

New Horizons in Glaucoma

Murray Fingeret, OD

Glaucoma Update

- Recent Advances in Therapy
 - Clinical Trials
 - OHTS, EMGT, AGIS, CNTGS
 - New Medications
 - Combination agents
 - Combigan (timolol-brimonidine)
 - Revised agents
 - Lumigan 0.01% (reduced concentration bimatoprost)
 - Generic Latanoprost
 - Saflutan – preservative free PG

Glaucoma Update

- Better understanding of disease pathophysiology
 - Ultrastructural - extracellular matrix, cell processes, cell-cell interaction, molecular biology
 - Risk factor assessment
 - IOP, age, race, heredity, corneal thickness
- New technologies
 - Structural assessment (OCT)
 - Functional assessment (FDT, HEP)

Glaucoma Update

- Evidence-based medicine
 - National Eye Institute clinical trials
 - Prospective cross-sectional and longitudinal studies
- New therapeutic approaches
 - Target IOP/Balancing efficacy, safety, and tolerability
 - Medications & Surgery
- What's else is new
 - New Medications
 - Blood Flow
 - Neuroprotection
 - Risk Assessment

The Impact of Clinical Trials on Glaucoma Management

- Questioning the role of IOP
 - Led to initiation of large, well-designed clinical trials
- Shift from practicing by tradition to that based upon evidence
- Does lowering IOP prevent or delay onset of glaucoma?
 - OHTS, EMGT, AGIS, CIGTS
- Does lowering IOP in newly diagnosed glaucoma slow progression of disease?

The Impact of Clinical Trials on Glaucoma Management

- Can Risk Factors be Identified?
 - Who is at highest risk of developing glaucoma or progressing to disabling visual loss?
- Clinical trials provide insight into many of these questions
- LOGTS – Low tension Glaucoma Treatment Study
 - Brimonidine neuroprotective, even without any IOP lowering
 - Timolol no help and possible harmful

**Protocol for Glaucoma Therapy
How Will This Model Change
in the Future?**

- 1st line PGs
- 2nd medication
 - Topical CAI or Beta Blocker or Alpha agonist
- 3rd Line
 - Fixed Combination agents
 - or
 - ALT/SLT
- How will this model vary in the future?

**Compliance and Glaucoma
Videotaped Evaluation of Eyedrop
Instillation in Glaucoma Patients with
Visual Impairment or Moderate to Severe
Visual Field Loss**

Ann L. Strenson, MD, MPH,^{1,2} James Kim, MD,^{1,2} David Green, MBA,¹ Colleen Profitt, MD,^{1,2}
Ann L. Rubin, MD,^{1,2}

Objective: Objectively evaluate the ability of visually impaired glaucoma patients to successfully administer a single drop into their eyes.

Design: Prospective observational study.

Participants: Seventy-two glaucoma patients with best-corrected visual acuity of 20/40 or worse, mean visual field (MD) of 10 degrees or worse, and moderate to severe visual field loss (VFL).

Measures and Main Results: Seventy-two glaucoma patients with best-corrected visual acuity of 20/40 or worse, mean MD of 10 degrees or worse, and moderate to severe VFL were included in the study. The mean age was 71.2 years (range 58-87 years). The mean duration of glaucoma was 10.1 years (range 1-30 years). The mean MD was 10.1 degrees (range 5-15 degrees). The mean VFL was 10.1 degrees (range 5-15 degrees). The mean number of drops administered was 1.4 (range 1-3). The mean number of attempts to administer a drop was 1.2 (range 1-3). The mean number of drops administered per eye was 0.7 (range 0-3). The mean number of attempts to administer a drop per eye was 0.6 (range 0-3). The mean number of drops administered per eye was 0.7 (range 0-3). The mean number of attempts to administer a drop per eye was 0.6 (range 0-3).

More than 90% of the subjects (192/204) had used eyedrops for >6 months, and were using a mean of 1.9±1.1 bottles of IOP-lowering medication. Despite this experience with previous eyedrop administration, only 71% were able to get any number of drops onto the ocular surface, even with multiple attempts. Only 52% of subjects were successful at instilling a single drop onto the ocular surface. This number further dropped to 39% when we altered our definition of “success” to subjects instilling just 1 eyedrop onto the eye, without touching the ocular surface. Subjects instilled a mean (standard deviation) of 1.4 (1.0) drops onto their eyes per application, using more than 1 attempt (1.2±0.6) to get a drop onto the eye. One quarter of the subjects instilled >1 drop. Table 3 provides details about number of drops used.

