Optometric Glaucoma Society/American Academy of Optometry Joint Symposium
Wednesday, November 7, 8:00 AM - 10:00 AM

Moderators: Justin Schweitzer, OD, FAAO
             Michael Chaglasian, OD, FAAO

IOP Variability: Causes and Clinical Significance (long)
Dr. Arthur Sit, Mayo Clinic, Rochester, Minnesota

Course Description: This lecture will discuss the variable nature of intraocular pressure, the physiologic basis of IOP variability, the clinical significance, and the treatments available to reduce IOP variations.

Objectives:
1. Understand the characteristics of IOP variations.
2. Explain the mechanisms for changes in IOP
3. Understand the clinical significance of IOP variations
4. Select therapies to minimize IOP variations

Outline:

Variations in intraocular pressure (IOP) have long been known, with Sidler-Huguenin first reporting diurnal variations in 1898. IOP fluctuation has been suggested as an independent risk factor for glaucoma. However, the evidence in the literature is inconclusive, and the nature of IOP fluctuations is incompletely understood. In this presentation, we will discuss the patterns of IOP variations as measured under laboratory conditions and in clinical studies, the evidence for the role of IOP variations in glaucoma pathogenesis, the mechanisms for IOP variations, and the implications for glaucoma therapy.

The role of body and head position in IOP variations has been an area of particular interest. In a recent study, we measured IOP in the sitting and recumbent positions, with the order of these sets of measurements randomized. In the sitting position, IOP was measured in neutral neck position, neck extension, and neck flexion, with the order of measurements randomized. In the recumbent positions, IOP was measured in the supine position, and right and left lateral decubitus positions, with the order of measurements also randomized. We found that, in normal subjects, IOP is lowest when measured while sitting with the neck in the neutral position. All other head and body positions result in an elevation of IOP compared with the position used for typical clinical measurements.

The mechanisms that determine the circadian pattern of IOP has been another area interest. IOP in the sitting position changes minimally during sleep, although aqueous humor flow
decreases by 50% or more at night. The explanation for this apparent discrepancy has been unclear. We recently investigated the circadian changes in aqueous humor dynamics in healthy subjects, using custom built devices to measure aqueous humor flow rate, outflow facility, and episcleral venous pressure. Uveoscleral flow was calculated by using the modified Goldmann equation. We found that the nocturnal decrease in aqueous humor flow rate compensated by a small decrease in outflow facility and a large decrease in uveoscleral outflow to maintain a stable IOP.

Although IOP varies constantly, not all therapies are equally effective throughout the 24-hour period. In particular, beta-blockers and alpha-agonists appear to have little effect during the nocturnal period. In contrast, therapies that improve outflow facility appear to minimize circadian fluctuations. Understanding IOP variations, the mechanisms involved, and the 24-hour efficacy of different therapies will allow us to optimize management of our glaucoma patients.
Refractive Surgery and Glaucoma
Robert M. Feldman, MD

I. LASIK/photorefractive keratectomy in glaucoma
II. Refractive cataract surgery in glaucoma
III. Minimally invasive glaucoma surgeries and refractive surgery
IV. Glaucoma management after LASIK
    A. Medical
    B. Surgical
V. Conclusions
I. LASIK/photorefractive keratectomy in glaucoma

Summary

Glaucoma patients present a unique set of challenges to physicians performing corneal refractive surgery. Corneal thickness, which is modified during corneal refractive surgery, plays an important role in monitoring glaucoma patients because of its effect on the measured intraocular pressure. Patients undergo a transient but significant rise in intraocular pressure during the laser-assisted in situ keratomileusis (LASIK) procedure with risk of further optic nerve damage or retinal vein occlusion. Glaucoma patients with filtering blebs are also at risk of damage to the bleb by the suction ring. Steroids, typically used after refractive surgery, can increase intraocular pressure in steroid responders, which is more prevalent among glaucoma patients. Flap interface fluid after LASIK, causing an artificially low pressure reading and masking an elevated pressure has been reported. The refractive surgeon’s awareness of these potential complications and challenges will better prepare them for proper management of glaucoma patients who request corneal refractive surgery.

Purpose

To determine the decrease of Goldmann tonometry after photorefractive keratectomy (PRK) and laser assisted in situ keratomileusis (LASIK) according to refraction prior to surgery.

