

Recent Advances in the Treatment of Glaucoma – The Need to Maintain Intraocular Pressure Over 24 Hours

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Abstract

In the treatment of glaucoma, maintenance of intraocular pressure (IOP) over a 24-hour period is of considerable importance. Some glaucoma medications do not sustain low IOP, allowing it to fluctuate with the potential to damage the optic nerve, leading to blindness. Several topically applied prostaglandins have become available, which have the advantage of maintaining 24-hour control. With these developments, it is timely to consider the relative merits of glaucoma surgery compared with medical treatments including eye drops and systemic medications, and which of the medications provides the most benefit to patients. Medications that control IOP over 24-hour periods require monitoring methods to assess their efficacy. Most determination procedures are carried out in a clinician or ophthalmologist's office and provide only a single measure at one point in time. These require fixed equipment and cannot provide an overview of IOP variation over time or indicate whether treatments are providing continuous control. A development to address this monitoring need is the Sensimed Triggerfish®. This system uses a soft contact lens with an embedded pressure-sensing chip and associated monitoring equipment to provide multiple readings over a 24-hour period. The initial clinical experience with this device led to an immediate treatment change in two-thirds of patients. A clinical trial evaluating the efficacy of a new prostaglandin treatment, tafluprost, over 24 hours using the contact lens IOP monitoring system is currently underway. Based on the initial data, tafluprost effectively reduces IOP during the full 24-hour period, further supporting its use in the treatment of glaucoma.

Keywords

Alpha-agonist, beta-adrenergic blocker, glaucoma, intraocular pressure, prostaglandin, tafluprost

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Elevated intraocular pressure (IOP) is the most important and the only modifiable, known risk factor for glaucoma^{1–8} and consequently, most therapeutic interventions are directed at its modification.^{1–31} Both the peak levels^{2–4,18,21} and fluctuations^{15,19,23} have been known to impact disease development and progression, even in cases with statistically normal pressures.^{1,2,6,9,10,15,20,30} Most authors concur that IOP peaks tend to be associated with visual field (VF) decline,^{10,22,31} but whether or not IOP fluctuation is a risk factor for progression of glaucoma is still controversial.^{10,11,13–16,19,23,26} This article is an attempt to elucidate the role of 24-hour IOP control and its relevance to current glaucoma practice, as well as emerging therapeutic and diagnostic techniques.

The Efficacy of Intraocular Pressure Reduction

The efficacy of IOP reduction in retarding the progression of glaucoma over a wide spectrum of disease – from low to high IOPs and from early to advanced disease – has been conclusively demonstrated.^{2–4,18,21}

In the Advanced glaucoma intervention study (AGIS), long-term IOP fluctuation was associated with VF progression in subjects with low mean IOP but not in patients with high mean IOP.¹⁵ Diurnal and

long-term IOP fluctuations were not found to be significant risk factors for progression of early glaucoma or ocular hypertension (OHT) in the Early manifest glaucoma trial (EMGT),¹³ the Malmö ocular hypertension study,¹² or the Ocular hypertension treatment study (OHTS).²³

Lowering IOP by at least 18% (mean) from baseline has been shown to result in at least a 40% reduction in rates of worsening of glaucoma over five years.^{2,5,18,21,28}

The mean IOPs of those who progress to blindness, however, have been reported to not differ from those who do not, with the severity of glaucoma at the time of diagnosis and the range of IOPs found during follow-up (long-term IOP fluctuation) being important predictive factors.^{17,27}

Evaluation of patients treated surgically who achieved low IOPs found that the group with lower IOP fluctuation demonstrated significantly better preservation of the VF than the group with higher fluctuation, with similar mean IOP and number of glaucoma medications.^{19,23}

IOP peaks (and thus higher ranges) during periods of noncompliance or loss of IOP control may therefore, be held indirectly responsible for glaucomatous progression in patients who otherwise have good IOP control.