**Twenty-Four-Hour Pattern of Intraocular Pressure in
the Aging Population**

Ann L. Strenson, MD, MPH,^{1,2} James Kim, MD,^{1,2} David Green, MBA,¹ Colleen Profitt, MD,^{1,2}
Ann L. Rubin, MD,^{1,2}

Objective: To characterize the 24-hour pattern of intraocular pressure (IOP) in a sample of the aging human population.

Methods: Twenty-one healthy volunteers 50 to 69 years of age were housed in a sleep laboratory for 24 hours. Experimental conditions were strictly controlled with a 16-hour light period and an 8-hour dark period. Sleep was encouraged in the dark period. Intraocular pressure was measured using a pneumotonometer every 2 hours (total of 12 times). Measurements were taken in both the sitting position and the supine position during the light/wake period and only in the supine position during the dark period.

Results: When the sitting IOP data from the light/wake period and the supine IOP data from the dark period were considered, elevation and reduction of IOP occurred around the scheduled lights-off and lights-on transitions, respectively. Mean IOP in the dark period was significantly higher than mean IOP in the light/wake period. The trough appeared at the end of the light/wake period, and the peak appeared at the beginning of the dark period. The magnitude of trough-peak difference was 8.6 ± 0.8 mm Hg (mean ± SEM). Cosine fits of 24-hour IOP data showed a significant 24-hour rhythm. When IOP data from just the supine position were analyzed, the trough-peak IOP difference was 3.4 ± 0.7 mm Hg, with similar clock times for the trough and the peak. Cosine fits of supine IOP data showed no statistically significant 24-hour rhythm.

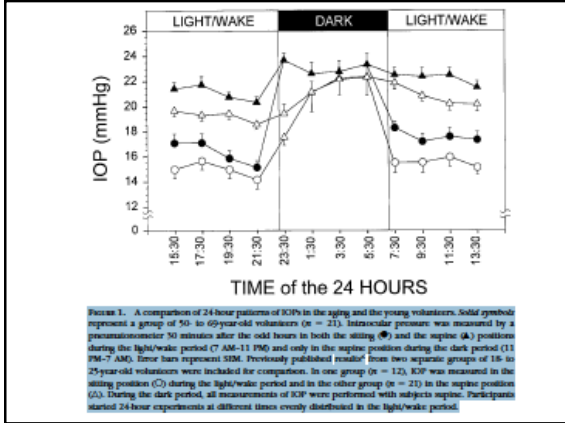
Conclusions: Nocturnal elevation of IOP occurred in this sample of the aging population. The trough of IOP appeared at the end of the light/wake period, and the peak appeared at the beginning of the dark period. The main factor in the nocturnal IOP elevation appeared to be the shift from daytime upright posture to supine posture at night. (*Invest Ophthalmol Vis Sci.* 1999;40:2912-2917)

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Comparing Diurnal and Nocturnal Effects of Brinzolamide and Timolol on Intraocular Pressure in Patients Receiving Latanoprost Monotherapy

John H. K. Liu, PhD, Felipe A. Naldini, MD, PhD, J. R. Ely, MD, Robert N. Weinreb, MD

Purpose: To compare the diurnal and nocturnal effects of brinzolamide and timolol on intraocular pressure (IOP) in patients already receiving monotherapy with latanoprost.

Design: Prospective, open-label, and crossover clinical trial.

Participants: Twenty-five patients with glaucoma or ocular hypertension (ages, 44–79 years) who were receiving treatment with 0.005% latanoprost once every evening.

Methods: Baseline data of 24-hour IOP were obtained in a sleep laboratory while patients were receiving latanoprost monotherapy. Measurements were taken every 2 hours in the sitting and supine positions during the 16-hour diurnal/wake period and in a supine position during the 8-hour nocturnal/sleep period. Patients were randomly assigned to receive an add-on treatment with either 1% brinzolamide 2 times per day or 0.5% timolol gel forming solution once every morning for 8 weeks, and then crossed over to receive the other add-on treatment. At the end of each add-on treatment period, 24-hour IOP data were collected.

Main Outcome Measures: Diurnal and nocturnal IOP means were compared among the baseline, the brinzolamide add-on treatment, and the timolol add-on treatments.

Results: During the diurnal period, the mean IOP under brinzolamide or timolol add-on treatment was significantly lower than the baseline IOP in both the sitting and supine positions. There was no statistical difference between the 2 add-on treatments. During the nocturnal period, the supine IOP under brinzolamide add-on treatment was significantly lower than both the baseline and the timolol add-on treatment. There was no difference in nocturnal IOP between the timolol add-on treatment and the baseline.

