Controversies in Glaucoma Therapy

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Chairman, National Glaucoma Society
Director, Glaucoma Institute @ Ophthalmic Consultants of Connecticut

1. To Sleep Perchance to Dream!
The Role of Sleep Dysfunction in Glaucoma
To Sleep Perchance to Dream

- Sleep Dysfunction: It’s Role in patient Health
- Sleep Apnea: The Impact of sleep dysfunction in glaucoma

TO SLEEP PERCHANCE TO DREAM

- MOJON DS, etal
  - OPTIC NEUROPATHY / SLEEP APNEA
  - OPHTH 105:874-77 1998
    - SEVEN PATIENTS
      - 3 SEVERE / NASAL STEPS 2 / ARCUATE DEFECT 3
      - 2 MODERATE / ARCUATE DEFECT
      - 1 MILD
      - ETIOLOGY- DECREASED BLOOD FLOW
Obstructive Sleep Apnea

- Bendel, R et al. (Mayo Clinic, Jacksonville)
- OAS - Repeated apnea episodes
  - Daytime symptoms
    - Daytime sleepiness
    - Chronic fatigue
    - Decreased cognitive function
  - Etiology
    - Collapse of the pharyngeal airway
    - Last 10-60 seconds

OSA

- Diagnosis
  - Overnight polysomnography
  - EEG, EMG, EOG, EKG, Nasal buccal airflow, and pulse oximetry (arterial oxygen)
- Respiratory Disturbance Index 10 >= OASS
- 83 patients with apnea
- Outcomes
  - Median age 62
  - Median RDI 37
  - Median IOP 16mmHg
OSA

- Outcomes
- 2.4% patients with OHTN
- 33% COAG
- No relation to gender, age, or BMI
- Relation between IOP increase and BMI level

Sleep Apnea & NTG

- Mojon DS et al; Ophthalmologica 2002
- 16 patients with NTG had PSN
- RDI > defined as mild
- < 45 - 0%
- 46-64 - 50%
- 65 & > 63%
Sleep Apnea: The Silent Assassin

- Co-Morbidities of Sleep apnea
  - Increased risk of CVA
  - Irregular Menstrual Cycles (40%)
  - Children May exhibit “Failure to Thrive”: T & A removal
  - Psychologic Dysfunction (32%)

2. Will The Real IOP Please Stand Up!
   Dr Goldmann Please Take a Seat!
WHAT IS THE ROLE OF IOP IN GLAUCOMA?

- Elevated pressure
- Normal pressure
- Low pressure
- Associated systemic disease
- Environmental
- Clinician induced

IOP in glaucoma
- A risk factor
- *Poor* for diagnosing POAG
- *Poor* predictor of disc and field damage
- *Used* for management (*AGIS - target IOP*)
  - Normal population distribution skewed (*non-bell shaped*)
  - Overlap between normal and glaucoma groups
Lowering IOP Reduces the Risk of Glaucomatous Progression

- Results of major studies on established glaucoma
  - Collaborative Normal-Tension Glaucoma Study
  - Collaborative Initial Glaucoma Treatment Study
  - Advanced Glaucoma Intervention Study

Sir James Alfred Ewing
Identified the phenomenon of hysteresis and coined the term in 1890

- A measurement that characterizes response to application and removal of force (load/unload)\(^1\)
  - Found in materials or systems that do not instantly follow forces applied to them but react slowly, or dissipate a portion of the applied energy \(^1\)
- More than 7500 papers published on hysteresis in a variety of medical fields\(^2\)
  - Various tissues and structures (tendon, lung, arteries, etc)
  - The importance of Corneal visco-elasticity had been discussed and explored (\textit{EX-VIVO}) prior to the ORA\(^3\)


Corneal Hysteresis (CH)

- The only in-vivo measurement of corneal/ocular biomechanics
  - CH specifically refers to the output of the measurement process performed by the Ocular Response Analyzer (ORA)\(^1,2\)
- Corneal Hysteresis reflects the ability of the corneal tissue to dissipate energy \(^1\)
  - Function of viscoelastic damping\(^2\)
  - Not a characterization of stiffness\(^3\)
- Provides insight into ocular properties that were not previously understood or conceived of

Ocular Response Analyzer Technology

Bi-direction Applanation Signal

• 2002: Clinical research with ORA commences
• 2005: The 1st generation ORA was made commercially available
• 2012: Generation II ORA was launched
• 3rd Generation “ORA G3” introduced September 2015

Measures:
• Corneal Hysteresis (CH)
• Goldmann-correlated IOP (IOP\(_{G}\))
• Corneal compensated IOP (IOP\(_{CC}\))
CH: Average Values in Normal Subjects

<table>
<thead>
<tr>
<th>CH Values in Normals around the world</th>
<th>N</th>
<th>CH*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil(^3)</td>
<td>105</td>
<td>10.1 ± 1.8</td>
</tr>
<tr>
<td>UK(^2)</td>
<td>272 pairs</td>
<td>10.2 ± 1.2</td>
</tr>
<tr>
<td>China(^3)</td>
<td>125</td>
<td>10.9 ± 1.5</td>
</tr>
<tr>
<td>Japan(^4)</td>
<td>204</td>
<td>10.2 ± 1.3</td>
</tr>
<tr>
<td>Spain(^3)</td>
<td>88</td>
<td>10.8 ± 1.5</td>
</tr>
<tr>
<td>USA(^6)</td>
<td>44</td>
<td>10.5 ± 1.2</td>
</tr>
</tbody>
</table>

*CH units are mmHg

CH distribution - Normals & Glaucoma

Glaucoma subjects have lower CH than normals, especially those who are still progressing in the disease.

Data courtesy New England College of Optometry and Mitsugu Shimmyo, MD
The Cornea and Glaucoma

- 2001 OHTS publication – the largest and longest glaucoma study in history

- CCT was the strongest independent indicator of conversion from ocular hypertension to POAG in the OHTS\(^1,2\)

- As a result, CCT has become an essential metric in glaucoma risk assessment
  - **Not** as an IOP correction factor
  - “Low,” “Medium,” “High” stratification system

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### Section 1: Introduction to Corneal Hysteresis

**CH: Average Values in Normal Subjects**

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<tr>
<td>*CH units are mmHg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>USA(^6)</td>
<td>44</td>
<td>10.5 ± 1.2</td>
</tr>
</tbody>
</table>

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Corneal Hysteresis found to be associated with progression

• The first observational study to investigate the relationship of Corneal Hysteresis to a variety of other parameters in a glaucoma population

• 230 POAG or suspected POAG patients were included in the study
  • POAG was defined by a reliable visual field that was abnormal according to OHTS criteria, with an optic nerve image, photo, or CDR thought to be consistent with the field damage by a fellowship-trained glaucoma specialist.
  • GAT, ORA, CCT and Axial Length measurements (IOL master) were recorded
  • Among persons with three or more reliable fields over three or more years, or with five reliable fields in less than three years, progression was defined as having achieved the OHTS standard of “conversion” (if previously normal), or (if previously damaged as evidenced by an abnormal GHT or PSD) having worsened by 1 dB or greater per year in either MD or PSD.
  • A stepwise model was not used nor were any hypotheses about interactions made.