Methods

Prospective simultaneous comparative case series of 53 myopic eyes (53 patients) that underwent PRK and 50 (50 patients) that underwent LASIK using the Summit Excimed SVS plus (Summit Technology, Inc., Walthan, MA, U.S.A.). PRK and LASIK were subdivided by refractive error into two subgroups of more than or less than -5 diopters (D). Central tonometric readings were taken prior to surgery and 12 months after surgery.

RESULTS:

In LASIK and PRK subgroups of more than -5 D, 85.7% (24) and 69.6% (24), respectively, gave lower readings than those taken before surgery. In LASIK and PRK subgroups of less than -5 D, 77.3% (17) and 53.3% (16),
respectively, gave lower readings. The difference between the two is significant (p < 0.001). Average tonometry falls by 2.8 mmHG in the LASIK subgroup of more than -5 D (p < 0.001) and by 2.8 mmHG in the LASIK subgroup of less than -5 D (p < 0.001) and by 1.7 mmHG in the PRK subgroup of more than -5 D (p < 0.010). In PRK subgroup of less than -5 D, the tonometric changes are not significant (p = 0.971).

Conclusions

High previous refraction (in PRK) and technique used determines lower final tonometric readings, bringing about more frequent and significant decreases in LASIK than in PRK for errors of more than and less than -5 D

II. Refractive cataract surgery in glaucoma

Summary

To summarize the role of cataract surgery in the glaucoma patient, in terms of the effect on intraocular pressure (IOP) as well as diagnostic and therapeutic considerations for those with both conditions. Recent evidence suggests that cataract extraction may produce a significant and sustained IOP reduction in individuals with open-angle glaucoma, ocular hypertension, and angle-closure glaucoma. Cataract removal may improve the practitioner's ability to interpret perimetric testing, and re-establishing perimetric and optic nerve imaging baselines is recommended after cataract surgery. The sequence of cataract surgery relative to glaucoma surgery impacts the likelihood of complications and surgical success. There are multiple benefits to perform cataract surgery prior to glaucoma surgery while cataract surgery after trabeculectomy increases the risk of subsequent filtration failure. As "minimally invasive glaucoma surgeries" continue to improve in terms of efficacy, there is an evolving role for combined cataract and glaucoma surgery in patients with early to moderate stages of glaucoma.

Cataract and glaucoma frequently exist together. Because the field of glaucoma surgical care is expanding and cataract surgery is becoming progressively safer, it is important to frequently re-evaluate our treatment paradigms. We review and evaluate current studies and treatment options.
Recent findings
New clinical evidence for using the CyPass, Kahook and Xen45 devices has been published recently and is summarized.

Conclusions
Surgical options for concurrently managing cataract and glaucoma have expanded in recent years. Endoscopic cyclophotocoagulation, trabecular micro-bypass stent, ab interno trabeculectomy, and canaloplasty may be performed in conjunction with cataract extraction to provide additional intraocular pressure (IOP) reduction. Studies evaluating these new glaucoma procedures combined with phacoemulsification generally include retrospective case series without a comparison group. Because cataract surgery alone is associated with IOP reduction, the relative contribution of the glaucoma procedure in lowering IOP cannot be determined in these studies. Randomized clinical trials are needed to better evaluate the efficacy and safety of newer glaucoma procedures in combination with cataract surgery.

III. Minimally invasive glaucoma surgeries and refractive surgery

Purpose
The purpose of the study is to report the outcomes of simultaneous cataract extraction (CE) and a new nonvalved glaucoma drainage device (GDD), Aurolab Aqueous Drainage Implant (AADI), in eyes with cataract and refractory glaucoma.

Methods
This was a non-comparative, interventional, retrospective study. Consecutive patients who underwent AADI together with phacoemulsification from June-2015 to January-2017 by a single fellowship trained glaucoma surgeon with documented 3-months of follow-up were included. The main outcomes were intraocular pressure (IOP), antiglaucoma medication (AGM), visual acuity, and complications.

Results
We included 19 eyes of 17 patients with average follow-up of 14.4 ± 8.4 months. IOP and AGM reduced from 36.9 ± 11.1 mmHg and 4 ± 0.8 preoperatively to 12 ± 4.5 mmHg and 0.8 ± 1.2, respectively (P < 0.001). Complications were seen in seven eyes (36.8%). Total success was seen in 17 eyes (89.5%). None of the patients lost vision.