Asrani et al. reported a strong correlation between fluctuation/variation and VF progression. However, the study was flawed in its design with assessment of IOP and VF progression being cross-sectional and longitudinal, respectively. Also, IOP was measured using home tonometry and the IOP fluctuation during a particular five-day period may not be considered indicative of fluctuation/variation in that same patient over several years during which period VF progression may or may not have occurred.

On the other hand, it must also be remembered that most of the evidence regarding IOP and fluctuation and variation from large, prospective, multicentre, randomised clinical trials is post-hoc analysis. These studies did not necessarily address initial study questions and thus should not, perhaps, be given the same status as analysis from these studies, which reflected the primary study goals.^{1,2,4-7,13,15,18,21,24,32}

In spite of inconclusive evidence to its relevance to glaucoma progression, there is considerable interest in the fluctuation of IOP. In the absence of conclusive evidence as to what is more damaging to the retinal ganglion cells and optic nerves – peak IOP, mean IOP or fluctuating IOP – the management of glaucoma should aim at modifying all three parameters. Moreover, studies to date on glaucoma progression have evaluated the impact of IOP fluctuations either between visits or only with limited daytime IOP measurements. The impact of 24-hour IOP fluctuations on glaucoma progression has still not been studied prospectively.³³

Twenty-four-hour Intraocular Pressure Control and Glaucoma Therapy – Assessment of Anti-glaucoma Medication in Terms of Intraocular Pressure Fluctuations Combination Therapy Versus Monotherapy

A recent meta-analysis for the IOP fluctuations revealed a statistical difference in the reduction of fluctuations from no treatment among all individual monotherapy treatments.³⁴ No further decrease in fluctuations was reported with addition of a drug from monotherapy, except in patients with pseudoexfoliative glaucoma. This finding requires careful attention in planning surgical treatment of glaucoma in patients with glaucoma progression in spite of adequate IOP control.^{34,35}

Evening and morning dosing of prostaglandins were noted to provide statistically equivalent changes in fluctuations from prior therapy.

In addition, exfoliative glaucoma patients demonstrated a statistically greater reduction in fluctuations versus primary open-angle glaucoma (POAG) per se and adding a medicine in was seen to result in a statistically significant decrease in fluctuation, but the addition of a third medication had no impact on fluctuation in these patients.³⁴

A post-hoc analysis of data²⁹ from two randomised, double-masked trials,^{36,37} revealed that significantly fewer patients treated with fixed combination latanoprost/timolol had a high diurnal IOP fluctuation after six months compared with those receiving either latanoprost or timolol monotherapy. The effect of non-fixed combination was not studied, however. The extent to which the somewhat lower mean

baseline IOP level and larger mean baseline IOP fluctuation in the fixed combination group contributed to these differences is unknown. Carbonic anhydrase inhibitor added as adjunctive therapy to beta-blocker significantly reduced IOP levels at all measurement time points in patients with POAG or exfoliation glaucoma.³⁸ The short-term IOP fluctuation with the combination (timolol plus dorzolamide/brinzolamide) has been found to be comparable with the use of a single-agent prostaglandin analogue by several authors.^{28,39-41}

Konstas et al. reported that the 24-hour diurnal IOP is lowered more, by a small but statistically significant amount, with timolol dorzolamide fixed dose combination, compared with latanoprost in POAG and OHT patients of Greek origin.⁴⁰ A fixed-combination prostaglandin and beta-blocker used once daily in the evening was reported to reduce mean daytime diurnal IOP more effectively than concomitant alpha-agonists and beta-blocker administered twice daily in patients with POAG or OHT.⁴²

Specific Medications

Prostaglandin Analogues

Prostaglandin analogues have been found to control short-term IOP fluctuation in patients more effectively than other single agents,⁴⁴⁻⁴⁹ although this finding is not consistent.^{50,51}

It has also been reported that topical medications that enhance outflow, such as prostaglandins, may provide better IOP stabilisation under stressful conditions than those that decrease aqueous humour production.^{52,53} This reduction from baseline was found to be maintained over the 24-month treatment period, with no sign of upward drift in IOP and with no difference in the reduction in IOP after 24 months with morning or evening dosing.⁵⁴