Conclusions: Corneal Hysteresis was the parameter most associated with progressive field worsening

<table>
<thead>
<tr>
<th>OR</th>
<th>LCL</th>
<th>UCL</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age per year &lt;65</td>
<td>1.12</td>
<td>1.01</td>
<td>1.24</td>
</tr>
<tr>
<td>Age per year &gt;65</td>
<td>1.08</td>
<td>1.01</td>
<td>1.15</td>
</tr>
<tr>
<td>GAT IOP per mmHg</td>
<td>1.22</td>
<td>0.95</td>
<td>1.58</td>
</tr>
<tr>
<td>Treatment</td>
<td>1847.6</td>
<td>3.16</td>
<td>10^6</td>
</tr>
<tr>
<td>IOP by treatment interaction</td>
<td>0.79</td>
<td>0.61</td>
<td>1.03</td>
</tr>
<tr>
<td>CCT per 100 microns</td>
<td>1.65</td>
<td>0.66</td>
<td>0.98</td>
</tr>
<tr>
<td>Years with glaucoma</td>
<td>1.00</td>
<td>0.96</td>
<td>1.04</td>
</tr>
<tr>
<td>Baseline IOP</td>
<td>0.99</td>
<td>0.93</td>
<td>1.06</td>
</tr>
<tr>
<td>CH per mmHg</td>
<td>0.81</td>
<td>0.66</td>
<td>0.98</td>
</tr>
</tbody>
</table>
Clinical Evidence – Study 3
CH Associated with Asymmetric Glaucoma Progression

- Investigated the relationship between CH and asymmetric POAG

- In a prospective cross-sectional study, ORA parameters were measured in 117 POAG patients with asymmetric visual fields (VF).
  - VF testing was performed with a static, automated, achromatic perimetry (24–2 test pattern, Mk II, model 750; Carl Zeiss Meditec, Inc.) using the SITA-standard program.
  - Asymmetry was defined as a 5-point difference between OD and OS using the (AGIS) scoring system.
  - Pearson correlation coefficients were used to determine correlation of various parameters with the AGIS scores. Receiver operating characteristic (ROC) curves were plotted for ORA and other glaucoma risk factors. Area under the curve (AUC) for each parameter was compared to determine the best predictor for the worse eye in POAG with asymmetric VF.

CH was the best discriminative index for the worse eye in asymmetric OAG.
- CH lower in 80% of worse eyes

### Table

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Worse Eye</th>
<th>Better Eye</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGIS II VF Score</td>
<td>8.1 ± 4.3</td>
<td>1.0 ± 1.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GAT mmHg</td>
<td>14 (12-17)</td>
<td>14 (12-16)</td>
<td>0.3</td>
</tr>
<tr>
<td>CCT (µm)</td>
<td>531.8 ± 34.7</td>
<td>532.3 ± 34.9</td>
<td>0.6</td>
</tr>
<tr>
<td>Drops (#)</td>
<td>2.2 ± 0.9</td>
<td>2.1 ± 2.6</td>
<td>0.9</td>
</tr>
<tr>
<td>CH (mmHg)</td>
<td>8.2 ± 1.9</td>
<td>8.9 ± 1.9</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Section 3: CH and the structural continuum

**CH is Associated with ONH Deformation in Glaucoma**

- Prospective experimental study of 100 subjects (38 with glaucoma, 62 without glaucoma)
- Data collected included SE, optic disc diameter, CCT, axial length, cylinder, GAT, Pascal IOP, OPA and CH.
- Elevation of IOP (approx 64 mm, 30 seconds) was induced OD on each subject with a modified LASIK suction ring.
- HRT-II was used to map the optic nerve surface before and during IOP elevation. Mean cup depth was calculated using built-in HRT data analysis software.
- Change in optic disc depth during IOP elevation was calculated for all right eyes, and tests for correlation with the parameters listed were performed.

CH, but not CCT or other anterior segment parameters, is associated with increased deformation of the optic nerve during transient IOP elevations in glaucoma patients but NOT in normal controls.¹

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**Clinical Evidence- Study 2**

**CH associated with progression in NTG eyes**

- Of the 39 eyes with low CH, 26 (66.7%) showed progression of VF damage while 13 (33.3%) showed no progression.
- Of the 43 eyes with high CH, 15 (34.9%) showed progression of VF damage, whereas 28 (65.1%) showed no progression.

These findings suggest that CH can be used as one of the prognostic factors for progression, independent of corneal thickness or IOP
Corneal Hysteresis in Glaucoma
Predictive of conversion to Glaucoma in pre-perimetric Glaucoma Suspects

Purpose: To investigate the role of CH as a risk factor for development of glaucoma in a prospective longitudinal study.

Results: Fifty four (19%) of the 287 eyes developed repeatable visual field defects during a 4 year follow-up.

CH was independently predictive of conversion to glaucoma even when adjusted for age, IOP, and CCT.

Each 1mmHg lower CH was associated with an increase of 21% in the risk of developing glaucoma during follow up

As of January 1, 2015, the measurement of Corneal Hysteresis is reimbursable by Medicare in the USA

CPT code 92145: Corneal hysteresis determination, by air impulse stimulation, unilateral or bilateral with interpretation and report
Surgical Continuous IOP Monitoring Device

- Nature Medicine 2014
  - Yossi Mandel, Bar-Ilan/ Stephen Quake, Stanford
  - Utilizes a variable float tube in the IOL
  - Smart Phone app allows acquisition of data
  - Anticipated in 2-3 years

ANOTHER REASON NOT TO BE A COUCH POTATOE!

