys. *Br J Ophthalmol* 2002; **86**: 238–242.
- Munoz B, West SK, Rubin GS, Schein OD, Quigley HA, Bressler SB *et al*. Causes of blindness and visual impairment in a population of older Americans: The Salisbury Eye Evaluation Study. *Arch Ophthalmol* 2000; **118**: 819–825.
- Quigley HA, Vitale S. Models of open-angle glaucoma prevalence and incidence in the United States. *Invest Ophthalmol Vis Sci* 1997; **38**: 83–91.
- Quigley HA. Proportion of those with open-angle glaucoma who become blind. *Ophthalmology* 1999; **106**: 2039–2041.
- Buckley C, Hadoke PW, Henry E, O'Brien C. Systemic vascular endothelial cell dysfunction in normal pressure glaucoma. *Br J Ophthalmol* 2002; **86**: 227–232.
- Gasser P. Why study vascular factors in glaucoma? *Int Ophthalmol* 1998; **22**: 221–225.
- Haefliger IO, Dettmann E, Liu R, Meyer P, Prunte C, Messerli J *et al*. Potential role of nitric oxide and endothelin in the pathogenesis of glaucoma. *Surv Ophthalmol* 1999; **43**(Suppl 1): S51–S58.
- Leske MC, Heijl A, Hussein M, Bengtsson B, Hyman L, Komaroff E. Factors for glaucoma progression and the effect of treatment: the early manifest glaucoma trial. *Arch Ophthalmol* 2003; **121**: 48–56.
- Osborne NN, Chidlow G, Nash MS, Wood JP. The potential of neuroprotection in glaucoma treatment. *Curr Opin Ophthalmol* 1999; **10**: 82–92.
- Palmberg P. Risk factors for glaucoma progression: Where does intraocular pressure fit in? *Arch Ophthalmol* 2001; **119**: 897–898.
- Ritch R. Exfoliation syndrome. *Curr Opin Ophthalmol* 2001; **12**: 124–130.
- Soltau JB, Zimmerman TJ. Changing paradigms in the medical treatment of glaucoma. *Surv Ophthalmol* 2002; **47** (Suppl): S2–S5.
- Leske MC, Heijl A, Hussein M, Bengtsson B, Hyman L, Komaroff E. Factors for glaucoma progression and the effect of treatment: the early manifest glaucoma trial. *Arch Ophthalmol* 2003; **121**(1): 48–56.
- Leske MC, Heijl A, Hussein M, Bengtsson B, Hyman L, Komaroff E. Factors for glaucoma progression and the effect of treatment: the early manifest glaucoma trial. *Arch Ophthalmol* 2003; **121**: 48–56.
- Collaborative Normal-Tension Glaucoma Study Group. The effectiveness of intraocular pressure reduction in the treatment of normal-tension glaucoma. *Am J Ophthalmol* 1998; **126**: 498–505.
- Bron A. Treatment of glaucomas. *Rev Prat* 2001; **51**: 2198–2201.
- Hedman K, Watson PG, Alm A. The effect of latanoprost on intraocular pressure during 2 years of treatment. *Surv Ophthalmol* 2002; **47** (Suppl 1): S65–S76.
- Rothman RF, Liebmann JM, Ritch R. Low-dose 5-fluorouracil trabeculectomy as initial surgery in uncomplicated glaucoma: long-term followup. *Ophthalmology* 2000; **107** (Suppl 6): 1184–1190.
- Uchida S, Suzuki Y, Araie M, Shigeeda T, Hara T, Shirato S. Long-term follow-up of initial 5-fluorouracil trabeculectomy in primary open-angle glaucoma in Japanese patients. *J Glaucoma* 2001; **10** (Suppl 6): 458–465.
- Wilensky JT. The role of medical therapy in the rank order of glaucoma treatment. *Curr Opin Ophthalmol* 1999; **10**: 109–111.
- Shaarawy T. Surgery for glaucoma in the 21st century. *Br J Ophthalmol* 2003; **87**: 250.
