Minimally-Invasive Glaucoma Surgery (MIGS)

Dominick L Opitz, OD
Associate Professor
Illinois College of Optometry

Phacoemulsification Cataract Surgery and Primary Open Angle Glaucoma (POAG)

- Increases the postoperative aqueous outflow facility of the TM
- Cultured trabecular meshwork cells have been found to release interleukins and tumor necrosis factors, which may lead to increased synthesis of MMPs in the TM

Effect of Cataract Surgery on IOP Reduction

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

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

Baseline IOP (mm Hg)

23-31 20-22 18-19 15-17 9-14 6.5 4.7 2.5 1.6 0.2

IOP (mm Hg)

22-31 n=19
20-22 n=62
18-19 n=86
15-17 n=223
9-14 n=198

How can the IOP lowering effects of cataract surgery be further enhanced?

- About 20% of patients undergoing cataract surgery have a concurrent diagnosis of glaucoma
  - in the U.S., this leads to over 700,000 patients per year who could benefit from this therapy.¹
- Microinvasive glaucoma surgeries (MIGS)
  - Ab Interno
  - Ab Exteno

Surgical Advances

FDA-Approved MIGS
- Trabectome
- Canaloplasty
- iStent

MIGS in FDA Trials
- Hydrus Stent
- CyPass Stent
- Xen Gel Stent
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
- High safety profile
- Rapid recovery

MIGS Concept

- Intervene earlier in disease, reducing morbidity of progression
- Reduce the need for more aggressive surgical options while preserving that option
- Reduce medication burden

Glaucoma Surgical Procedures: Ab externo vs. ab interno

<table>
<thead>
<tr>
<th>Ab externo</th>
<th>Ab interno</th>
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<tbody>
<tr>
<td>Major incision/sutures required</td>
<td>Micro incision</td>
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<tr>
<td>Drainage assist</td>
<td>Enhanced drainage via natural, physiologic outflow pathway</td>
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<tr>
<td>Artificial outflow pathway – bleb</td>
<td>Highly safe – similar profile to cataract surgery</td>
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<td>Potential early and late serious complications</td>
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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
- 50-75% of total resistance to aqueous humor outflow is found in the juxtacanalicular tissue of the TM

MIGS options to reduce IOP:
- Improve conventional outflow via bypass TM to Schlemm's canal
- Enhance uveoscleral outflow
- Enable outflow through subconjunctival space

Trabectome (NeoMedix)

- FDA-approved
- Uses micro-electrocautery to ablate a 60°to 120° strip of the trabecular meshwork and the inner wall of Schlemm's canal.
- Allows aqueous direct access to the outflow collectors channels of Schlemm's canal causing reduction in IOP.
- Ab interno
- Can be performed as a standalone glaucoma procedure or in combination with cataract extraction.

Trabectome

- Removal of the nasal 60° to 120° of the trabecular meshwork (TM) and the inner wall of Schlemm's canal
- A 1.8-mm temporal clear corneal incision with a "proprietary single-use handpiece"
Electron-micrographs of TM after Trabectome

- Removal of the nasal 60º to 120º of the trabecular meshwork (TM) and the inner wall of Schlemm canal
- A 1.8-mm temporal clear corneal incision with a "proprietary single-use handpiece"

Efficacy of Trabectome

- 31% reduction in IOP (from 26.3 mm Hg ±7.7 to 16.6 mm Hg ±4)¹
- 28% reduction in postoperative medications 1 year after surgery in 538 eyes that underwent the Trabectome procedure only.¹
- Trabectome yields a 30% to 40% reduction in IOP with end pressures in the mid-teens.²,³
- Complications
  - Hyphema
  - IOP spike
- No risk of hypotony
  - IOP cannot be reduced below episcleral venous pressure,


Canaloplasty

- Ab externo
- Combines non-penetrating deep sclerectomy with dilation of Schlemm canal
- Conjunctival dissection and formation of a scleral flap are required
- The goal of the procedure is to increase conventional outflow by catheterizing and visodilating Schlemm canal
- Placing an intracanalicular tension suture distends the TM and stents the canal open