Beta-blockers

Beta-adrenergic blockers have been shown to control short-term IOP fluctuation but not as well as prostaglandins and carbonic anhydrase inhibitors.^{54,58,59} Topical beta-blockers appear to have minimal effects on the production of aqueous humour during the nocturnal period, with a once-daily beta-blocker and a prostaglandin both effectively lowering IOP during the diurnal period (7 am to 11 pm), but only the prostaglandin reduced IOP during the nocturnal period. Previous studies have shown that beta-blockers have limited efficacy in lowering IOP at night, whereas prostaglandin analogues demonstrate a sustained 24-hour IOP-lowering effect.^{33,44-47,49}

Alpha-agonists

Alpha-adrenergic agonists have been shown to control short-term IOP fluctuation less effectively than the prostaglandins and more effectively than beta-blockers. But like beta-blockers, they have been found to be less effective at night.^{40,61}

Carbonic Anhydrase Inhibitors

Carbonic anhydrase inhibitors have been found to be less effective than prostaglandin analogues in lowering IOP during a 24-hour period, but, unlike the beta-blocker, the carbonic anhydrase inhibitor has been reported to maintain efficacy during the night.⁶²

Compliance and Intraocular Pressure Fluctuation

Poor adherence and compliance are often encountered in clinical practice and therefore, the assessment of any therapeutic modality must be able to account for missed doses. The prospective, open-label

study in patients with open-angle glaucoma or ocular hypertension, in this regard, evaluated the diurnal and nocturnal IOP reductions after omission of up to two doses of a prostaglandin analogue. The IOP-lowering impact of the prostaglandin analogue was found to be attenuated in the diurnal period but sustained at night.⁶³

Surgeries and Intraocular Pressure Fluctuation

Surgery has the potential to reduce IOP more effectively than drugs, as it can lower the IOP to low teens, achieve long-term IOP reduction, minimise IOP fluctuations and lower the cost with minimal systemic side effects. The major drawbacks are potentially devastating, albeit rare, ocular side effects.^{64,65}

Surgery Versus Medication

Laser Trabeculoplasty – Argon Laser Trabeculoplasty

Argon laser trabeculoplasty was reported to decrease mean short-term IOP fluctuation by 30% when compared to IOP before surgery.⁶⁶⁻⁶⁸ However, such a reduction may not reflect any significant change in percentage reduction relative to IOP peak or trough since these values also are reduced by the treatment.

Laser Trabeculoplasty – Selective Laser Trabeculoplasty

A pilot study by Kothy et al. revealed that although none of the 26 eyes showed mean diurnal IOP reduction of 20% or more, selective laser trabeculoplasty (SLT) resulted in a significant decrease in the amplitude of diurnal IOP fluctuation. A significant decrease was seen in mean IOP at the six-month visit and in IOP fluctuation at both three- and six-month visits in the 15 eyes that did not require supplemental IOP-lowering medication, compared with baseline values.⁶⁹

A comparison of the effect of 360 and 180 degrees of SLT treatment as a primary therapy on the inter-visit IOP fluctuation in patients followed up for a period of six months to two years revealed that the percentage of eyes with inter-visit IOP fluctuation (SD ≤ 2 mmHg) was significantly greater in the former (86%) than in the latter (52%). The odds of achieving IOP fluctuation ≤ 2 mmHg were 5.7 times greater with 360 degrees than with 180-degree SLT.⁷⁰

A randomised, masked, prospective comparison of the effect of SLT on IOP control and diurnal tension curves (DTCs) of patients with open-angle glaucoma (OAG) and OHT to the effect of latanoprost revealed that the success in fluctuation reduction was 50% for SLT and 83% for latanoprost. SLT significantly reduced the IOP fluctuation, but latanoprost was more effective (2.5mmHg versus 3.6mmHg, respectively).⁷¹