- Janz NK, Wren PA, Lichter PR, Musch DC, Gillespie BW, Guire KE *et al*. The Collaborative Initial Glaucoma Treatment Study: interim quality of life findings after initial medical or surgical treatment of glaucoma. *Ophthalmology* 2001; **108**: 1954–1965.
- Ritch R. Initial treatment of exfoliative glaucoma. *J Glaucoma* 1998; **7**: 137–140.
- Hitchings R. Initial treatment for open-angle glaucoma—medical, laser, or surgical? Surgery is the treatment of choice for open-angle glaucoma. *Arch Ophthalmol* 1998; **116**: 241–242.
- Jampel HD. Initial treatment for open-angle glaucoma—medical, laser, or surgical? Laser trabeculectomy is the treatment of choice for chronic open-angle glaucoma. *Arch Ophthalmol* 1998; **116**: 240–241.
- Higginbotham EJ. Initial treatment for open-angle glaucoma—medical, laser or surgical? Medication is the treatment of choice for chronic open-angle glaucoma. *Arch Ophthalmol* 1998; **116**: 239–240.
- Pliushko DG. Drug treatment of the initial stage of glaucoma. *Oftalmol Zh* 1981; **36**: 4–8.
- Khaw PT, Cordeiro MF, Cordiero MF. Towards better treatment of glaucoma. *Br Med J* 2000; **320**: 1619–1620.
- Rouland JF, Le Pen C, Gouveia PC, Berto P, Berdeaux G. Cost-minimisation study of dorzolamide versus brinzolamide in the treatment of ocular hypertension and primary open-angle glaucoma: in four European countries. *Pharmacoeconomics* 2003; **21**: 201–213.
- Ogawa T, Ogawa A, So K. Target intraocular pressure and risk factors for progression of visual field loss in primary

- open-angle glaucoma. *Nippon Ganka Gakkai Zasshi* 2002; **106**: 488–493.
- 33 The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. The AGIS Investigators. *Am J Ophthalmol* 2000; **130**: 429–440.
- 34 Briggs MC, Jay JL. Age over 46 years does not affect the pressure lowering effect of trabeculectomy in primary open angle glaucoma. *Br J Ophthalmol* 1999; **83**: 280–284.
- 35 Ustundag C, Diestelhorst M. Effect of mitomycin C on aqueous humor flow, flare and intraocular pressure in eyes with glaucoma 2 years after trabeculectomy. *Graefes Arch Clin Exp Ophthalmol* 1998; **236**: 734–738.
- 36 Wilson RP, Steinmann WC. Use of trabeculectomy with postoperative 5-fluorouracil in patients requiring extremely low intraocular pressure levels to limit further glaucoma progression. *Ophthalmology* 1991; **98**: 1047–1052.
- 37 Saiz A, Alcuaz A, Maquet JA, de la Fuente F. Pressure-curve variations after trabeculectomy for chronic primary open-angle glaucoma. *Ophthalmic Surg* 1990; **21** (Suppl 11): 799–801.
- 38 Migdal C, Gregory W, Hitchings R. Long-term functional outcome after early surgery compared with laser and medicine in open-angle glaucoma. *Ophthalmology* 1994; **101**: 1651–1656.
- 39 Watson PG, Barnett MF, Parker V, Haybittle J. A 7 year prospective comparative study of three topical beta blockers in the management of primary open angle glaucoma. *Br J Ophthalmol* 2001; **85**: 962–968.
- 40 Watson PG. Latanoprost. Two years' experience of its use in the United Kingdom. Latanoprost Study Group. *Ophthalmology* 1998; **105**: 82–87.
- 41 Alm A, Camras CB, Watson PG. Phase III latanoprost studies in Scandinavia, the United Kingdom and the United States. *Surv Ophthalmol* 1997; **41**(Suppl 2): S105–S110.