- PASSO, M et al; Arch Ophth-Vol 109 Aug 1991
- EXERCISE TRAINING REDUCES IOP AMONG GLAUCOMA SUSPECTS
  - 13 SEDENTARY ADULTS/25-60 Y/O
  - <1 HOUR/WEEK OF EXERCISE PRIOR TO STUDY FOR 6 MONTHS
  - IOP > 22mmHg MULTIPLE MEASUREMENTS
EXERCISE AND IOP

• BASELINE COMPREHENSIVE EXAM
• 12 WEEKS/ 40 MINUTES /DAY/4 DAYS
• OUTCOMES
  • BASELINE IOP 23.8 mmHg
  • POST TRAINING IOP 19.2 mmHg
• SYSTEMIC RESPONSE SIMILAR( BP, HEART RATE )
• IOP AFTER DECONDITIONING 24mmHg

3. Alternate Day Therapy in Glaucoma
Diurnal IOP Fluctuation & Visual Field Loss

- Greater diurnal IOP fluctuation resulted in greater visual field progression

- Home applanation tonometry by 64 patients 5X daily for 5 days

- Visual field progression of patients was tracked over 8 years

Asrani, et. al. *Large diurnal fluctuations in intraocular pressure are an independent risk factor in patients with glaucoma*, J. Glaucoma, 9, 134-142, 2000
Diurnal IOP Fluctuation in Glaucoma Patients

![Graph showing IOP fluctuation]

POAG Off Treatment | POAG Controlled | Normal Eyes | Travoprost 0.004%

Drance SM. Arch Ophth, 1963;70: 302-311
Drance SM. Arch Ophth, 1960; 64: 494-501
H.B. Dubiner
Travatan Administration Results in Effective Diurnal Reduction in Intraocular Pressure Over 36 Hours and Lower Pressures Up to 3.5 Days Without Further Dosing. Presented at ARVO Meeting: May 2002

Alternate Day Therapy

- Twice daily dosing increases IOP relative to once daily dosing
- Xalatan and Lumigan combined can increase IOP, even to 50s
- Anytime IOP is >30 with prostaglandin, it is overdosed
- Once daily can be overdose if there is inflammation/endogenous prostaglandin
 Persistence of IOP Response

- Labovitz RA et al; Arch Ophth 2001
- Comparison of Lumigan vs Timolol
- Maintenance of IOP at 48 hours post D/C 5.6mmHg
- 7.2 - 8.2 mmHg at peak effect
- 28 Day control showed less than
- Timolol was 3.4-3.9 mmHg at peak.

 Alternate Day Therapy

- 30% reduction first day, 25% reduction second day
- IOP will be one point higher on second day
  - Doro. ARVO 2007
Alternate Day Therapy

• Reduced cost
• Reduced hyperemia, ache, dry eye
• Reduced long term conjunctival inflammation promoting trabeculectomy scarring

Alternate Day Therapy: Practical Tips

• Starting every other day improves tolerability in prostaglandin novices
• Aching and high IOP suggest overdose
• Wash face after instillation
Alternate Day Therapy: Compliance

- Not a problem for organized patients
- Some keep a calendar
- Some choose 3 or 4 days of the week
- Some choose odd or even days

Alternate Day Therapy Post SLT

- SLT somewhat less effective in patients already on prostaglandin
  - Suggesting that part of SLT induces prostaglandin like effects
- QD prostaglandin could be an overdose after SLT
  - Especially first year after laser
Alternate Day Therapy: Initial Review

- 22 patients with well controlled glaucoma over a two year period.
- Switched from daily therapy to alternate day treatment following complaints of cosmetic/ anterior segment problems
- Average IOP pre-switch: 16.2 mmHg
- Post switch IOP at 1 week, 1 month and 3 months average: 16.67 mmHg

Diurnal Pressure: All Talk, No Action?
Habitual IOP (mm Hg)

<table>
<thead>
<tr>
<th>Clock Time</th>
<th>Sitting</th>
<th>Supine</th>
<th>Sitting</th>
</tr>
</thead>
<tbody>
<tr>
<td>3:30 PM</td>
<td>28</td>
<td>26</td>
<td>24</td>
</tr>
<tr>
<td>5:30 PM</td>
<td>22</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>7:30 PM</td>
<td>20</td>
<td>18</td>
<td>16</td>
</tr>
<tr>
<td>9:30 PM</td>
<td>18</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>11:30 PM</td>
<td>16</td>
<td>14</td>
<td>12</td>
</tr>
</tbody>
</table>


Timolol gel

icare HOME

IOP SELF-MONITORING ANYWHERE ANYTIME
Icare HOME tonometer

- IOP, date, time, eye recognition (right/left) and measurement quality are all stored in the internal memory.
- Data is transferred to a PC for further analysis by the prescribing physician.
- New features: positioning light, automatic eye recognition system, series or single measurements, new user interface panel.

Icare® EasyPos: Positioning Light

Red and green light signals help patients correctly position the tonometer.

Correct alignment Incorrect alignment Incorrect alignment
Icare® EyeSmart: Automatic Eye Recognition

The tonometer includes an automatic eye recognition system that identifies which eye is being measured.

- Two infrared LED transmitters below probe (1)
- One infrared LED sensor above probe (2)
- The infrared light is reflected from nose back to the sensor
- The sensor knows from which transmitter the reflected infrared light came from and thus which eye, right or left, was measured
- The resulting eye indication is stored into the memory of the tonometer

New User Interface Panel

- Simple Indicator Lights and Audible Alerts
- Interpretation only by a health care professional
- Does not display the IOP measurement
  - Mitigating concerns that the patient or caregiver might improperly use the information provided by the device
The Role of Perfusion Pressure in Glaucoma

Hypoperfusion

- flow = pressure/resistance
- perfusion pressure = BP - IOP
- mean arterial BP = diastolic + 1/3 syst-diastolic
- nocturnal hypotension is greatest risk
Nocturnal Hypotension: Another Reason to Get a Good Nights Sleep

- TIBA Medical
- ABPM 2400
- 24 hour Serial BP Monitoring
- Role in Glaucoma Management

Nocturnal Hypotension

- TIBA Medical
- Reimbursement
  - Commercial
  - Medicare
- ICD-9 Codes
- www.tibamedical.com
Ocular Perfusion Pressure and Glaucoma Progression

Ocular Perfusion Pressure (OPP) = BP – IOP
(BP is mean arterial pressure, diastolic BP, or systolic BP)

Low ocular perfusion pressure has been shown to be strongly associated with the prevalence of glaucoma progression in multiple population-based surveys

Leske et al. Ophthalmology 114 (11), November 2007

Habitual IOP and Pulse Pressure

![Graph showing habitual IOP and pulse pressure over time.](image)
An Evidence-Based Review of Prognostic Factors for Glaucomatous Visual Field Progression

Paul J. Enner, MD, 1, 2 Ian S. Schrouten, MD, PhD, 1 Henry J. Becker, MD, PhD, 1 Fred Hendrikse, MD, PhD, 2 Martin H. Priiti, MD, PhD, 1 Carroll A. Weikers, MD, PhD 1

Purpose: To examine which prognostic factors are associated with glaucomatous visual field progression.

Design: Knowledge of prognostic factors helps clinicians to select patients at risk of glaucomatous visual field progression and intensify their treatment.