Conclusions: In patients already receiving the latanoprost monotherapy, adding brinzolamide or timolol significantly reduced IOP during the diurnal period. However, only the brinzolamide add-on treatment had an IOP-lowering efficacy during the nocturnal period.

Financial Disclosures: Proprietary or commercial disclosures may be found after the references. Ophthalmology 2009;118:449–454 © 2009 by the American Academy of Ophthalmology.

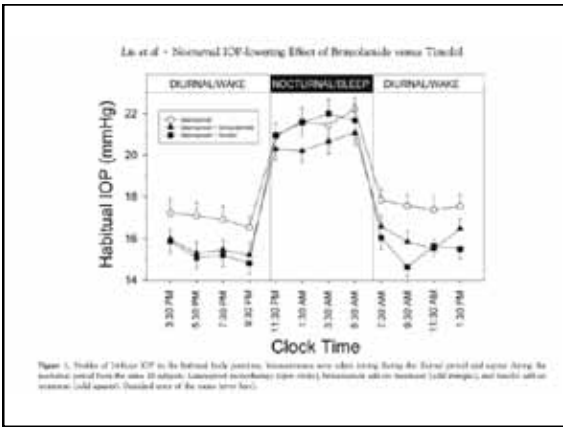


Figure 1. Profile of 24-hour IOP in the habitual body positions. Measurements were taken every 2 hours during the diurnal period and every 2 hours during the nocturnal period from the same 25 subjects. Latanoprost monotherapy (open circles), brinzolamide add-on treatment (filled triangles), and timolol add-on treatment (filled squares). (Detailed view of the same time here.)

Effect of Laser Trabeculoplasty on Nocturnal Intraocular Pressure in Medically Treated Glaucoma Patients

Alexander C. Lee, MD,¹ Sarah Masad, MD,¹ Robert N. Weinreb, MD,¹ David F. Kojak, MD,² John H. K. Liu, PhD¹

Purpose: To evaluate the effects of laser trabeculoplasty on 24-hour intraocular pressure (IOP) in a group of medically treated open-angle glaucoma patients.

Design: Prospective experimental study.

Participants: Eighteen open-angle glaucoma patients.

Methods: Laser trabeculoplasty (LTP) was performed on 28 eyes of 18 glaucoma patients. Twenty-four-hour IOP data were collected in a sleep laboratory before and 45 to 80 days after the procedure. Measurements of sitting and supine IOP were taken during the 16-hour diurnal/wake period, and measurements of supine IOP were taken during the 8-hour nocturnal/sleep period in 2-hour intervals.

Main Outcome Measures: Changes in the mean, peak, and range of IOP during the office-hour, diurnal, nocturnal, and 24-hour periods.

Results: Compared with the baseline, changes in the mean, peak, and range of IOP were not significant during the office-hour period and during the diurnal period in either the sitting or the supine position. The mean, peak, and range of IOP were reduced significantly during the nocturnal period in the supine position. Mean and peak 24-hour IOP were reduced significantly in the habitual body positions (sitting during the diurnal period and supine during the nocturnal period). The reduction of mean 24-hour IOP in the supine position also was significant.

Conclusions: In this group of medically treated open-angle glaucoma patients, laser trabeculoplasty reduced IOP more consistently during the nocturnal period than during the diurnal period. Ophthalmology 2009;118:650–656 © 2009 by the American Academy of Ophthalmology.

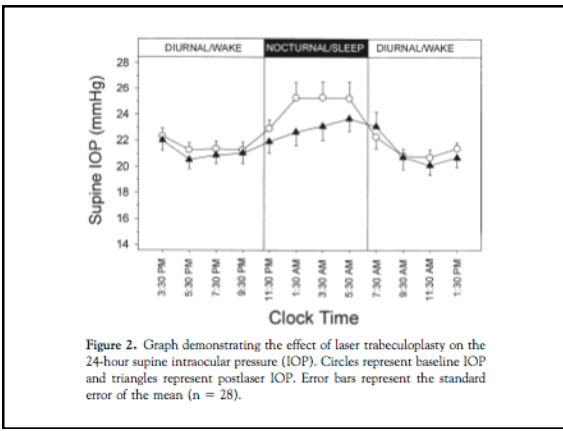


Figure 2. Graph demonstrating the effect of laser trabeculoplasty on the 24-hour supine intraocular pressure (IOP). Circles represent baseline IOP and triangles represent post-laser IOP. Error bars represent the standard error of the mean (n = 28).