Efficacy of Canaloplasty

- 3 year, multicenter, prospective study of 89 pts.
  - 34% mean decrease in IOP from baseline (23.5 mm Hg ±4.5 to 15.5 mm Hg ±3.5)
  - 53% mean reduction in postoperative medications (1.9 ±0.8 to 0.9 ±0.9)
- When combined with phaco/CE/PCIOL
  - 42% mean decrease in IOP (23.5 mm Hg ±5.2 to 13.6 mm Hg ±3.6)
  - 80% mean reduction of postoperative medications (1.5 ±1 to 0.3 ±0.5).

3-Year Canaloplasty & Combined:

<table>
<thead>
<tr>
<th>Data Point</th>
<th>Baseline</th>
<th>6 Months</th>
<th>12 Months</th>
<th>24 Months</th>
<th>36 Months</th>
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<tbody>
<tr>
<td>Group 1: Canaloplasty Only</td>
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<tr>
<td>Mean IOP</td>
<td>25.5 ± 4.5</td>
<td>15.1 ± 3.0</td>
<td>16.1 ± 2.9</td>
<td>15.1 ± 4.0</td>
<td>15.5 ± 3.5</td>
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<tr>
<td>Mean Medications</td>
<td>1.9 ± 0.8</td>
<td>0.4 ± 0.7</td>
<td>0.8 ± 0.8</td>
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<td>0.9 ± 0.9</td>
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| Mean IOP | 20.5 ± 5.2 | 12.8 ± 3.9 | 13.8 ± 4.1 | 13.4 ± 3.2 | 13.8 ± 3.5 |
| Mean Medications | 1.5 ± 1.0 | 0.1 ± 0.3 | 0.1 ± 0.4 | 0.2 ± 0.4 | 0.3 ± 0.5 |

Group 2: PhacoCanaloplasty

| Mean IOP | 25.5 ± 4.5 | 15.1 ± 3.0 | 16.1 ± 2.9 | 15.1 ± 4.0 | 15.5 ± 3.5 |
| Mean Medications | 1.9 ± 0.8 | 0.4 ± 0.7 | 0.8 ± 0.8 | 0.8 ± 0.8 | 0.9 ± 0.9 |

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| Mean Medications | 1.5 ± 1.0 | 0.1 ± 0.3 | 0.1 ± 0.4 | 0.2 ± 0.4 | 0.3 ± 0.5 |
The iStent® Trabecular Micro-Bypass Stent System

- New FDA approved therapy for the treatment of mild to moderate open angle glaucoma in conjunction with cataract surgery:
  - First available ab interno, micro-bypass stent for glaucoma treatment
  - Improves aqueous outflow through the natural physiologic pathway
  - Proven to improve patient outcomes by safely reducing IOP
  - Micro invasive, astigmatically neutral procedure performed under topical anesthesia as an attractive alternative to traditional surgery

**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

**iStent® Specifications**

*iStent is the smallest medical device known to be implanted in the human body and weighs just 60 µg*

- iStent dimensions are customized for a natural fit within the 270 µm canal space
- Made of surgical-grade nonferromagnetic titanium
- Heparin-coated to promote self-priming

**Mechanism of Action: Anatomic Placement & Rationale**

iStent® is an ab interno trabecular micro-bypass stent for the treatment of glaucoma:

- Placed in inferonasal locations with high presence of collector channel congregations
- Designed to improve continuous, physiological outflow in the lower nasal quadrants

**The Role of Collector Channels in Reducing IOP**

- There are numerous collector channels leaving Schlemm’s canal at irregular intervals
- Bypassing the trabecular meshwork in the inferonasal quadrant is an optimal site to maximize outflow through Schlemm’s canal
- Increasing outflow through the lower nasal quadrant has a significant impact on increasing outflow and lowering IOP as compared to targeting quadrants with lower collector channel congregations
Preoperative Considerations

• iStent Candidate
  – Mild to moderate open angle glaucoma (no more severe than a mean deviation of -12dB)
  – Visually significant cataract is present on examination
  – Patient desires to reduce dependence on glaucoma medications

Any patient with cataracts being treated for mild to moderate open angle glaucoma with medications may be a potential candidate for an iStent. See Directions for Use for a complete list of Contraindications and Precautions.