Comparison of Surgery and Medical Therapy

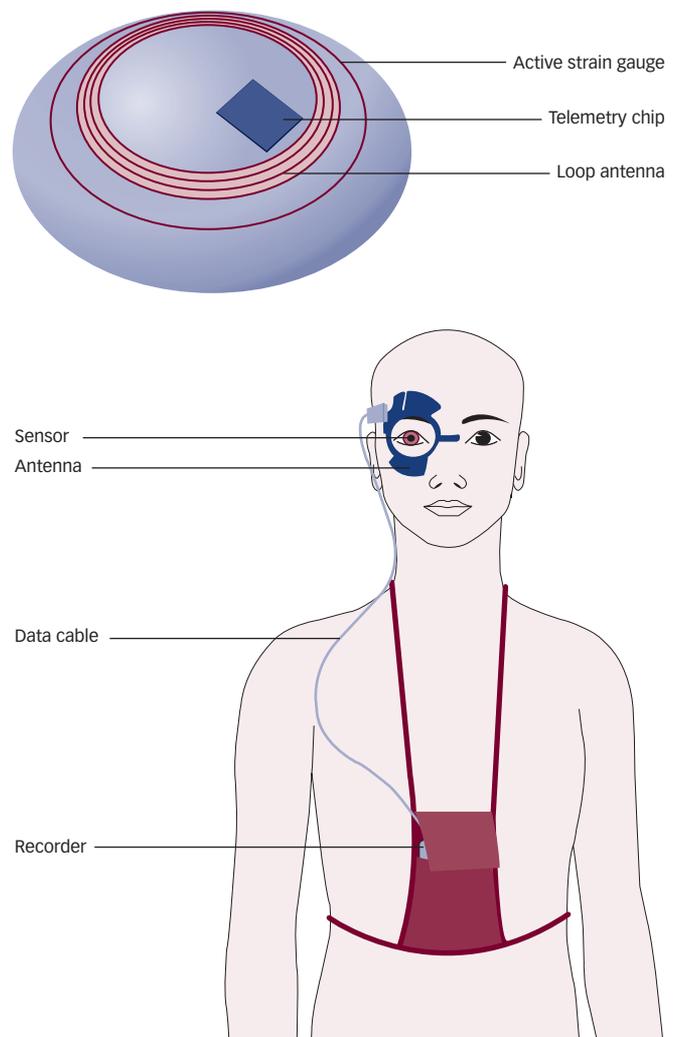
Various authors have reported that short-term IOP fluctuation is better controlled with surgical therapy in comparison to medication.^{64,65,72-76}

Incisional Surgeries

Trabeculectomy

Medeiros et al. compared the diurnal IOP fluctuation and IOP rise after a water drinking test (WDT) between medical treatment and trabeculectomy. No statistically significant difference in mean IOP was found. The IOP fluctuation during the DTC was significantly greater in the former as compared with the surgical group (3.2 ± 1.5 mmHg versus 2.2 ± 1.7 mmHg). Additionally, the IOP peak and fluctuation during the WDT was significantly greater in the medically treated group compared with the surgically treated group.⁷⁶

Figure 1: The Triggerfish® System



Reproduced with permission from Sensimed AG.⁸⁴

A well-functioning trabeculectomy was found to result in a statistically lower mean, peak and range of IOP for the 24-hour day than the maximum-tolerated medical therapy in patients with advanced glaucoma. The 24-hour range of IOP was 2.3 ± 0.8 mmHg for the surgical group and 4.8 ± 2.3 mmHg for the medical group, with the majority of peak IOPs occurring outside of normal office hours.⁷²

Mansouri et al.⁷⁴ compared the quality of diurnal IOP control and IOP fluctuation during a WDT in a group of 60 POAG patients, 20 patients treated with latanoprost as monotherapy treatment and 40 with surgery without adjuvant medical therapy (20 patients each with trabeculectomy and deep sclerectomy with collagen implant, [DSCI]). The authors found that mean IOP during the diurnal period was significantly lower for trabeculectomy (10.1mmHg) and DSCI (13.7mmHg) than latanoprost (15.7mmHg), but the IOP fluctuation was similar between the groups. During the WDT, IOP change from baseline to peak was significantly greater for the latanoprost group (5.2mmHg) than the trabeculectomy group (2.4mmHg; $p=0.0002$).