Diurnal and Nocturnal Effects of Brimonidine Monotherapy on Intraocular Pressure

John H. K. Liu, PhD, Felipe A. Naldini, MD, PhD, J. R. Ely, MD, Robert N. Weinreb, MD

Purpose: To investigate the effect of brimonidine monotherapy on intraocular pressure (IOP) during the diurnal and nocturnal periods.

Design: Prospective, open-label, and crossover clinical trial.

Participants: Twenty-five patients with glaucoma or ocular hypertension (ages, 44–79 years) who were receiving treatment with 0.005% latanoprost once every evening.

Methods: Baseline data of 24-hour IOP were obtained in a sleep laboratory while patients were receiving latanoprost monotherapy. Measurements were taken every 2 hours in the sitting and supine positions during the 16-hour diurnal/wake period and in a supine position during the 8-hour nocturnal/sleep period. Patients were randomly assigned to receive an add-on treatment with either 0.1% brimonidine 2 times per day or 0.5% timolol gel forming solution once every morning for 8 weeks, and then crossed over to receive the other add-on treatment. At the end of each add-on treatment period, 24-hour IOP data were collected.

Main Outcome Measures: Diurnal and nocturnal IOP means were compared among the baseline, the brimonidine add-on treatment, and the timolol add-on treatments.

Results: During the diurnal period, the mean IOP under brimonidine or timolol add-on treatment was significantly lower than the baseline IOP in both the sitting and supine positions. There was no statistical difference between the 2 add-on treatments. During the nocturnal period, the supine IOP under brimonidine add-on treatment was significantly lower than both the baseline and the timolol add-on treatment. There was no difference in nocturnal IOP between the timolol add-on treatment and the baseline.

Conclusions: In patients already receiving the latanoprost monotherapy, adding brimonidine or timolol significantly reduced IOP during the diurnal period. However, only the brimonidine add-on treatment had an IOP-lowering efficacy during the nocturnal period.

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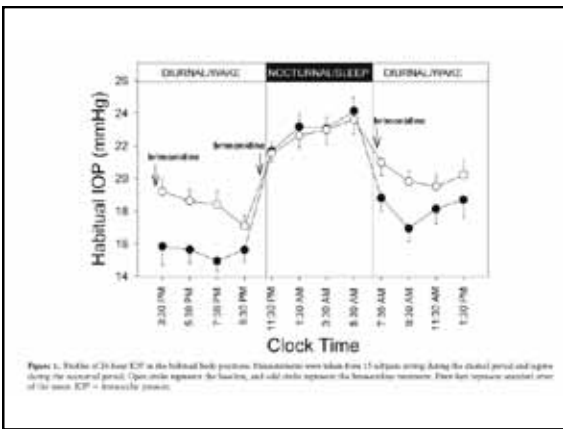


Figure 3. Profile of 24-hour IOP in the habitual body positions. Measurements were taken every 2 hours during the diurnal period and every 2 hours during the nocturnal period from the same 25 subjects. Latanoprost monotherapy (open circles), brimonidine add-on treatment (filled triangles), and timolol add-on treatment (filled squares). (Detailed view of the same time here.)

Cerebrospinal Fluid Pressure in Glaucoma A Prospective Study

Zaveri RM, MD,^{1,2} Jost B, MD,^{1,2} Gaoqing Tian, MD,³ Yi Zhou, MD,² Kr Ma, MD,¹ Shuang Li, MD,² Hongyan Wang, MD,² Bin Li, MD,¹ Xiaojun Zhang, MD,² Ningli Wang, MD²

Purpose: To assess whether a low cerebrospinal fluid pressure (CSF-P) is associated with open-angle glaucoma in eyes with normal intraocular pressure (IOP).

Design: Prospective, interventional study.

Participants: The study included 43 patients with open-angle glaucoma (14 with a normal IOP, and 29 with an elevated IOP) and 71 subjects without glaucoma.

Interventions: All patients underwent standardized ophthalmologic and neurologic examinations and measurement of lumbar CSF-P.

Main Outcome Measures: Cerebrospinal fluid pressure and IOP.

Results: Lumbar CSF-P was significantly ($P < 0.001$) lower in the normal IOP glaucoma group (9.8 ± 2.2 mmHg) than in the high IOP glaucoma group (11.7 ± 2.7 mmHg) or the control group (12.9 ± 1.0 mmHg). The trans-lamina cribrosa pressure difference (ICP minus CSF-P) was significantly ($P < 0.001$) higher in the normal IOP glaucoma group (8.8 ± 3.6 mmHg) and the high-IOP glaucoma group (12.3 ± 4.1 mmHg) than in the control group (1.4 ± 1.7 mmHg). The anterior glaucomatous visual field test was negatively correlated with the height of the CSF-P and positively correlated with the trans-lamina cribrosa pressure difference, in the control group, CSF-P was significantly correlated with both systolic blood pressure ($P = 0.04$) and IOP ($P < 0.005$). The trans-lamina cribrosa pressure difference was not significantly associated with blood pressure ($P = 0.375$).

