Advances in Glaucoma Surgical Therapy

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Considerations

Impact of subsequent or prior procedures
Realistic expectations on intraocular pressure control and continuing medical therapy
Expected and tolerable side effects and complications

Trends

Streamlining of existing procedures
- Express Minishunt
- Use of Fibrin glue to reduce suturing
- Alternative tube placement techniques

Less invasive procedures
- Canaloplasty
- Trabectome
- Gold Shunt
- Glaukos shunt
- ECP

Trabecular Bypass Flow Hypothesis

Zhou et al introduced a hypothesis that evaluated the effect of a theoretical channel created through the TM (a trabecular bypass) on the facility of outflow and IOP. The authors established equations that govern the pressure and circumferential flow in Schlemm’s canal. Two types of bypasses permitting either unidirectional or bidirectional flow were incorporated to derive the facility of outflow and the reduced IOP.

Results:
- In normal healthy eyes, the facility of outflow increased by 13% and 26% in the presence of a unidirectional and bidirectional bypass, respectively.
- Circumferential flow was significant only in the immediate quadrant to the bypass.
- In either case, the higher the baseline IOP, the greater the reduction.

Theoretical Evidence

Grant demonstrated in 1963 that 75% of resistance to aqueous outflow occurs in the trabecular meshwork (TM). Grant also found that the locus of abnormal (and normal) resistance to out-flow of aqueous humor in primary open-angle glaucoma(s) is at, or just proximal to, the inner wall of Schlemm’s canal.

Johnson et al confirmed that the inner wall of TM is the site of greatest outflow resistance in the normal eye, as well as the increased outflow resistance in the glaucomatous eye.

It follows that reducing trabecular meshwork resistance may be an effective way to restore physiologic outflow.
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.1,2,3

1AAO Preferred Practice Pattern; Primary Open Angle Glaucoma. AAO Committee 2003.

Newly Diagnosed (Pseudo Patient)
- Top MIG's in 2018
  - Glaukos iStent
  - Xen Glaucoma Implant
  - CyPass
  - Canaloplasty
  - Trabeculectomy
- Treatment Algorithm

Trabeculectomy with Express Minishunt

Express Mini-shunt 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

Express Mini-shunt Disadvantages
- Needs some suturing as in trabeculectomy
- Dependent on patient healing
- Anti-metabolites still routinely used
- Patient has bleb
- Hypotony possible

Reasons to use the Express
- Simplify procedure
- Shorten surgery time
- Decrease tissue manipulation
- Eliminate need for iridectomy
- Decrease chance of ostium obstruction
- Regulate flow in short term
- Create less short term inflammation
Arguments Against
Expense
Foreign body
Metal in eye
Corneal contact

Patient Selection
Same as trabeculectomy
May work better in high risk patients
ICE patients
NV patients
Shallow/synechiae

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)

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%)


Patient Selection
Same as trabeculectomy
May work better in high risk patients
ICE patients
NV patients
Shallow/synechiae

Retrospective Case Series
Final percent IOP lowering was similar
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
Quick visual recovery
- The Ex-PRESS group required fewer postoperative visits compared with the trabeculectomy group (P < .000).


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

Results
The mean preoperative IOP was 23.7 ± 9.3 and the mean postoperative IOP on the last follow up day was 10.4 ± 4.5 (p<0.001) over a mean follow up period of 199 days (range 29-608).
The mean number of medications used preoperatively was 2.83 ± 1.1 and postoperatively was 0.023 ± 1 (p<0.001).
Complications as hypotony, bleb leak, choroidal detachment, and transient hyphema were detected.

Outcomes
Studies overall suggest compared to trabeculectomy-
- Less severe hypotony
- Less bleeding
- Less inflammation
- Faster visual recovery
- Similar long term IOP control

ECP/TCP

ECP Advantages
Quick procedure, especially in cataract setting
Titratable
Can be done with outflow procedures
Hypotony unlikely

ECP Disadvantages
Some learning curve to avoid complications
Inflammation possible
IOP does not decrease rapidly
Difficult to do in some eyes

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**
(Among 409 Aqueous Veins)

**Aqueous Veins**

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

**iStent® Surgery**
Inject a viscoelastic into the anterior chamber. Use a miotic if desired to help open the angle.

**US IDE Trial – Primary Endpoint**
Percent of Patients with IOP ≤ 21 mm Hg Without Medication Use

- **Cataract Surgery**
- **iStent ®**

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


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

- At 2 years, 95% of eyes had an IOP ≤15 mmHg, 100% ≤18 mmHg...

- 50% were on 0 medications, compared to 6% preop...

- At 2 years, mean IOP reduction was 22% with a 56% reduction in mean medications...

- IOP reduction higher with higher baseline IOP...

- Patients with pre-op IOP ≥26 achieved mean IOP reduction of 11.28 mm Hg...