Methods: By consulting relevant databases, we identified 2738 articles published up to September 2010, of which 86 articles investigating prognostic factors for visual field progression in patients with open-angle glaucoma (OAG) were eligible. We summarized results for each factor in tables, noting the direction of the association between the prognostic factor and progression, and the accompanying P value. Four authors, working blind to the factors, independently judged the extent to which a prognostic factor was associated with glaucomatous visual field progression. If there were different associations for normal-tension glaucoma (NTG) studies, they were judged separately. Consensus was reached during group meetings.

Main Outcome Measures: A ranking of all studied prognostic factors for glaucomatous visual field progression according to their likelihood of being prognostic.

Results: A total of 103 different prognostic factors were investigated in 86 articles. The following factors were clearly associated with glaucomatous visual field progression: age, disc hemorrhages (for NTG), baseline visual field loss, baseline intraocular pressure (IOP), and fluctuation syndrome. An association was unlikely for family history of glaucoma, arteriosclerosis, systemic hypertension, visual acuity, sex (for NTG), systolic blood pressure, myopic refractive error (for NTG), and Raynaud’s phenomenon.

Conclusions: The factors we found clearly associated with progression could be used in clinical practice and for developing clinical prediction models. For many other factors, further research is necessary.

Financial Disclosure(s): The author(s) have no proprietary or commercial interest in any materials discussed in this article. Ophthalmology 2013;120:512-519 © 2013 by the American Academy of Ophthalmology.

EMGT RFs for Progression

Table 2. Baseline and Follow-up Factors for Progression in the Early Manifest Glaucoma Trial, All Patients (n = 255)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Reference</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment group</td>
<td>Control</td>
<td>0.53 (0.39-0.72)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Higher intraocular pressure (IOP), mmHg</td>
<td>&lt;21</td>
<td>1.77 (1.29-2.43)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Exfoliation</td>
<td>None</td>
<td>2.12 (1.30-3.46)</td>
<td>0.0026</td>
</tr>
<tr>
<td>No. of eligible eyes</td>
<td>1</td>
<td>1.88 (1.35-2.63)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Older age (ys)</td>
<td>&lt;68</td>
<td>1.51 (1.11-2.07)</td>
<td>0.0095</td>
</tr>
<tr>
<td>Lower systolic perfusion pressure (mmHg)</td>
<td>&gt;125</td>
<td>1.42 (1.04-1.94)</td>
<td>0.0268</td>
</tr>
<tr>
<td>Worse mean deviation (dB)</td>
<td>&gt;-4</td>
<td>1.38 (1.00-1.91)</td>
<td>0.0510</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>&gt;160</td>
<td>0.69 (0.44-1.07)</td>
<td>0.0971</td>
</tr>
<tr>
<td>Follow-up factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Initial change in IOP (baseline − 3-mo IOP)</td>
<td>Per mmHg lower</td>
<td>0.92 (0.89-0.96)</td>
<td>0.0001</td>
</tr>
<tr>
<td>b. IOP at first follow-up visit (3-mo IOP)</td>
<td>Per mmHg higher</td>
<td>1.13 (1.03-1.18)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>c. Mean IOP at follow-up (time dependent)</td>
<td>Per mmHg higher</td>
<td>1.12 (1.07-1.16)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>d. Percent of visits with disc hemorrhages (time dependent)</td>
<td>Per % higher</td>
<td>1.02 (1.01-1.02)</td>
<td>0.0014</td>
</tr>
<tr>
<td>e. Central corneal thickness (μm)</td>
<td>Per 40 μm lower</td>
<td>1.25 (1.01-1.55)</td>
<td>0.0422</td>
</tr>
</tbody>
</table>
Drance Hem and Progression

The Relationship between Intraocular Pressure Reduction and Rates of Progressive Visual Field Loss in Eyes with Optic Disc Hemorrhage

Felipe A. Medeiros, MD, PhD,1,2 Luciana M. Alencar, MD, PhD,1,2 Pamela A. Sample, PhD,1 
Linda M. Zangwill, PhD,1 Remo Sasvar Jr., MD,1,2 Robert N. Weinreb, MD1

Purpose: To evaluate rates of visual field progression in eyes with optic disc hemorrhages and the effect of intraocular pressure (IOP) reduction on these rates.

Design: Observational cohort study.

Participants: The study included 510 eyes of 348 patients with glaucoma who were recruited from the Diagnostice Innovation in Glaucoma Study (DIGS) and followed for an average of 8.2 years.

Methods: Eyes were followed annually with clinical examination, standard automated perimetry visual fields, and optic disc stereophotographs. The presence of optic disc hemorrhages was determined on the basis of masked evaluation of optic disc stereophotographs. Evaluation of rates of visual field change during follow-up was performed using the visual field index (VFI).

Main Outcome Measures: The evaluation of the effect of optic disc hemorrhages on rates of visual field progression was performed using random coefficient models. Estimates of rates of change for individual eyes were obtained by best linear unbiased prediction (BLUP).

Results: During follow-up, 97 (12%) of the eyes had at least 1 episode of disc hemorrhage. The overall rate of VFI change in eyes with hemorrhages was significantly faster than in eyes without hemorrhages (-0.86%/year vs. -0.36%/year, respectively, P<0.001). The difference in rates of visual field loss pre- and post-hemorrhage was significantly related to the reduction of IOP in the post-hemorrhage period compared with the pre-hemorrhage period (β = -0.61; P<0.001). Each mmHg of IOP reduction was associated with a difference of 0.33%/year in the rate of VFI change.

Conclusions: There was a beneficial effect of treatment in slowing rates of progressive visual field loss in eyes with optic disc hemorrhage. Further research should elucidate the reasons why some patients with hemorrhages respond well to IOP reduction and others seem to continue to progress despite a significant reduction in IOP levels.

Financial Disclosure(s): Proprietary or commercial disclosure may be found after the references. Ophthalmology 2010;113:1439-1448

Los Angeles Latino Eye Study

- Cross-sectional study of 6,357 Latinos, >40 years in Los Angeles, CA.
- Persons with low diastolic and systolic perfusion pressures had a higher risk of POAG.
- DOPP <50 mmHg, the prevalence of glaucoma rapidly increases linearly.

SM a 40 y/o white female was referred for evaluation of glaucoma. Current Tx was Timolol and Alphagan.

- VA 20/20 OD/OS
- Ta 12/12 @ 10
- SLE: wnl
- DFE: 0.7 OD / 0.9 OS
- VF: Early near fixation loss OS
- Gonioscopy: CB 360 OU
- Medical Hx: LBP (100/65), pulse 54, Raynaud’s, Migraine HA
- Family Hx: Negative
Visual Field Loss
Patient is contraindicated for beta blockers.
How Low Can You Go!