IV. Glaucoma management after LASIK

A. Medical

Summary
Variability in central corneal thickness (CCT) is a potent confounder of most tonometry techniques, especially Goldmann applanation tonometry. The Ocular Hypertension Treatment Study (OHTS) provided important information regarding predictive factors for the eventual development of glaucoma in patients at risk of the disease. Among the most striking of the OHTS' findings was that CCT was a powerful predictor of glaucoma risk. In this review, studies subsequent to the OHTS report will be reviewed and placed in the context of what is known about CCT and its relation with tonometry and glaucoma risk.

Recent findings
Several well-designed studies have since expanded on this hypothesis, confirming that CCT bears an inverse relation with the risk of developing glaucoma damage. Other investigators have confirmed the presence of racial differences in CCT and pilot studies suggest that CCT may vary systematically in different forms of glaucoma.

Conclusions
The absence of a widely-accepted algorithm for the correction of IOP measurements should not prevent the widespread adoption of pachymetry as part of the comprehensive eye exam, as knowledge of an individual's CCT provides valuable information about their glaucoma risk. Topical management to lower IOP remains the mainstay of treatment in these cases.

B. Surgical

Summary
As IOP is the only modifiable risk factor in the treatment of glaucoma to date, traditional diagnostic and treatment algorithms may not be appropriate for refractive surgery patients. Glaucoma remains a relative contraindication to refractive procedures, but as new diagnostic modalities emerge, our ability to diagnose and manage these patients
may improve. More uniform recommendations need to be implemented to improve our long-term management of these patients.

Patients considering corneal refractive surgery undergo extensive preoperative testing, but current protocols may not address the management of glaucoma appropriately. This review outlines the current body of literature on the diagnostic and management challenges that exist in the treatment of glaucoma patients undergoing laser ablative surgery, and makes recommendations to improve current perioperative protocols.

Recent findings
As permanent structural alterations to the cornea after laser-assisted in-situ keratomileusis surgery make Goldmann applanation tonometry inaccurate, the advent of new diagnostic modalities and recommendations to accurately measure postoperative intraocular pressure (IOP) and subtle damage to the optic nerve have been further analyzed and tested.

V. Conclusions
Is Glaucoma a reversible disease?

Jay Katz, MD

I. Definition of glaucoma
II. Statistics on blindness and glaucoma
III. Review of the optic nerve and visual pathway
IV. Overview of the pathophysiology of glaucoma
V. Factors influencing retinal ganglion cell survival
VI. Scope of the problem with glaucoma
VII. Glaucoma – current treatment strategies
VIII. Clinical examples of reversibility
IX. Systematic studies of structural and functional improvement in glaucoma
X. Challenges ahead
Is Glaucoma Reversible?

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Disclosures
Consulting Fees: Aerie Pharmaceuticals, Angio Therapeutics, Alcon Laboratories, Alimera Sciences, Allergan, Diopsys, ForSight Vision, InnFocus, Inotek, Mati Therapeutics, Vitaris Therapeutics

Speaking honorarium: Alcon Laboratories, Allergan, Bausch + Lomb

Contracted Research: Aerie Pharmaceuticals, Alcon Laboratories, Allergan, Diopsys, Heidelberg Engineering, Mati Therapeutics

Ownership Interest: Aerie Pharmaceuticals; Glaukos Corporation; Mati Therapeutics

What is Glaucoma?
Definition of Glaucoma

Current Definition

“Primary open angle glaucoma is a multifactorial optic neuropathy characterized by acquired loss of retinal ganglion cells and optic nerve atrophy.”

What Helps Maintain Retinal Ganglion Cell Survival?

Pathology

- IOP
- ischemia
- Toxic Factors
- Loss of Tropic Input

Optic Nerve Damage

RGC Death

Nutrient delivery

And waste removal

The immune system

Intrinsic survival pathways

Targeting in Brain (LGN)
**Glaucoma Treatment**

**Aim: Lower Target Pressures**

- Evidence from controlled, prospective, randomized clinical trials:
- Reducing IOP to lower target pressures can prevent glaucoma and slow or stop progression
  - iHTS
  - EMGT
  - CNTS
  - AGIS

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**Consistently Low IOP Reduces Vision Loss in Advanced Glaucoma**