Conclusions: In open-angle glaucoma with normal IOP, CSF-P is abnormally low, leading to an abnormally high trans-lamina cribrosa pressure difference. Pathogenetically, a low CSF-P in normal IOP glaucoma may be similar to a high IOP in high-IOP glaucoma. Consequently, the glaucomatous visual field defect is positively correlated with the trans-lamina cribrosa pressure difference and inversely correlated with the CSF-P. In nonglaucomatous subjects, CSF-P, blood pressure, and IOP are significantly associated with each other.

Financial Disclosures: The authors have no proprietary or commercial interest in any of the materials discussed in this article. Ophthalmology 2010;117:258-266 © 2010 by the American Academy of Ophthalmology.

Table 3. Measurements of Lumbar Cerebrospinal Fluid Pressure in Patients with Normal-Pressure Glaucoma, High-Pressure Glaucoma, and Nonglaucomatous Subjects

	Normal-Pressure Glaucoma Group	P-Value	High-Pressure Glaucoma Group	P-Value	Control Group
N	14		29		71
Cerebrospinal fluid pressure (mmHg)	9.8 ± 2.2	0.03	11.7 ± 2.7	<0.001	12.9 ± 1.0
Median	10.1		12.1		12.9
Range	8.1-13.9		6.6-18.1		1.0-18.9

P values: Statistical significance of the difference between the group in the preceding column and the group in the next column (Dunn-Whitney U test). The difference in cerebrospinal fluid pressure was statistically significant ($P < 0.001$) also for the comparison between the normal-pressure glaucoma group and the control group.

Structural Lid Changes Secondary to the Use of PGs

- Enophthalmos develops
- Loss of periorbital fat
- Deepening of the sulcus
- Most obvious when person using medication unilaterally
- More common in Caucasians
- More common with bimatoprost
- Appears to be reversible, in least in part

Deepening of Lid Sulcus from Topical Bimatoprost Therapy

LEE S, PROPHETA J, AND HAN M. *Journal of Clinical Ophthalmology*, 2010; 14(12): 1000-1002

OBJECTIVE: Report on a case of unilateral enophthalmos and deepening of the lid sulcus associated with the use of topical bimatoprost.

DESIGN: Case report.

SETTING: A tertiary care ophthalmology clinic.

PATIENT: A 65-year-old woman with a long history of unilateral enophthalmos and deepening of the lid sulcus on the right side, which had been present since childhood. She had been using topical bimatoprost 0.03% eye drops for glaucoma for 10 years.

RESULTS: The patient's enophthalmos and deepening of the lid sulcus were significantly worse on the right side compared with the left side. The enophthalmos was 4 mm on the right side and 2 mm on the left side. The deepening of the lid sulcus was 4 mm on the right side and 2 mm on the left side.

CONCLUSIONS: Topical bimatoprost therapy may be associated with unilateral enophthalmos and deepening of the lid sulcus. The mechanism of this association is unclear.

Periorbital Changes Associated With Topical Bimatoprost

Thompson JG, MD,¹ Jost B, MD,^{1,2} Jost B, MD,^{1,2} Gaoqing Tian, MD,³ Yi Zhou, MD,² Kr Ma, MD,¹ Shuang Li, MD,² Hongyan Wang, MD,² Bin Li, MD,¹ Xiaojun Zhang, MD,² Ningli Wang, MD²

Purpose: To describe the periorbital changes associated with the use of topical bimatoprost.

Design: Prospective, interventional study.

Participants: The study included 43 patients with open-angle glaucoma (14 with a normal IOP, and 29 with an elevated IOP) and 71 subjects without glaucoma.

Interventions: All patients underwent standardized ophthalmologic and neurologic examinations and measurement of lumbar CSF-P.

Main Outcome Measures: Cerebrospinal fluid pressure and IOP.