- Meds: Alphagan P, Lumigan, Ginkgo
- Ta:14/11 @ 9:30
- Migraines increased x 4 weeks, episode of syncope x 1 week
- Serial BP 2 AM 58/30 / pulse 54

NTG- Differential Diagnosis

- Diurnal Variation
- Vasculitis
- Optic Atrophy
  - Old AION
  - Previous RBON
- Compressive ON
- Chronic marijuana use
- Prior Hypotensive episodes
- Systemic Beta-Blocker
- “Burned out” Glaucoma
- Sub-acute angle closure
- History steroid use
- Ocular Ischemic Syndrome
Nocturnal Hypotension: Its role in Visual Field Progression

- Graham SL, Drance S: Surv Ophthalmol Jun 1999
- 84 patients 24 hour ambulatory BP
- Nocturnal BP variables were lower in patients with progressive VF loss
- Patients with > nocturnal dips were more likely to show VF loss even with good IOP control
- Increased risk of disc hem's

NORMAL TENSION: ABNORMAL RESULTS

- ANDERSON et al AJO
  - EXAMINED NTG'S FOR MULTIPLE VARIABLES (AGE, GENDER, BP AND MIGRAINES)
  - MIGRAINES, DISC HEM'S MOST NOTABLE RISK FOR PROGRESSION
  - AGE, RACE NEXT
  - 230 PATIENTS/NTG/IOP< 20mm Hg
NTG

- 99 WOMEN/61 MEN
- 23 WOMEN WITH H/O MIGRAINES
- 2 MEN
- WOMEN WITH MIGRAINES HAD FASTEST RATE OF PROGRESSION

THE BIG DIPPER

- STIMADA K et al, CIRCULATION 1990 COLLIGNON N et al INT OPH 1998
  - NOCTURNAL HYPOTENSION OCURS IN 10% OF POPULATION
  - “BIG DIPPERS” > 10%
  - INCREASED RISK OF MI AND LOWER LIMB ISCHEMIA
  - INCREASED RISK OF VF LOSS AND DISC DAMAGE
Treatment of Low Blood Flow

- middle aged women with history of low BP
- increase salt
- licorice extract (glycerrhinic acid) is aldosterone agonist
- elderly patients taking BP meds with BP <130/75
- if no heart disease or stroke, discuss reduced anti-hypertensive therapy

90 Years of ZEISS and Retinal Imaging

1. First commercial Retina Camera in the early 1920s.
3. First FDA-Cleared OCTA in late 2015

ZEISS is a revered brand worldwide, not just in Eye Care. We are involved in dozens of other markets at the highest levels.
Zeiss AngioPlex™ = One Fast Cubic Scan x4

3 mm X 3 mm Angio

- 245 B-Scans (cuts)
- Each Repeated 4x
  w/FastTrac™ LSO Lock-On
- 245 axial A-Scans per B-Scan, e 1024 voxels deep

Total = 240,000 A-scans, ~ 5.0 secs

Normal 3x3 Angio Cube OD - Full Retina (L) and Deep Plexus (R)
This case courtesy of Carolyn Majcher, OD. Incarnate Word, San Antonio
Glaucoma

Superficial
Glaucoma

Superficial
Dry Eye Syndrome in Glaucoma

I Tear Deficiency
II Evaporative 2\textsuperscript{nd} to Goblet Cell Deficiency / Mucin Deficiency
III Blepharitis / Meibomian Gland Disease
IV Exposure Keratopathy

Dry Eye Syndrome Co-Conspirators
Exacerbate or Masquerade DES

1. SLK (superior limbic keratoconjunctivitis)
2. Medicomentosa (topical medication toxicity)
3. SPK of Thygeson
4. Mucous Fishing Syndrome
5. Contact Lens Related Toxicity
6. Chemical Toxicity (eg hairspray toxicity)
7. Allergic / Atopic Conjunctivitis
8. Conjunctivochalasis (CCh)
9. Floppy Lid Syndrome
Current and Emerging Therapies

- Established
  - Cyclosporine A (Restasis)
  - Thermal pulsation therapy (LipiFlow)

- Emerging
  - Lifitegrast (Xiidra)
  - Nasal neurostimulation (Allergan/Oculeve)

- Pipeline – Phase II-III
  - New delivery vehicles
  - Nanoparticle technology
  - New small-molecule therapies

Cyclosporine A (Restasis)

- Immunosuppressive agent when administered systemically
- Inhibits T-cell activation, enabling patients to produce their own tears\(^1\)
- In clinical trials:
  - Increased tear production (superior Schirmer scores)
  - Reduced corneal staining
  - Increased goblet cell density
  - Reduced reliance on artificial tears

RESTASIS® (cyclosporine ophthalmic emulsion) 0.05% Helped Moderate and Severe Patients Make More of Their Own Real Tears1, 2

![Graph showing mean % change in Schirmer scores over time](image)


Thermal Pulsation Therapy (LipiFlow)

- Only approved treatment for MGD
- Heats inner lid to 42.5°C combined with simultaneous pulsation for gland evacuation
  * Protects cornea and globe from heat and pressure
- Outcomes:
  * Sustained effects over 12 months with 1 treatment1
    * 50% reduction in symptoms
    * 3x improvement in MG secretions
  * Improves comfort & MG function after cataract surgery
  * Increases comfortable CL wear time3

Emerging Treatments

Lifitegrast

- First prescription FDA approved drop to treat signs AND symptoms of DED
- Lifitegrast versus vehicle was evaluated for safety and efficacy in four clinical trials with a total of 2,133 patients, Age range 19–97 yrs (mean 59)

- Primary Endpoints
  - Improvement in the signs (measured by Inferior Corneal Staining Score)
  - Symptoms of dry eye disease (measured by Eye Dryness Score)
Integrins and the Immunological Synapse: Role in Inflammation

- Integrins are transmembrane receptors that bridge the cell-cell interactions
- LFA-1
  - Cell-surface protein on T cell
- ICAM-1
  - Cell surface protein on APC
  - Also present on conjunctival endothelial and epithelial cells
  - Expressed at higher levels in patients with dry eye disease

**LFA-1 and ICAM-1 binding is central to the immunological response**

**Lifitegrast: MOA**

- Lifitegrast binds to integrin receptor LFA-1
- Blocks the interaction of LFA-1 with ICAM-1 that signals the start of the inflammatory cycle. May inhibit:
  - T-cell activation
  - T-cell migration
  - Secretion of inflammatory cytokines
Primary End Point: Eye Dryness Score