- Mean IOP
  - 20.7 mm Hg
  - 16.9 mm Hg
  - 14.7 mm Hg
  - 12.3 mm Hg

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**Glaucoma: Loss of Retinal Ganglion Cells (Neurons)**

- RGCs remaining
- Optic disc cupping
- Blindness
- Glaucoma patient
- Untreated
- Treated
- Normal individual
- Lifespan of patient
Glaucoma

- Could retinal ganglion cells in the optic nerve be dysfunctional prior to death and be restored to health?
- Treatment:
  - IOP reduction
  - Improved ocular perfusion
  - Neurotrophic factors
  - Stem cells

Clinical Examples of Reversibility

- Myocardial infarction
- Stroke
- Spinal cord injury

Structural and Functional Improvement in Glaucoma

- Flammer J, Drance SM
  Reversibility of a glaucomatous visual field defect after acetazolamide therapy

- Schwartz B, Takamoto T, Heijl P
  Ophthalmologica. 1987; 192:121-127
  Measurements of reversibility of optic disc cupping and pallor in ocular hypertension and glaucoma
  4 cases: reversal of cupping and pallor of the optic disc. 2 patients showed regression of visual field loss.
Reversibility of optic disc cupping: A phenomenon that may change the management of glaucoma

Katz 1989
- 3 glaucoma specialists masked to the clinical course independently reviewed optic disk stereophotographs and visual fields taken before and after treatment
- 1/3 reversal of optic disk cupping
- 1/3 of visual fields improved
- associated with the degree of intraocular pressure reduction

Reversal of optic disc cupping after glaucoma surgery analyzed with a scanning laser tomograph

Mark Leis 1999
- 85% patients having IOP reduction of greater than 40% showed improvement in optic disc parameters
- amount of improvement correlated highly with the percent reduction of IOP
Michael Waisbourd 2016
- Improved GCC appearance following the intervention
- Grading of visual fields by two observers showed improvement

Joseph Caprioli 2016
- The magnitude of IOP reduction correlated with long-term improvement postoperatively
- >½ of eyes had improving VF locations postoperatively

Blood Flow and Glaucoma
Costa Ocular Perfusion Pressure in Glaucoma Acta Ophthalm 2014
Improved Ocular Circulation Following Glaucoma Surgery

Jack Trible 1994

Retinal Arterial Hemodynamic Effects of Betaxolol and Timolol
American Journal of Ophthalmology

Harris, Spaeth, Sergott, Katz 1995
3 mo Tx
• Timolol > betaxolol in lowering IOP
• Increased 30% with betaxolol and no diff with timolol

Disparity due to increased IOP or reduced IOP may result in glaucomatous changes
Cell death (Retinal Ganglion Cells) is Controlled by Competing Signals

1) neurotrophins
2) Cell death mediators (neurotoxins)

VF progression (points per linear regression)
Brimonidine-treated patients 9.1%
Timolol-treated patients 39.2%
(P = .001)
Mean treated IOP was similar for brimonidine and timolol-treated patients at all time points
pilot series in glaucoma: improved visual function (perimetry and contrast sensitivity)
11 eyes progressed despite low IOP prior to intervention
Women Blinded By Unproven Stem Cell Treatments

New York Times
- *Women Blinded By Unproven Stem Cell Treatments*
- *March 15, 2017* • Three patients were blinded after getting stem cells from fat at a Florida clinic

**SCOTS**
Stem Cell Ophthalmology Treatment Study (SCOTS) for retinal and optic nerve diseases: a case report of improvement in relapsing auto-immune optic neuropathy

**Challenges Ahead**
- Source of stem cells
- Placement technique
- Guiding RGCs to LGN/Visual Cortex
- Synaptic hookup that provides vision

**Electrical stimulation in glaucoma**
Treated group improvement in visual field of 4 vs. sham stimulation 1.5%
Vision restoration training

Sabel
• Computer-based
• Visual field defects caused by glaucoma can be improved by repetitively activating residual vision through training the visual field borders and areas of residual vision
• Neuroplasticity of the visual cortex or higher cortical areas is the proposed mechanism of action.

Summary: Glaucoma May be Reversible

• IOP reduction
  • magnitude of IOP reduction crucial
• enhanced ocular perfusion
• neurotrophins
• stem cells
• stimulating visual pathway (electrical and light)

The End
(but at the Infancy of Vision Restoration Research in Glaucoma)