Results: Lumbar CSF-P was significantly ($P < 0.001$) lower in the normal IOP glaucoma group (9.8 ± 2.2 mmHg) than in the high IOP glaucoma group (11.7 ± 2.7 mmHg) or the control group (12.9 ± 1.0 mmHg). The trans-lamina cribrosa pressure difference (ICP minus CSF-P) was significantly ($P < 0.001$) higher in the normal IOP glaucoma group (8.8 ± 3.6 mmHg) and the high-IOP glaucoma group (12.3 ± 4.1 mmHg) than in the control group (1.4 ± 1.7 mmHg). The anterior glaucomatous visual field test was negatively correlated with the height of the CSF-P and positively correlated with the trans-lamina cribrosa pressure difference, in the control group, CSF-P was significantly correlated with both systolic blood pressure ($P = 0.04$) and IOP ($P < 0.005$). The trans-lamina cribrosa pressure difference was not significantly associated with blood pressure ($P = 0.375$).

Conclusions: In open-angle glaucoma with normal IOP, CSF-P is abnormally low, leading to an abnormally high trans-lamina cribrosa pressure difference. Pathogenetically, a low CSF-P in normal IOP glaucoma may be similar to a high IOP in high-IOP glaucoma. Consequently, the glaucomatous visual field defect is positively correlated with the trans-lamina cribrosa pressure difference and inversely correlated with the CSF-P. In nonglaucomatous subjects, CSF-P, blood pressure, and IOP are significantly associated with each other.

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In conclusion, it is important to inform patients about the potential of an altered cosmetic appearance associated with the chronic use of bimatoprost. Orbital changes associated with topical bimatoprost also need to be recognized as more than just a cosmetic issue. First, failure to recognize the association between unilateral bimatoprost use and relative enophthalmos may lead to unnecessary imaging studies of the orbit and confound neuro-ophthalmologic evaluations. Second, although a few millimeters of enophthalmos are usually not clinically significant,³¹ periorbital eyelid changes may make it difficult to obtain accurate IOP measurements and may create a challenge to achieve adequate exposure during anterior segment surgery. Although the side-effect mechanisms require further investigation, the potential for their occurrence should be recognized when bimatoprost is prescribed in the treatment of glaucoma.

New Prostaglandin

- Tafluprost (Saflutan)
 - PG developed by Santeen and marketed by Merck
 - Preservative Free
 - Dispensed in single unit vials since does not have preservative
 - Efficacy appears to be comparable to other PGs
 - Issue of cost and ease of use



Initiating Therapy for Glaucoma Monocular Trials

- Managing glaucoma comes down to lowering IOP
 - IOP is a challenging parameter because it's biologically dynamic.
 - It changes over time
 - This IOP variability has therapeutic consequences
 - When we initiate IOP-lowering therapy, spontaneous IOP variability can confound our ability to assess therapeutic response
 - We need to characterize the pre-treatment baseline IOP and on-treatment IOP
 - each of those requires more than one IOP measurement

Initiating Therapy for Glaucoma

- The monocular drug trial was designed to assess efficacy of a medication
- IOP is measured in both eyes, then one eye is treated for a month or so
- IOP is measured in both eyes again
- In theory, the change in the treated eye is a combination of therapeutic and spontaneous IOP variability
- The change in the untreated eye is pure spontaneous IOP change
- If we subtract one from the other, we should be able to isolate the therapeutic component and know how well the drug worked
- Does it work?

Initiating Therapy for Glaucoma

- Realini conducted the first statistical analysis of the monocular drug trial in 2004
 - Realini T, Fechtner RD, Atreides SP, Gollance S. The unocular drug trial and second-eye response to glaucoma medications. *Ophthalmology* 2004;111:421-6.
- Evaluated the charts of 52 patients who had undergone a monocular drug trial and then had the drug added to the other eye.
 - “Does the monocular trial predict second eye IOP reduction?” The answer was no.
 - There was no correlation between first eye and second eye IOP reductions to the same medication when the monocular drug trial was used

Initiating Therapy for Glaucoma

- The monocular drug trial requires that a number of key assumptions be true
 - that spontaneous IOP variation is symmetric between fellow eyes
 - that the diurnal curve is reproducible over time
 - that medication has no crossover effect

The Utility of the Monocular Trial

Data from the Ocular Hypertension Treatment Study

Araki M, Blomair, MEJ, MOCE, Dhaaly S, Wilson, MA, Mac O, Urdias, PAU, Paul Patil, MD, PMA,² Rosen N, Wainreb, MD,² Tzafir Miller, MD,² Rifkin T, Chang, MD,² Michael A. Kass, MD,² for the Ocular Hypertension Treatment Study Group

Objective: To determine whether adjusting the intraocular pressure (IOP) change of the trial eye for the IOP change of the fellow eye (i.e., monocular trial) is a better assessment of medication response than testing each eye independently.