Lifitigrast Effects on Signs/Symptoms

- Onset of action in as early as 2 weeks\(^1\)
  - Larger reduction in dryness observed at week 6
  - Larger reduction in inferior corneal staining at week 12
- Initiate treatment for signs or symptoms of Dry Eye

Primary End Point: Inferior Corneal Staining

<table>
<thead>
<tr>
<th>Study</th>
<th>Favors Xildra</th>
<th>Favors Vehicle</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
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<tr>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ICSS Treatment Difference in the Mean Change From Baseline

Xildra (n=58)  
Vehicle (n=58)

Xildra (n=295)  
Vehicle (n=295)

Xildra (n=358)  
Vehicle (n=356)

Xildra (n=355)  
Vehicle (n=356)

Safety of Lifitegrast Ophthalmic Solution 5.0% in Patients With Dry Eye Disease: A 1-Year, Multicenter, Randomized, Placebo-Controlled Study

Eric D. Dowdwell, MD, FAAO‡, Paul M. Karpitch, OD, FAAO†, Parag A. Mangude, MD,†  
Kelly K. Nichols, OD, MPH, PhD,‡, Aperna Raychaudhuri, PhD,‡, Monica Ray, OD, MPH, FAAO‡, and Charles P. Sumba, MD§

Purpose: To evaluate the safety of lifitegrast ophthalmic solution 5.0% in patients with dry eye disease compared with placebo.

Methods: This was a 12-month, randomized, double-masked, multicenter study to evaluate the safety of lifitegrast ophthalmic solution 5.0% in patients with dry eye disease. Patients were randomized to receive lifitegrast 5.0% ophthalmic solution (n = 295) or placebo (n = 295) twice daily for 110 days. The primary outcome was the incidence and severity of ocular adverse events and systemic adverse events. Additional adverse events, laboratory parameters, and vital signs were evaluated. Results: The safety population comprised 590 participants (295 lifitegrast; 295 placebo). There were no serious adverse events. Xilrafus, an allergen, that binds to the eye and induces a chronic inflammatory response, was also evaluated. Xilrafus was 94.2% in the placebo group and 98.0% in the lifitegrast group. The study is the first to evaluate the effect of lifitegrast on the ocular surface.

Conclusion: Lifitegrast ophthalmic solution 5.0% seemed safe and well tolerated in this study, with no significant adverse events detected. Further study is needed to evaluate the long-term effects of lifitegrast on the ocular surface.

Lifitegrast is a small-molecule integrin antagonist that was developed as a treatment for dry eye disease. It works by targeting integrins, which are proteins that bind to the extracellular matrix and play a role in cell-cell and cell-matrix interactions. In the current study, lifitegrast was administered twice daily for 12 months to 590 patients with dry eye disease. The results showed no significant differences in ocular adverse events between the lifitegrast and placebo groups. However, further study is needed to evaluate the long-term effects of lifitegrast on the ocular surface.

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**Clinical Science**

**Effect of Oral Re-esterified Omega-3 Nutritional Supplementation on Dry Eyes**

Alice T. Epitropoulou, MD*, Eric D. Dannenfield, MD, F, Zuhin A. Shah, MPH, LI Edward J. Holland, MD, F Michael Gross, MD, F, William J. Paulson, MD, F, Cynthia Marzorati, MD, F, Stephen E. Lane, MD, F, Melissa Toy, MD, F** Frank A. Bucci, Jr, MD, F† and Henry D. Perry, MD‡

**Purpose**: To assess the effect of oral re-esterified omega-3 fish oil in patients with dry eye disease. Patients were randomized to receive re-esterified omega-3 fatty acids or placebo for 12 weeks. The primary outcomes were the changes in signs and symptoms of dry eye disease.

**Results**: One hundred five subjects completed the study. They were randomized to omega-3 (n = 64) and control group (n = 41). The omega-3 group experienced a significant reduction in signs and symptoms of dry eye disease compared to the control group. The omega-3 group showed a 25% reduction in symptoms, while the control group showed no change.

**Key Words**: dry eye, omega-3 fatty acids, tear composition, re-esterified omega-3, meibomian gland dysfunction (Cornea 2018;0:0-0)

Dry eye disease (DED) is a common, yet complex, condition that affects millions of people around the world. The symptoms of dry eye disease include redness, irritation, and discomfort. However, the underlying causes of dry eye disease are not fully understood. Recent studies have suggested that omega-3 fatty acids may play a role in the management of dry eye disease.

The rationale for treatment with oral omega-3 supplementation is based on the anti-inflammatory properties of omega-3 fatty acids. Omega-3 fatty acids have been shown to reduce inflammation and promote a healthier tear film.

The study results indicate that oral re-esterified omega-3 supplementation is effective in reducing the signs and symptoms of dry eye disease. Further research is needed to determine the optimal dosage and duration of treatment for optimal results.
**Dosing Protocol – Dry Eye Omega Benefit**

**Therapeutic Dose** - Four capsules daily with meals

**Indications:**
- Ocular Surface Inflammation
- Pre-surgical Patients

**Supplement Facts**

<table>
<thead>
<tr>
<th>Component</th>
<th>Servings Per Container: XX</th>
<th>% Daily Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calories (energy)</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Calories from Fat</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Total Fat</td>
<td>4.5 g</td>
<td>7%*</td>
</tr>
<tr>
<td>Poyunsaturated Fat</td>
<td>0 g</td>
<td></td>
</tr>
<tr>
<td>Monounsaturated Fat</td>
<td>1 g</td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td>10 mg</td>
<td>3%*</td>
</tr>
<tr>
<td>Protein</td>
<td>&lt;1 g</td>
<td></td>
</tr>
<tr>
<td>Vitamin D (as D3 Cholecalciferol)</td>
<td>1000 IU</td>
<td>250%</td>
</tr>
<tr>
<td>Omega-3 Fatty Acids as TG**</td>
<td>2588 mg</td>
<td></td>
</tr>
<tr>
<td>EPA (Eicosapentanoic acid) as TG**</td>
<td>1880 mg</td>
<td></td>
</tr>
<tr>
<td>DHA (Docosahexanoic acid) as TG**</td>
<td>995 mg</td>
<td></td>
</tr>
<tr>
<td>Additional Omega-3 Fatty Acids as TG**</td>
<td>428 mg</td>
<td></td>
</tr>
</tbody>
</table>

* Percent Daily Values are based on a 2,000 calorie diet.
* Daily Value not established.
** Saturated Fatty Acids

Ingredients: Highly Refined and Concentrated Omega-3 Fish Oil (anchovy, sardine, mackerel), Capsule Shell (gelatin, glycerin, purified water), Natural Mixed Berry/Orange Flavor, Natural Mixed Tocopherols (soy), and Cholecalciferol.