Diagnostic testing
• Manifest refraction and Brightness acuity testing
• Careful slit lamp examination
  – Evaluate for secondary glaucoma’s such as pseudoxfoliation syndrome and pigment dispersion syndrome
• Glaucoma workup
  – Visual field – the severity of the glaucoma
  – Optic nerve head OCT
  – Pachymetry
  – IOP
  – Gonioscopy – evaluating for synchiae, iris processes, narrow anatomical angles, angle recession or any other abnormalities of the angle structure that may interfere with placement of the iStent
  – Dilated fundus examination – rule out moderate/severe retinal pathology
  – Optic nerve head evaluation

Surgical Procedure

• The iStent® is inserted ab interno through the clear, cornea phaco-incision and can be performed under topical anesthesia
• The physiological preservation of the trabecular meshwork ensures a natural episcleral back pressure of 8 to 11 mm Hg, with minimal risk for hypotony

iStent® Surgical Procedure

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

Postop Management
- Steroid response can be an issue
- Rx same steroid and schedule as with cataract surgery alone
  - Tapering more quickly may be warranted at times to help reduce IOP
- NSAIDs – same as with cataract surgery
- Hold glaucoma meds if mild disease and/or ++ aqueous vein flow (same day IOP check)
- “Final effect” on IOP not until 2-3 months postop

Potential Post-op Complications
- Hyphema
  - Usually nothing more than circulating RBC’s
- IOP spike
  - All GLC patients have higher risk for IOP spikes after cataract surgery
- PAS to iStent
- Inability to insert into TM
  - Pt cooperation

Postop Hyphema
- Adequate pressurization at end of case important
- If hyphema significant, patient may complain of cloudy vision
- Treatment of hyphema
  - Usually no additional intervention
    - Time!
  - Tx elevated IOP
    - No miotics
    - Consider cycloplegia and increasing steroid

iStent® Images

iStent® Images – Post-operative 1 day; Proper Placement
iStent® Images – 6 months Post-Op; Proper Placement

Clinical Data

iStent® Pivotal US IDE Trial

Prospective, randomized, multi-centered study of POAG patients who underwent iStent + cataract surgery vs. cataract surgery (CE) alone

- 290 subjects at 29 sites
  - 240 randomized subjects with cataract and mild-to-moderate OAG (1:1 randomization)
  - 50 additional non-randomized subjects for safety
- Patient population
  - Mild-to-moderate POAG (also PXE and PDS)
  - IOP ≤ 24 mm Hg on 1-3 medications
  - Post-medication washout IOP 22 – 36 mm Hg
- Efficacy endpoints
  - Primary: IOP ≤ 21 mm Hg without medications at month 12
  - Secondary: IOP reduction ≥ 20% without medications at month 12
- Follow-up through 2 years postoperative

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 ≥20% IOP 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
Two-year Follow Up to US IDE Trial

- To assess the long-term safety and efficacy of a single stent with concomitant cataract surgery versus cataract surgery alone
  - Patients implanted with a single stent in conjunction with cataract surgery had significantly better IOP control on no medication through 24 months than patients having cataract surgery alone
  - Both groups had a similar favorable long-term safety profile
- iStent® shows a positive safety and efficacy profile for a single stent over the 2-year period
- The results support iStent® as an effective treatment option for mild-to-moderate glaucoma patients who also have cataracts

Summary

A single iStent® implanted during cataract surgery is designed to:
- Reduce IOP while potentially reducing or eliminating medication use
- Spare the conjunctiva
- Decrease risk of large IOP fluctuations associated with nonadherence to medication
- Avoid serious complications associated with end-stage filtration and shunt surgeries
- Minimize risks of iatrogenic hypotony and bleb formation
- Safely preserve potential for future treatment options

iStent® - The “first” MIGS device

Of the FDA-Approved, Which Lowers IOP Best?