Design: Analysis of data from a prospective, randomized, clinical trial.

Participants: Two hundred six participants with ocular hypertension randomized to the observation group and later started on a topical prostaglandin analog (PGA).

Methods: Participants were started on a topical PGA in 1 eye and returned in approximately 1 month to determine medication response. The IOP response of the trial eye was determined by the IOP change between baseline and 1 month in the trial eye alone (unadjusted method) and by adjusting for the IOP change in the fellow eye between the same visits (adjusted method). Our "gold standard" for medication response was the IOP change in the trial eye between up to 2 pre- and 2 posttreatment visits on the same medication. Pearson correlation was used to compare the gold standard with the unadjusted and adjusted methods. In addition, symmetry of IOP response between trial and fellow eyes to the same medication was determined by comparing the trial eye IOP change between up to 2 pre- and 2 posttreatment visits to the fellow eye IOP change between the same visits.

Main Outcome Measures: Correlation of IOP change of the trial eye using the gold standard to the IOP change of the trial eye using the unadjusted and adjusted methods.

Results: The correlation of IOP change using the gold standard to the IOP change using the unadjusted and adjusted methods were $r = 0.43$ and $r = 0.41$, respectively. The correlation of IOP change of both eyes between the same pre- and posttreatment visits was $r = 0.81$.

Conclusions: The monocular trial (i.e., adjusted method) appears equivalent to testing each eye independently (i.e., unadjusted method); however, neither method is adequate to determine medication response to topical PGA. Each eye tests a similar IOP response to the same PGA. Further studies to understand IOP fluctuations are necessary to improve current methods of assessing medication response.

Financial Disclosures: Proprietary or commercial disclosures may be found after the references. Ophthalmology 2011;120:1000-1006 © 2010 by the American Academy of Ophthalmology.

Diurnal Intraocular Pressure Patterns are Not Repeatable in the Short Term in Healthy Individuals

Tony Itzaki, MD,¹ Robin N. Wainreb, MD,² Stephen E. Wronski, PhD³

Purpose: To evaluate the short-term repeatability of diurnal intraocular pressure (IOP) patterns in eyes of subjects without glaucoma.

Design: Observational cohort study.

Participants: Forty healthy subjects without glaucoma.

Methods: Subjects underwent 12-hour diurnal IOP assessment sessions from 8:00 AM to 8:00 PM on 2 visits 1 week apart. Intraocular pressure was assessed by Goldmann applanation tonometry. An analysis was performed to determine the agreement of individual diurnal IOP patterns from the first visit to the second visit. The intraclass correlation coefficient (ICC) was used to analyze both agreement of IOP values at each time point between visits and IOP change over periods between time points between visits.

Main Outcome Measures: Diurnal IOP patterns.

Results: Between-visit agreement of IOP values at each time point generally was fair to good, with ICCs ranging from 0.37 to 0.62 in right eyes and from 0.35 to 0.71 in left eyes. Between-visit agreement of IOP change over time between time points was uniformly poor and often below that expected by chance alone, with ICCs ranging from -0.25 to 0.15 in right eyes and from -0.40 to 0.22 in left eyes.

Conclusions: Eyes of healthy individuals do not manifest a sustained and reproducible diurnal IOP pattern when measured by Goldmann tonometry. A single-day assessment of IOP incompletely characterizes the diurnal IOP pattern.

Financial Disclosures: The authors have no proprietary or commercial interest in any materials discussed in this article. Ophthalmology 2010;117:1705-1706 © 2010 by the American Academy of Ophthalmology.

Generics are the reality of the day

- Most medications are available generically
- Are they similar to legend drugs?
- FDA does regulate concentration
- Medications available are
 - Beta blockers such as Timolol, levobunolol
 - Alpha agonists such as Brimonidine 0.2%, 0.15% (Sept 2009)
 - Pilocarpine
 - Dorzolamide and Timolol-Dorzolamide
 - Latanoprost - March 2011
 - Bimatoprost and Travoprost will be generic in 2014

Generic Medications

- Approximately 75% of all medications dispensed are generic
 - IMS Health
- In regards to ophthalmic drugs, until recently most were branded
- We are now seeing an increase in the medications available generically
- In March 2011, Latanoprost became a generic agent
- Questions exist when a generic is used
 - Is there a difference between the agents?