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**Nasal Neurostimulation**

- Targets the nasolacrimal reflex by stimulating an ophthalmic branch of afferent trigeminal nerve fibers in nasal cavity
- Results in upregulation of parasympathetic activity in the superior salivatory nucleus of the brain
- Stimulates the lacrimal glands to increase tear production
- Immediate response to stimulation
Nasal Neurostimulation: Corneal & Conjunctival Staining

Corneal staining was reduced relative to baseline in both eyes

Conjunctival staining was reduced relative to baseline in both eyes
Nasal Neurostimulation: Symptoms Reduced

Nasal neurostimulation induces mucin secretion from goblet cells.

Nasal Neurostimulation: Mucin Secretion

- Nasal neurostimulation induces mucin secretion from goblet cells
Visual Impairment and Intracranial Pressure - VIIP

Optic Disc Edema, Globe Flattening, Choroidal Folds, and Hyperopic Shifts Observed in Astronauts after Long-duration Space Flight

Thomas H. Mader, MD,1 C. Robert Gibson, OD,2 Anastasia F. Pass, OD, JD,3 Larry A. Kramer, MD,4 Andrew G. Lee, MD,5 Jennifer Figueiras, PhD,6 William J. Torner, MD,6 Joseph P. Derosa, MD,6 Douglas R. Hamilton, MD, PhD,7 Ashot Sargsyan, MD,7 John L. Phillips, PhD,7 Duc Tran, DO,2 William Lipsky, MD,2 Jung Choi, OD,2 Claudia Stern, MD, PhD,9 Rafik Koroumian, MD,10 James D. Polk, DO9

Axonal Transport

Glaucoma occurs when IOP is higher than ICP

VIIP, IIH, and Hypotony are diseases when ICP is higher than IOP
4 Signs of VIP

- Papilledema
- Globe flattening
- Choroidal Folds
- Hyperopic Shift

The Clinical Data Story

Micropipette tissue pressure measurements in dog (B) as the micropipette is passed from the vitreous region, the prelaminar region, the lamina and into the retrolaminar optic nerve.

Depth of penetration (µm)

Pressure (mmHg)

- 450
- 480
- 520
- 558
- 595
- 660
- 756
- 1034
- 842
- 919
- 998

Time

| 153 seconds | 10 seconds | 18s | 7 sec | 137 seconds |


CSF pressure

Translaminar pressure difference
6. Trab’s vs Tubes: A New Paradigm

Opp’s Move Over for the New Kid in Town!

(FIGURE 1) The current hypothesis suggests wearing the goggies for as little as 6 hours a day might be able to mitigate the pressure effect.

(Photo courtesy of John Berdahl, MD)
Baerveldt

Baerveldt Patch Graft Placement
Baerveldt Advantages

• Effective for almost all types of glaucoma
• Able to do when other procedures are not possible
• Not dependent on patient healing
• Can implant multiple devices

TUBE SHUNT SURGERY

• Tube in anterior chamber connects to a reservoir sutured to posterior globe
  • reservoir (plate) prevents scar from blocking tube opening
  • scar around reservoir will limit IOP
TUBE PROBLEMS

• Gradual failure due to scarring around reservoir
• Erosion of tube through conjunctiva
  • Consequent serious risk of infection
• Decompensation of corneal endothelium
  • can occur even without contact of tube and endothelium
  • corneal transplants usually fail over several years if tube is in anterior chamber
  • tube can be moved to posterior chamber after vitrectomy

Common tube types

• Ahmed has a valve to limit early hypotony
• Baerveldt has larger surface area
  • 1-2 points lower than Ahmed
  • but greater risk of suprachoroidal hemorrhage
Physiologic outflow

- Two subsections:
  - Trabecular meshwork
  - Schlemm’s canal and episcleral veins
- Conventional fistulization surgery bypasses both
- Non-penetrating may bypass just TM or both sections

7. MIGS: The Future of Glaucoma Therapy
MIGS – Micro-Invasive Glaucoma Surgery

- Ab-interno approach
- Clear corneal micro-incision (<2.0mm)
- Conjunctival sparing
- Minimally traumatic
- Negligible disruption of normal anatomy/physiology
- Excellent biocompatibility
- Efficacious
- Extremely high safety profile
- Rapid recovery

Current OAG Treatment Algorithm

1. Newly Diagnosed POAG Patient
2. Prescription Therapy (30 – 90 Days)
3. Laser Trabeculoplasty
4. Switch or Add Rx Therapy
5. Add More Rx Therapy
6. Invasive Surgery Trabeculectomy

Drug therapy has been the standard of care in glaucoma for over 30 years. Approximately 50% of patients are taking 2 or more medications increasing the disease management challenges of glaucoma and financial burden to patients and the healthcare system.2,3

1. AAO Preferred Practice Pattern: Primary Open Angle Glaucoma – AAO committee 2003
Effect of Cataract Surgery on IOP Reduction

According to Preferred Practice Patterns, cataract surgery with IOL implantation alone results in a modest reduction in IOP of less than 2mm Hg on average.¹

1. Chart review of 588 normotensive and OHT subjects²
2. 53% had a mean reduction of 1.6 to 2.5 mm Hg²

<table>
<thead>
<tr>
<th>Baseline IOP (mm Hg)</th>
<th>23-31</th>
<th>20-22</th>
<th>18-19</th>
<th>15-17</th>
<th>9-14</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>19</td>
<td>62</td>
<td>86</td>
<td>223</td>
<td>196</td>
</tr>
</tbody>
</table>

- Chart review of 588 normotensive and OHT subjects²
- 53% had a mean reduction of 1.6 to 2.5 mm Hg²

Selective and Argon Laser Trabeculoplasty

- Compared to medications, SLT demonstrates similar IOP reductions (6-8mm Hg from baseline), safety, and tolerability, and no issues with compliance/adherence¹
- Following laser trabeculoplasty, many patients require the addition of medication to maintain target IOP

OAG Patients Washed out of Medication, 360° SLT group²
- required additional medication @ 1yr
- did not require additional medication @ 1yr

Newly Diagnosed Patients, ALT group³
- required additional medication @ 2 yrs
- did not require additional medication @ 2 yrs

Primary Source of Resistance: Diseased Trabecular Meshwork

- Abnormality of the trabecular meshwork (TM) is the primary source of elevated intraocular pressure (IOP) in open-angle glaucoma\(^1\)
- 50-75% of total resistance to aqueous humor outflow is found in the juxtacanalicular tissue of the TM\(^2,3\)
- Bypassing the TM allows access to Schlemm's canal and the distal system in order to improve aqueous outflow through the conventional outflow pathways

---

\(^1\)Grant WM. Further studies on facility of flow through the trabecular meshwork. Arch Ophthalmol. 1958;60(4):523-33.
\(^2\)Rosenquist R, Epstein D, Melamed S, Johnson M, Grant WM. Outflow resistance of enucleated human eyes at two different perfusion pressures and different extents of trabeculotomy.