At 3 years mean IOP was <15 mm Hg with an 86% reduction in medications...

- Consecutive series of 82 eyes: decision to implant based on patient desire to reduce topical meds and intent to offer surgical treatment with favorable safety profile.

- Similar outcome validated adherence to study design (manage to threshold IOP).

- For iStent subjects, IOP reduction with significantly less medication (P=0.001).

• Similar outcome validated adherence to study design (manage to threshold IOP).

• For iStent subjects, IOP reduction with significantly less medication (P=0.001).
Outcomes Through 48 Months After MIGS with 2 Trabecular Bypass Stents in Eyes with OAG Not Controlled on 1 Medication

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TRUSTEE DARTMOUTH MEDICAL SCHOOL

DEMOGRAPHICS AND PREOPERATIVE CHARACTERISTICS

39 subjects enrolled; 30 completed Month 48

Gender (n) 22 male / 17 female
Race 100% Caucasian
Age (Mean ± SD) 66.7 ± 10.0 years (Range 50-90)
Lens Status (n) 35 phakic / 4 pseudophakic
Preoperative C/D Ratio (Mean ± SD) 0.7 ± 0.2
Preoperative Medicated IOP (Mean ± SD) 20.6 ± 2.0 mmHg
Preoperative Unmedicated (Post-washout) IOP (Mean ± SD) 24.1 ± 1.4 mmHg

Type of Medications (%; n)
- Beta-blocker: 56.4% (n=22)
- Carbonic anhydrase inhibitor: 25.6% (n =10)
- Prostaglandin analogue: 15.4% (n =6)
- Alpha agonist: 2.6% (n=1)

FAVORABLE SAFETY PROFILE

- All subjects underwent uncomplicated implantation of 2 iStent devices
- No device-related adverse events were observed and no subjects experienced hypotony
- AEs mostly involved BCVA loss due to progression of pre-existing cataract
- BCVA, C/D ratio, VF, and central corneal thickness generally stable over time

MEAN IOP OVER TIME

Mean IOP ≤ 15.2 mmHg through M48
87% of eyes did not require ocular hypotensive meds post-implantation

POSTOPERATIVE IOP

Primary and secondary endpoints at 13 months were achieved by 92% of eyes
At month 48, both endpoints achieved by 90% of eyes

Favorable safety profile

| Event | N/All (%)
|-------|---------|
| BCM loss due to progression of pre-existing cataract (1 of 4 subjects had cataract) | 1 (3.2)
| Death | 2 (6.9)
| Cataract progression | 1 (3.2)
| Early postoperative hypotony (same subject with initial cataract) | 1 (3.2)
| Initial hypotony (same subject with hyphema) | 1 (3.2)
| Proliferative diabetic retinopathy | 1 (3.2)
| Scar from age-related macular degeneration | 1 (3.2)
| Secondary surgical intervention (cataract surgery) | 1 (3.2)

Total Adverse Events: 12 (30.8%)
Total Subjects with Adverse Events: 10 (25.6%

Co-Management Coding

iStent implantation is described by CPT code 0191T
- 0191T is a Category III (new technology) code
- 0191T has no assigned Relative Value Units or Global Period
- There is no postop co-management fee for any T-code
- Medicare carriers will not recognize modifiers -54 & -55 for 0191T

Modifiers -54 & -55 can still be appended to CPT code 66984
- Modifier -54: surgical care only
- Modifier -55: all/part of outpatient postoperative care
- Surgeon MUST initiate the notification to Medicare by using modifier -54 with the claim
- In localities where Medicare has a higher physician payment for 0113T than for 66984 and where 66984 is reduced by 50%, payment for 66984-550 will be reduced by 50%
Ivantis /Hydrus Microstent

The FDA's approval was based on the 24-month results from the HORIZON trial, the largest MIGS study to date. The study included 556 mild to moderate glaucoma patients randomly assigned to undergo cataract surgery with or without the microstent. More than 77% of patients with the implant exhibited a significant decline in unmedicated IOP, compared with 58% of the control group. On average, the device reduced IOP by 7.5 mmHg, approximately 2.3 mmHg more than the cataract surgery-only group.
Hydrus Microstent

Cypass: Suprachoroidal Stent

Cypass: Suprachoroidal Stent
Stephen Lane, Chief Medical Officer, Alcon, said, “Although we are removing the product from the market now out of an abundance of caution, we intend to partner with peer-review literature benchmarks of cataract-related endothelial cell loss. FDA and other regulators to explore labeling changes that would support the reintroduction of the CyPass Micro-Stent in the future.”

At two years post-surgery, there was little difference in endothelial cell loss between the CyPass Micro-Stent and cataract surgery-only groups, and results were consistent with those observed at the time of cataract surgery, as compared to subjects undergoing cataract surgery alone.