Generics in Glaucoma

- FDA requires generics to have the same active ingredients
 - Inactive ingredients may vary from legend drug
 - Topical ophthalmic generics are NOT tested for bioequivalence or therapeutic equivalence
 - Do not have to demonstrate same rate and extent of drug absorption
 - Do not have to demonstrate similar pharmacologic effects
 - ? If generics provide comparable IOP reduction as legend drug
 - Still some generics from India are available via internet drugstores

Generic Medications

- Currently available ophthalmic glaucoma drugs in generic form
 - Beta blockers
 - Timolol, levobunolol, carteolol
 - Alpha-adrenergic agonist
 - Brimonidine 0.15, 0.2%
 - Topical carbonic anhydrase inhibitor
 - Dorzolamide
 - Parasympathomimetics
 - Pilocarpine
 - Fixed Combination
 - Dorzolamide/timolol
 - Oral carbonic anhydrase inhibitors
 - Acetazolamide
 - Methazolamide
 - Prostaglandins
 - Latanoprost

Future Glaucoma Agents Cytoskeletal Agents

- Cytochalasins
- Ethacrynic acid
- Tricrynafen
- Protein kinase C activators
- Protein kinase inhibitors
 - Rho-kinase inhibitors
 - Statins

Rho-kinase Inhibitors Outflow-Enhancing Drugs

- Glaucoma medication that reduces the IOP by reducing the resistance to aqueous outflow within the trabecular meshwork
- There is an age related increase in contractile tone in smooth muscle
- Inhibition with Rho Kinase inhibitors reduces contractile tone of smooth muscle
- Increase aqueous outflow by relaxing TM tissue
 - Effect lasts for 12 hours

Rho-kinase Inhibitors

- May also improve blood flow to the optic nerve
 - Reduce vasospasm
- May be neuroprotective
- Need a target cell specific medication
 - Non specific Rho Kinase inhibitor may be undesirable effects throughout body
 - Novartis, Inspire, Santeen, Senju all working on medication

Glaucoma Update

- Adenosine receptor agonists
 - Enhance extracellular matrix turnover in the trabecular meshwork
 - Outflow enhancing agent

Glaucoma Update

- Drug Delivery Devices
 - Started 35+ years ago with the Ocusert
 - Devices now available to implant materials in vitreous
 - Still need stable anterior segment device such as
 - Extended wear contact lens
 - Punctal plug

Glaucoma Update

- Contact Lens Drug Delivery Device
 - Pros
 - Consistent, sustained, efficient delivery of medication
 - Little waste
 - Enhanced compliance
 - Reduced side effects since more even drug
 - Cons
 - Cost
 - Fall out and no agent going to eye
 - Insertion technique

Punctal Plug Drug Insertion System QLT, inc.

- Currently filled with Latanoprost
- Concept is for drug core to last for 90 days
 - Improve drug adherence
- Retention is a concern requiring further modification of punctal insert
 - 75% retention rate at 30 days
- 22% IOP reduction
 - Only 14 drops released in 30 days
 - Explains moderate efficacy
 - Drug core release is being optimized to improve release

Surgical Procedures

- Where is their place in the glaucoma tx paradigm?
 - TVT study examining role of tubes versus trab.
- Will they be safe enough to move up to primary therapy?
- Will SLT become a primary agent?
 - Is it repeatable?
- Will trabeculectomy be replaced by safer procedures?
 - Express implant, trabecutome, etc

Where We Are Going

- Glaucoma drainage implants
- New surgical approaches
 - Express implant
 - Trabectome
 - Glaukos trabecular bypass micro-stent
 - Eyepass glaucoma implant
 - Canaloplasty
 - Gold-micro shunt

OCULAR PERFUSION PRESSURE AND OAG- A POSSIBLE LINK?

- As a general definition, ocular perfusion pressure is expressed as the difference between the blood pressure (BP) and the intraocular pressure (IOP)
- Therefore, depending on the blood pressure measurement used for the calculation, it is necessary to specify whether one refers to systolic, diastolic or mean perfusion pressure

Ophthalmic Perfusion Pressure

- Ophthalmic Perfusion Pressure (OPP) usually calculated as
- Mean Arterial Blood Pressure (MAP) minus Intraocular Pressure (IOP)
 - $OPP = MAP - IOP$
- $MAP = \text{Diastolic Blood Pressure} + \frac{2}{3} (\text{Systole} - \text{Diastole})$

OCULAR PERFUSION PRESSURE AND OAG- A POSSIBLE LINK?

- Adequate perfusion is key to maintain normal tissue function
- Low ocular perfusion pressure at the optic disc may be deleterious by causing ischemia and decreased blood flow, thus leading to glaucoma damage
- Vascular dysregulation has been proposed as an important mechanism in this process
 - may cause unstable perfusion pressure with wide fluctuations, e.g., with nocturnal dips.