- 42 Chen TC, Wilensky JT, Viana MA. Long-term follow-up of initially successful trabeculectomy. *Ophthalmology* 1997; **104**: 1120–1125.
- 43 Suzuki R, Dickens CJ, Iwach AG, Hoskins Jr HD, Hetherington Jr J, Juster RP et al. Long-term follow-up of initially successful trabeculectomy with 5-fluorouracil injections. *Ophthalmology* 2002; **109**: 1921–1924.
- 44 Niesel P, Flammer J. Correlations between intraocular pressure, visual field and visual acuity, based on 11 years of observations of treated chronic glaucomas. *Int Ophthalmol* 1980; **3**: 31–35.
- 45 Flammer J, Eppler E, Niesel P. Quantitative perimetry in the glaucoma patient without local visual field defects. *Graefes Arch Clin Exp Ophthalmol* 1982; **219**: 92–94.
- 46 Asrani S, Zeimer R, Wilensky J, Gieser D, Vitale S, Lindenmuth K. Large diurnal fluctuations in intraocular pressure are an independent risk factor in patients with glaucoma. *J Glaucoma* 2000; **9**: 134–142.
- 47 Medeiros FA, Pinheiro A, Moura FC, Leal BC, Susanna R Jr. Intraocular pressure fluctuations in medical versus surgically treated glaucomatous patients. *J Ocul Pharmacol Ther* 2002; **18**: 489–498.
- 48 Orzalesi N, Rossetti I, Bottoli A, Invernizzi T, Fumagalli E, Fogagnolo P. Comparison of latanoprost, brimonidine and a fixed combination of timolol and dorzolamide on circadian intraocular pressure in patients with primary open-angle glaucoma and ocular hypertension. *Acta Ophthalmol Scand Suppl* 2002; **236**: 55.
- 49 Norell S. Medication behaviour. A study of outpatients treated with pilocarpine eye drops for primary open-angle glaucoma. *Acta Ophthalmol Suppl* 1980; (Suppl 143): 1–28.
- 50 Norell SE. Improving medication compliance: a randomised clinical trial. *Br Med J* 1979; **2**: 1031–1033.
- 51 Kosoko O, Quigley HA, Vitale S, Enger C, Kerrigan L, Tielsch JM. Risk factors for noncompliance with glaucoma follow-up visits in a residents' eye clinic. *Ophthalmology* 1998; **105**: 2105–2111.
- 52 Rotchford AP, Murphy KM. Compliance with timolol treatment in glaucoma. *Eye* 1998; **12**(Part 2): 234–236.
- 53 Fingeret M, Schuettenberg SP. Patient drug schedules and compliance. *J Am Optom Assoc* 1991; **62**: 478–480.
- 54 Granstrom PA. Progression of visual field defects in glaucoma. Relation to compliance with pilocarpine therapy. *Arch Ophthalmol* 1985; **103**: 529–531.
- 55 Norell SE. Improving medication compliance: a randomised clinical trial. *Br Med J* 1979; **2**: 1031–1033.
- 56 Konstas AG, Maskaleris G, Gratonidis S, Sardelli C. Compliance and viewpoint of glaucoma patients in Greece. *Eye* 2000; **14**(Part 5): 752–756.
- 57 Patel SC, Spaeth GL. Compliance in patients prescribed eyedrops for glaucoma. *Ophthalmic Surg* 1995; **26**: 233–236.
- 58 Kass M, Meltzer D, Gordon M. A miniature compliance monitor for eyedrop medication. *Arch Ophthalmol* 1984; **102**: 1550–1554.
- 59 Reardon G, Schwartz G, Mozaffari E, e. Patient persistency with pharmacotherapy in the management of glaucoma. *Eur J Ophthalmol* 2003; **13**(Suppl 4): 52.
- 60 Diestelhorst M, Schaefer C, Beusterien K, Plante K, Fain J, Mozaffari E et al. Persistency and clinical outcomes associated with latanoprost and beta-blocker monotherapy: evidence from a European retrospective cohort study. *Eur J Ophthalmol* 2003; **13**(Suppl 4): S21–9.