Deep Sclerectomy

Mansouri et al.⁷⁴ reported in the aforementioned study that the mean IOP during the DTC differed significantly between the treatment groups and variation in IOP throughout the day was significant, but

this variation was comparable. Post-hoc comparison disclosed a lower average IOP during DTC in the trabeculectomy group compared with the other two groups, but the difference between DSCI and latanoprost was not significant. During the WDT, the difference in IOP change from baseline to peak was borderline significant between the latanoprost (5.2mmHg) and DSCI group (3.8mmHg).

Twenty-four-hour Intraocular Pressure Recording – Newly Available Technology

The newly available Sensimed Triggerfish® device is a disposable silicone contact lens with an embedded micro-electromechanical system, which measures changes in corneal curvature induced by variations in IOP. An antenna, mounted around the eye, receives the data, which are then transmitted to a recorder (see *Figure 1*). Measurements are taken every 600 seconds for a duration of 60 seconds, giving a total of 144 measurements over a 24-hour period. The results obtained are presented in an arbitrary unit and not mmHg. The initial clinical experience with the Triggerfish device has yielded a good safety and tolerability profile.

The observed corneal changes compared well with the published literature on contact lens complications. The data obtained were highly relevant and led to an immediate treatment change in two-thirds of patients. The device has the potential to improve clinical care of glaucoma patients in the same way that continuous blood pressure monitoring or home measurements of blood glucose levels have done for patients with high blood pressure or diabetes. Important questions need to be answered such as the effect of night-time changes in corneal thickness and ocular movements on the precision of the device.⁷⁵

A clinical trial evaluating the efficacy of tafuprost (Taflotan®, Saflutan®), the recently launched prostaglandin analogue, over 24 hours using the contact lens IOP monitoring system is currently underway at the University of Geneva. Based on the initial data, tafuprost effectively reduces IOP during the full 24-hour period.

Implications in Clinical Practice

IOP is not a static number; instead, it tends to fluctuate throughout the 24 hours. It is also clear that mean IOP is a strong predictor of glaucomatous damage. A desired therapeutic target is therefore a uniform reduction of IOP throughout the 24 hours.

It has been reported that IOP measurements, using modified diurnal curve (8 am to 5 pm) testing in glaucoma patients controlled at their target IOP, were significantly higher than isolated office IOP measurements. Monitoring the 24-hour IOP can, in some instances, also provide useful insight and lead to changes in the management of glaucoma patients.^{38,73,75,77–83} Significantly higher peak pressures and wider fluctuation have been reported outside the typical office hours on 24-hour IOP monitoring, resulting in augmentation of medical therapy, laser and/or surgery in significant proportions of the study cohort.^{75,77}

A 24-hour control of IOP can be potentially accomplished by optimal dosing and choice of medical therapy based on the intrinsic 24-hour IOP and aqueous humour flow rate pattern.

The setting of IOP measurements (e.g. office, sleep lab, etc.) and the number and timing of measurements obtained are all important factors in assessment of fluctuations of IOP. The World Glaucoma Association (WGA) guidelines advocate a minimum of IOP measurements at 8 am, 12 pm, 4 pm and 8 pm to assess its diurnal variation.

A clinically measurable target pressure for fluctuation, similar to mean pressures to prevent glaucomatous progression, is yet to be identified.

Conclusions

Reducing IOP is presently the most accepted and most practised evidence-based, therapeutic approach for glaucoma patients. Given that there is sufficient evidence that IOP fluctuation may impact progression, the aim of management of glaucoma thus, is to achieve a target IOP with minimal diurnal fluctuation. ■

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