---

iStent® Indication for Use
(US Label)

The iStent Trabecular Micro-Bypass Stent is indicated for use in conjunction with cataract surgery for the reduction of intraocular pressure (IOP) in adult patients with mild to moderate open-angle glaucoma currently treated with ocular hypotensive medication.
Distribution of Aqueous Veins

De Vries 1947

201 Aqueous Veins in Left Eyes
208 Aqueous Veins in Right Eyes

Recipient Episcleral Vein

Aqueous Vein
iStent® Surgical Procedure

- iStent® rails are seated against scleral wall of Schlemm’s canal
- iStent® Snorkel sits parallel to the iris plane

[Image: Photo courtesy of Ike Ahmed, MD]

[Image: Photo courtesy of Tom Samuelson, MD]
US IDE Trial –
Primary Endpoint

Percent of Patients with IOP ≤21 mm Hg Without Medication Use

- At 12 months, 72% of iStent® subjects with IOP ≤ 21 mm Hg without medication vs. 50% with cataract surgery alone (P<0.001)

US IDE Trial –
Secondary Endpoint

Percent of Patients with IOP ≤20% Reduction in IOP Without Medication Use

- At 12 months, 66% of iStent® subjects with ≥ 20% IOP reduction without medication vs. 48% with cataract surgery alone (P=0.003)
**iStent® Pivotal US IDE Trial**

**Significant IOP and Medication Reductions**

At 12 months:

- >30% reduction from baseline IOP
  - Similar outcome validated adherence to study design *(manage to threshold IOP)*
  - For iStent subjects, IOP reduction with significantly less medication *(P=0.001)*
  - 15% of iStent vs. 35% cataract group on medication

---

**Percent of Patients on Ocular Hypotensive Medication**

![Graph showing percentage of patients on ocular hypotensive medication](image)


---

**iStent® US IDE Trial - 2-year Follow-up on IOP and Medications**

**Mean IOP Over Time - Consistent Cohort**

- **iStent + Cataract Surgery**
- **Cataract Surgery Only**

**Mean Medications Over Time - Consistent Cohort**

**Materials**

- Permanent, collagen derived, gelatin implant, 6 mm long
- Implant is soft, compressible, and flexible when hydrated
- Material and design mitigate traditional implant issues
  - Absence of Migration
  - Tissue-conforming
  - Non-inflammatory

**Methods**

- Pre-loaded, disposable Inserter
- Handles like IOL inserter
- Straightforward procedure
- With or without cataract surgery
- Removable and/or repeatable
- Mild, Moderate & Refractory Glaucoma

---

**Mechanism of Action**

**Ab Interno Sub-Conjunctival Drainage**

- Surgical “Gold Standard” IOP reduction in minimally invasively procedure
- Clinically proven outflow pathway
- Bypasses all potential outflow obstructions
- Conjunctiva sparing: alternative surgical options remain
- Single implant delivers desired effectiveness

**Gelatin Material is**

**Tissue Conforming**
*Mean preoperative IOP is best medicated. Patients were not washed out prior to surgery.

**InnFocus, Inc.**

- Based in Miami, Florida
- Founded in 2004
- Biomaterials-based company
- Have worked closely with Bascom Palmer Eye Institute
- Two of the three inventors of the InnFocus MicroShunt are from BPEI
  - Francisco Fantes, M.D.
  - Jean Marie Parel, Ph.D.
- The third inventor is Leonard Pinchuk, Ph.D, D.Sc., who is the President and CEO of InnFocus.
The Device: The InnFocus MicroShunt™
(previously known as the MIDI Arrow)

- Outer diameter is 350 μm
- Lumen diameter is 70 μm
- 8.5 mm long
- Matches the compliance of ocular tissue
- Conforms to the curvature of the eye
- Does not require a cadaver patch
  - Soft, flexible, rubbery, no erosion
- Atraumatic fins prevent
  - Migration
  - Peri-tubular leakage
- No MRI interference

Hagen-Poiseuille Equation

\[ D = \frac{4 \sqrt{2.547 \times 10^6 Q L}}{P_0 - P_L} \]

Dominican Republic: Average Change in Intraocular Pressure with Time:
Alone and Implanted in Combination with Phacoemulsification

![Graph showing average change in intraocular pressure with time for MicroShunt alone and combined with Phacoemulsification in the Dominican Republic.](image)

- MicroShunt with Phacoemulsification: N=23
- MicroShunt Alone: N=19
- N=2
Trabeculectomy with Express Minishunt

Express Minishunt Advantages

• Reduces operating time
• Eyes appear to be quieter earlier in post-op course
• No iridectomy
• Uniform opening
• If hypotony occurs, tends to be less severe
Resident Surgery with Ex-PRESS

- No difference
  - postoperative IOP
  - proportional decrease in IOP
- Ex-PRESS group
  - Significantly less medication to control IOP at 3 months
  - No difference at 6 months or 1 year (P≥0.28)
  - More Ex-PRESS patients had good IOP control without meds at 3 (P=0.057) and 6 months (P=0.076)
  - No difference was found in the rates of sight-threatening complications (P≥0.22)

Seider MI. Resident-performed Ex-PRESS Shunt Implantation Versus Trabeculectomy J Glaucoma. 2011 Apr 25. [Epub ahead of print]

Retrospective Case Series

- Moorefields Bleb Grading System
  - Less vascularity and height but more diffuse area associated with the Ex-PRESS blebs
  - Fewer cases of early postoperative hypotony and hyphema
  - Final percent IOP lowering was similar
  - Quicker visual recovery
    - The Ex-PRESS group required fewer postoperative visits compared with the trabeculectomy group (P < .000).

Ex-PRESS in prior operated eyes

- Success complete in 60 (60%) and qualified in 24 (24%) eyes
- Mean IOP
  - 27.7 ± 9.2 mm Hg with 2.73 ± 1.1
  - 14.02 ± 5.1 mm Hg with 0.72 ± 1.06 drugs (p < 0.0001)
- Failure
  - Uncontrolled IOP (11%)
  - bleb needling (4%)
  - persistent hypotony (1%)


5 year study Ex-press vs Trabeculectomy

- EX-PRESS more effective without medication
  - At year 1 12.8% of patients required IOP meds after EX-PRESS implantation vs 35.9% after trabeculectomy
  - At year 5 (41% versus 53.9%)
- Responder rate was higher with EX-PRESS
- Time to failure was longer
- Surgical interventions for complications were fewer after EX-PRESS implantation