- 61 Beck AD, Grossniklaus HE, Hubbard B, Saperstein D, Hauptert CL, Margo CE. Pathologic findings in late endophthalmitis after glaucoma filtering surgery. *Ophthalmology* 2000; **107**: 2111–2114.
- 62 Freedman J, Gupta M, Bunke A. Endophthalmitis after trabeculectomy. *Arch Ophthalmol* 1978; **96**: 1017–1018.
- 63 Krzystolik MG, Ciulla TA, Topping TM, Baker AS. Exogenous Aspergillus niger endophthalmitis in a patient with a filtering bleb. *Retina* 1997; **17**: 461–462.
- 64 Higginbotham EJ, Stevens RK, Musch DC, Karp KO, Lichter PR, Bergstrom TJ et al. Bleb-related endophthalmitis after trabeculectomy with mitomycin C. *Ophthalmology* 1996; **103**: 650–656.
- 65 Freedman SF, McCormick K, Cox TA. Mitomycin C-augmented trabeculectomy with postoperative wound modulation in pediatric glaucoma. *J AAPOS* 1999; **3**: 117–124.
- 66 Mandal AK, Bagga H, Nutheti R, Gothwal VK, Nanda AK. Trabeculectomy with or without mitomycin-C for paediatric glaucoma in aphakia and pseudophakia following congenital cataract surgery. *Eye* 2003; **17**: 53–62.
- 67 Azuara-Blanco A, Katz LJ. Dysfunctional filtering blebs. *Surv Ophthalmol* 1998; **43**: 93–126.
- 68 Ayyala RS, Bellows AR, Thomas JV, Hutchinson BT. Bleb infections: clinically different courses of 'blebitis' and endophthalmitis. *Ophthalmic Surg Lasers* 1997; **28**: 452–460.
- 69 Kresloff MS, Castellari AA, Zarbin MA. Endophthalmitis. *Surv Ophthalmol* 1998; **43**: 193–224.
- 70 Wolner B, Liebmann JM, Sassani JW, Ritch R, Speaker M, Marmor M. Late bleb-related endophthalmitis after

- trabeculectomy with adjunctive 5-fluorouracil. *Ophthalmology* 1991; **98**: 1053–1060.
- 71 Greenfield DS, Suner IJ, Miller MP, Kangas TA, Palmberg PF, Flynn HW, Jr. Endophthalmitis after filtering surgery with mitomycin. *Arch Ophthalmol* 1996; **114**: 943–949.
- 72 Ishida M, Takeuchi S. Vitrectomy for the treatment of expulsive hemorrhage. *Jpn J Ophthalmol* 2000; **44**: 571.
- 73 Tuli SS, WuDunn D, Ciulla TA, Cantor LB. Delayed suprachoroidal hemorrhage after glaucoma filtration procedures. *Ophthalmology* 2001; **108**: 1808–1811.
- 74 Edmunds B, Thompson JR, Salmon JF, Wormald RP. The National Survey of Trabeculectomy. III. Early and late complications. *Eye* 2002; **16**: 297–303.
- 75 Anderson D. Normal tension glaucoma study. Collaborative normal tension glaucoma study. *Curr Opin Ophthalmol* 2003; **14**: 86–90.
- 76 Shaarawy T, Karlen M, Schnyder C, Achache F, Sanchez E, Mermoud A. Five-year results of deep sclerectomy with collagen implant. *J Cataract Refract Surg* 2001; **27**: 1770–1778.
- 77 Ambresin A, Borruat FX, Mermoud A. Recurrent transient visual loss after deep sclerectomy. *Arch Ophthalmol* 2001; **119**: 1213–1215.
- 78 Chiselita D. Non-penetrating deep sclerectomy versus trabeculectomy in primary open-angle glaucoma surgery. *Eye* 2001; **15**: 197–201.