The COMPASS study demonstrated a statistically significant reduction in IOP at two years post-surgery in subjects implanted with the CyPass Micro-Stent at moderate primary open-angle glaucoma based on the results of the landmark two-year COMPASS study. The US Food and Drug Administration (FDA) approved the CyPass Micro-Stent in July 2016 for use in conjunction with cataract surgery in adult patients with mild-to-moderate primary open-angle glaucoma. In this study, the CyPass Micro-Stent group demonstrated a statistically significant reduction in IOP, compared to the group who underwent cataract surgery alone. The CyPass Micro-Stent group exhibited statistically significant endothelial cell loss compared to the group who underwent cataract surgery alone.

On the subjects who participated in the COMPASS study for an additional three years, with analysis of the completed data set at five years post-surgery. At five years, the CyPass Micro-Stent group maintained a statistically significant reduction in IOP compared to the group who underwent cataract surgery alone. The move is based on an analysis of five-year post-surgery data from the COMPASS-XT long-term safety study. The COMPASS-XT study was designed to collect safety data and clinical outcomes of the CyPass Micro-Stent for up to five years post-surgery. The results of the COMPASS-XT study were consistent with those of the original COMPASS study, demonstrating a statistically significant reduction in IOP at five years post-surgery in subjects implanted with the CyPass Micro-Stent at moderate primary open-angle glaucoma.

Alcon also advised surgeons to immediately cease further implantation with the CyPass Micro-Stent and to return any unused devices to Alcon.
CyPass Recall

![CyPass Recall Graph]

Endothelial Cell Loss Rate per Year

- 1% loss
- 2% loss
- 3% loss
- 4% loss
- 5% loss
- 6% loss
- 7% loss
- 8% loss
- 9% loss
- 10% loss
- 11% loss
- 12% loss
- 13% loss
- 14% loss
- 15% loss

XEN Glaucoma Implant™ Materials and Methods

**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
  - 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

XEN Glaucoma Implant™ Mechanism of Action

**All Internal 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

**Allergan:XEN**

- Gelatin Material is Tissue Conforming

Initial Clinical Results: From A Multi-Center Study on Early Moderate Stage Population

<table>
<thead>
<tr>
<th>% IOP Reduction</th>
<th>IOP (mmHg)</th>
<th>Washout IOP</th>
<th>Washout IOP % Reduction</th>
<th>Best Medication IOP</th>
<th>Best Medication % Reduction</th>
<th>Best Medication</th>
<th>Washout IOP % Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>IOP 21.5 g. 5</td>
<td>10 (28)</td>
<td>10 (28)</td>
<td>-28%</td>
<td>10 (28)</td>
<td>-27%</td>
<td>10 (28)</td>
<td>10 (28)</td>
</tr>
<tr>
<td>IOP 21.6 g. 5</td>
<td>10 (28)</td>
<td>10 (28)</td>
<td>-27%</td>
<td>10 (28)</td>
<td>-26%</td>
<td>10 (28)</td>
<td>10 (28)</td>
</tr>
<tr>
<td>IOP 21.7 g. 5</td>
<td>10 (28)</td>
<td>10 (28)</td>
<td>-26%</td>
<td>10 (28)</td>
<td>-25%</td>
<td>10 (28)</td>
<td>10 (28)</td>
</tr>
<tr>
<td>IOP 21.8 g. 5</td>
<td>10 (28)</td>
<td>10 (28)</td>
<td>-24%</td>
<td>10 (28)</td>
<td>-23%</td>
<td>10 (28)</td>
<td>10 (28)</td>
</tr>
</tbody>
</table>

*Note: Washout IOP calculated at +30% from medicated IOP.

POAG Only

- Mean preoperative IOP in best medicated. Patients were not washed out prior to surgery.
Initial Clinical Results: From A Multi-Center Study on Severe/Refractory Population

<table>
<thead>
<tr>
<th></th>
<th>12M</th>
<th>18M</th>
<th>24M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean IOP (mmHg)</td>
<td>13.9±4.6</td>
<td>12.9±4.7</td>
<td>10.7±3.9</td>
</tr>
<tr>
<td>Mean Meds # per Mdx</td>
<td>3.1±1.4</td>
<td>3.3±1.3</td>
<td>3.3±1.2</td>
</tr>
</tbody>
</table>

Mean washout IOP: 22.6±4.3 mmHg

Mean post-op IOP: 22.6±4.3 mmHg

Mean post-op Meds: 3.1±1.3

Mean % reduction:
- 12M: 66%
- 18M: 66%
- 24M: 57%

% IOP reduction from Best Rx:
- 12M: 38%–52%
- 18M: 43%–55%
- 24M: 39%–53%

% IOP <21 mmHg and/or –20%
- 12M: 100%
- 18M: 100%
- 24M: 100%

% IOP <18 mmHg and/or –20%
- 12M: 97%
- 18M: 100%
- 24M: 100%

% IOP <16 mmHg and/or –30%
- 12M: 79%
- 18M: 92%
- 24M: 83%

Canaloplasty: akin to Angioplasty

“Canaloplasty is hydraulic angioplasty of Schlemm’s Canal with implantation of a suture stent”

How does Canaloplasty work?