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<tr>
<th></th>
<th>Trabectome</th>
<th>Canaloplasty</th>
<th>iStent</th>
</tr>
</thead>
<tbody>
<tr>
<td>IOP decrease from baseline</td>
<td>31-40%</td>
<td>34%</td>
<td>Not reported</td>
</tr>
<tr>
<td>IOP decrease in combo with cataract extraction</td>
<td>18%</td>
<td>42%</td>
<td>14-16%</td>
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CyPass (Transcend Medical)

- 6.2mm x 0.3mm fenestrated stent
- Targets the suprachoroidal space via a supraciliary location
- Designed to improve uveoscleral outflow by creating a controlled cyclodialysis.
- Clinical studies:
  - Baseline IOP 24.5 mmHg. With one stent, mean IOP after 1 year was 16.4 mmHg (34.7% IOP reduction)¹
  - Baseline IOP 21mmHg, IOP reduced by 35-40% when combined with cataract removal.²


Other Ab Interno MIGS not yet approved…

1. Hydrus Stent (Ivantus)
2. CyPass Stent (Transcend Medical)
3. Xen Gel Stent (AqueSys)
CyPass (Transcend Medical)

COMPASS: The COMPASS clinical trial is a randomized, controlled, multicenter study comparing the safety and efficacy of CyPass Micro-Stent with cataract surgery vs. cataract surgery alone, as part of the US regulatory approval process.

Hydrus Microstent (Ivantis)

- Described as an “intracanalicular scaffold.”
  - The device, about the size of an eyelash
  - Made from nitinol, a highly elastic, biocompatible alloy used in many implantable medical devices.
- Inserted into Schlemm’s canal during cataract surgery
- Increases outflow by allowing aqueous to bypass the trabecular meshwork, and by dilating Schlemm’s canal.
- The device’s non-luminal open design improves flow into the canal and gives it better access to collector channels

Hydrus Microstent

- Multi-centered, mild-moderate glaucoma
  - 2 Groups:
    - Group 1: Combined Hydrus and cataract extraction
    - Group 2: Hydrus only
- Group 1 results:
  - Mean IOP decreased from 21.1 mmHg to 15.6 mmHg at 6 months
  - Medication use decreased from 2.1 meds to 0.4 per patient.
- Group 2 Results:
  - Mean IOP dropped from 21.6 ±4.4 mmHg at baseline to 16.9 mmHg at six months
  - Medication use dropped from 1.7 to 0.6 at six months

Xen Gel Stent (AquSys)

- First ab interno subconjunctival approach for lowering IOP.
- It involves a soft, flexible, permanent gelatin implant, about the diameter of a human hair.
- The implant procedure can be done alone, or as part of cataract surgery.
- The implant is placed through a small, self-sealing corneal incision using an inserter; it’s implanted into the subconjunctival space opposite the incision.
- The gelatin material is non-inflammatory, exerts minimal stress on surrounding tissue and doesn’t migrate once placed.
- The surgery doesn’t disrupt the conjunctiva, so it leaves all other options open for future use if needed, and it can be repeated
Xen Gel Stent Clinical Trials

- A summary of all international clinical results with 118 Subjects
  - Mean pre-op IOP of 23 mmHg, using three medications.
  - At 12 months postop, mean IOP was 15.4 ±4.5
  - at 18 months it was 14.5 ±3.1
  - at 24 months it was 14.3 ±5.1 mmHg
    - Average 9.1 mmHg decrease from pre-op
  - Median number of postop medications was one at all postop time points, with 33 percent using no meds at all at 24 months.