- 79 El Sayyad F, Helal M, El-Kholify H, Khalil M, El-Maghraby A. Nonpenetrating deep sclerectomy versus trabeculectomy in bilateral primary open-angle glaucoma. *Ophthalmology* 2000; **107**: 1671–1674.
- 80 Gandolfi S, Cimino L. Deep sclerectomy without absorbable implants and with unsutured scleral flap: prospective, randomized 2-year clinical trial vs trabeculectomy with releasable sutures. *Conference Proceedings*. Fort Lauderdale, USA, 2000.
- 81 Mermoud A, Schnyder CC, Sickenberg M, Chiou AG, Hediguer SE, Faggioni R. Comparison of deep sclerectomy with collagen implant and trabeculectomy in open-angle glaucoma. *J Cataract Refract Surg* 1999; **25**: 323–331.
- 82 Carassa R. Viscocanalostomy versus trabeculectomy: a 12 months prospective randomized study. *Conference Proceedings*. Boston, USA, 2000.
- 83 O'Brart DP, Rowlands E, Islam N, Noury AM. A randomised, prospective study comparing trabeculectomy augmented with antimetabolites with a viscocanalostomy technique for the management of open angle glaucoma uncontrolled by medical therapy. *Br J Ophthalmol* 2002; **86**: 748–754.
- 84 Gordon MO, Beiser JA, Brandt JD, Heuer DK, Higginbotham EJ, Johnson CA et al. The Ocular Hypertension Treatment Study: baseline factors that predict the onset of primary open-angle glaucoma. *Arch Ophthalmol* 2002; **120**: 714–720.
- 85 Cvenkel B, Ihan A. Ocular surface changes induced by topical antiglaucoma monotherapy. *Ophthalmologica* 2002; **216**: 175–179.
- 86 Costagliola C, Prete AD, Incorvaia C, Fusco R, Parmeggiani F, Di Giovanni A. Ocular surface changes induced by topical application of latanoprost and timolol: a short-term study in glaucomatous patients with and without allergic conjunctivitis. *Graefes Arch Clin Exp Ophthalmol* 2001; **239**: 809–814.
- 87 Watson PG, Jakeman C, Ozturk M. The complications of trabeculectomy (a 20-year follow-up). *Eye* 1990; **4**: 425–438.
- 88 Moltano A, Bosma N, Kittelson J. Otago glaucoma surgery outcome study: long-term results of trabeculectomy—1976 to 1995. *Ophthalmology* 2003; **106**: 1742–1750.
- 89 Broadway D, Grierson I, O'Brien C, Hitchings R. Adverse effects of topical antiglaucoma medications. II. The outcome of filtration surgery. *Arch Ophthalmol* 1994; **112**: 1446–1454.
- 90 Kansal S, Moster MR, Gomes MC, Schmidt Jr CM, Wilson RP. Patient comfort with combined anterior sub-Tenon's, topical, and intracameral anesthesia versus retrobulbar anesthesia in trabeculectomy, phacotrabeculectomy, and aqueous shunt surgery. *Ophthalmic Surg Lasers* 2002; **33**: 456–462.
- 91 Sauder G, Jonas JB. Topical anesthesia for penetrating trabeculectomy. *Graefes Arch Clin Exp Ophthalmol* 2002; **240**: 739–742.
- 92 Vicary D, McLennan S, Sun XY. Topical plus subconjunctival anesthesia for phacotrabeculectomy: one year follow-up. *J Cataract Refract Surg* 1998; **24**: 1247–1251.
- 93 Farrell TA. Minimizing the systemic effects of glaucoma medications. *Geriatrics* 1991; **46**, 61–64, 73.
- 94 Fraunfelder FT, Meyer SM. Systemic side effects from ophthalmic timolol and their prevention. *J Ocul Pharmacol* 1987; **3**: 177–184.
- 95 Bourgeois JA. Depression and topical ophthalmic beta adrenergic blockade. *J Am Optom Assoc* 1991; **62**: 403–406.