Restores normal outflow physiology by internal filtration of aqueous

By stretching the trabecular meshwork

Thereby increasing the permeability of the trabecular meshwork

Preventing collapse of Schlemm’s Canal, thereby

Preventing blockage of outflow channels

Use of Microcatheter in Canal

- A flexible microcatheter with lighted beacon tip
- Injects viscoelastic to dilate the entire 360° of the canal and collector system
- Facilitates passage of tensioning suture to maintain patency of the canal

Canaloplasty Basics

Viscoelastic injection
- Dilates the canal
- May increase permeability of the trabecular meshwork
- Dilates the ostia of the collector channels

Multipurpose 10-0 Polypropylene suture stent:
- Maintains Schlemm’s Canal opening to allow fluid to flow circumferentially
- Places tension on the trabecular meshwork to increase permeability
- The mechanical equivalent of Pilocarpine
Canaloplasty, Viscodilation

Canaloplasty, Suture Tension

UBM Imaging

Rejuvenate the outflow system in patients with glaucoma

Restore a healthy IOP
- Without penetrating the eye
- Without creating a bleb or fistula
- Without undue postoperative care

Effects of Suture Tension

Ex-Vivo Perfusion Study - Utilizing Morton Grant Flow Model

Pressurize globe to a range of physiologic pressures
Apply tension to a suture implanted through the canal
Measure outflow facility (uL/Min / mmHg)

Canaloplasty, Suture Tension

Canaloplasty

IOP [mm Hg]

Baseline 1D 1W 1M 3M 6M 12M 18M 24M
Canaloplasty Multicenter Study

Prospective study

Inclusion criteria:
- Baseline treated IOP of ≥ 16 mmHg with history of IOP ≥ 21
- Age > 18 Years
- Diagnosed with primary open angle glaucoma, pigmentary glaucoma, exfoliative glaucoma, or POAG with narrow but not occludable angles after laser iridectomy

Exclusion criteria
- More than 2 laser trabeculoplasty
- Chronic uveitis
- PAS or history of angle closure

Results

16 Centers
184 eyes
- 161 (88.0%) Successful Dilation
- 154 (84.0%) Successful Suture Placement
- 46 (25.0%) Combined with Cataract Surgery
- 2 (0.9%) Failed to Complete Procedure
- 11 (6.0%) Converted to Trabeculectomy/Tube Shunt
- 2 (1.0%) Surgically Revised
- 46 (25%) Combined Canaloplasty Cataract

Lost to Follow-up
- 4 (2.0%) Reported deceased
- 1 (0.5%) Patient withdrew from study
- 6 (3.0%) Lost to Follow-up

Canaloplasty Combined with Phacoemulsification Cataract Surgery

A subset of eyes in the prospective, international multi-center study of canaloplasty to treat open angle glaucoma also presented with visually significant cataract and were treated with combined surgery.
Combined Procedure Results

<table>
<thead>
<tr>
<th>Baseline</th>
<th>6 Months</th>
<th>12 Months</th>
<th>18 Months</th>
<th>24 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avg</td>
<td>0.38</td>
<td>0.21</td>
<td>0.21</td>
<td>0.18</td>
</tr>
<tr>
<td>SD</td>
<td>0.34</td>
<td>0.25</td>
<td>0.24</td>
<td>0.17</td>
</tr>
<tr>
<td>%</td>
<td>0.4</td>
<td>0.4</td>
<td>0.4</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Trabectome

Advantages
- Quick procedure
- Hypotony unlikely
- Ab-interno approach eliminates dependence on dissection
- Can do in many types of glaucoma

Disadvantages
- Need to be able to visualize angle
- Bleeding common
- Very low IOPs unlikely
- Cannot do in eyes with canaloplasty

SOLX GMS Plus+
Gold Micro Shunt

IOP Reduction Without a Bleb
External Device Comparison

Consistency

Blebless Drainage

Gold Shunt

Shunt in Proper Position

UBM of Gold Shunt

Consistency

Blebless Drainage

Gold Shunt

Shunt in Proper Position

UBM of Gold Shunt

Consistency

Blebloss Drainage

Gold Shunt

Shunt in Proper Position

UBM of Gold Shunt
Telemetrics: The Future of Medicine

Launch Point Technologies

IOL Tonometry

http://www.launchpnt.com/portfolio/medical/intraocular-pressure-sensor

There's an App for That

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
- In development