- 96 Waldock A, Snape J, Graham CM. Effects of glaucoma medications on the cardiorespiratory and intraocular pressure status of newly diagnosed glaucoma patients. *Br J Ophthalmol* 2000; **84**: 710–713.
- 97 Leibowitz HM, Krueger DE, Maunder LR, Milton RC, Kini MM, Kahn HA et al. The Framingham Eye Study monograph: an ophthalmological and epidemiological study of cataract, glaucoma, diabetic retinopathy, macular degeneration, and visual acuity in a general population of 2631 adults, 1973–1975. *Surv Ophthalmol* 1980; **24**: 335–610.
- 98 Burrows B, Barbee RA, Cline MG, Knudson RJ, Lebowitz MD. Characteristics of asthma among elderly adults in a sample of the general population. *Chest* 1991; **100**: 935–942.
- 99 Kaiser HJ, Flammer J, Stumpf D, Hendrickson P. Longterm visual field follow-up of glaucoma patients treated with beta-blockers. *Surv Ophthalmol* 1994; **38**(Suppl): S156–S159.
- 100 Orzalesi N, Rossetti I, Bottoli A, Invernizzi T, Fumagalli E, Fogagnolo P. Comparison of latanoprost, brimonidine and a fixed combination of timolol and dorzolamide on circadian intraocular pressure in patients with primary open-angle glaucoma and ocular hypertension. *Acta Ophthalmol Scand Suppl* 2002; **236**: 55.
- 101 Arieta C, Amaral M, Matuda E, Crosta C, Carvalho Moreira FD, Jose N. Dorzolamide x Apraclonidine in the prevention of the intraocular pressure spike after Nd:YAG laser posterior capsulotomy. *Curr Eye Res* 2002; **25**: 237–241.
- 102 Day DG, Schacknow PN, Wand M, Sharpe ED, Stewart JA, Leech J et al. Timolol 0.5%/dorzolamide 2% fixed combination vs timolol maleate 0.5% and unoprostone 0.15% given twice daily to patients with primary open-angle glaucoma or ocular hypertension. *Am J Ophthalmol* 2003; **135**: 138–143.
- 103 Honrubia FM, Larsson LI, Spiegel D. A comparison of the effects on intraocular pressure of latanoprost 0.005% and the fixed combination of dorzolamide 2% and timolol 0.5% in patients with open-angle glaucoma. *Acta Ophthalmol Scand* 2002; **80**: 635–641.

- 104 Simmons ST. Efficacy of brimonidine 0.2% and dorzolamide 2% as adjunctive therapy to beta-blockers in adult patients with glaucoma or ocular hypertension. *Clin Ther* 2001; **23**: 604–619.
- 105 Strohmaier K, Snyder E, DuBiner H, Adamsons I. The efficacy and safety of the dorzolamide-timolol combination versus the concomitant administration of its components. Dorzolamide-Timolol Study Group. *Ophthalmology* 1998; **105**: 1936–1944.
- 106 Strahlman E, Tipping R, Vogel R. A six-week dose–response study of the ocular hypotensive effect of dorzolamide with a one-year extension. Dorzolamide Dose–Response Study Group. *Am J Ophthalmol* 1996; **22**(2): 183–194.
- 107 Vold SD, Riggs WL, Jackimiec J. Cost analysis of glaucoma medications: a 3-year review. *J Glaucoma* 2002; **11**: 354–358.
- 108 Vold SD, Wiggins DA, Jackimiec J. Cost analysis of glaucoma medications. *J Glaucoma* 2000; **9**: 150–153.
- 109 Kobelt G. Health economics, economic evaluation, and glaucoma. *J Glaucoma* 2003; **11**: 531–539.
- 110 Gandolfi S, Quaranta L, Cimino L, Bettelli S. Deep sclerectomy versus trabeculectomy. Prospective Randomized Clinical trial. 4-year interim analysis. *Proceedings of the Second International Congress on Glaucoma Surgery*. Luxor, Egypt, 2003.