MIGS in Kids
Is there a role?

James D. Brandt, M.D.
Professor of Ophthalmology & Vision Science
Vice-Chair for International Programs & New Technology
Director, Glaucoma Service
Tschannen Eye Institute
University of California, Davis

Financial Disclosures

- Allergan
  - Consulting
    - Proposed PI of planned Phase 3 clinical trial of the bimatoprost sustained-release ring insert
    - Forsight Vision5 Laboratories (acquired by Allergan in 2016)
      - Research Support
      - PI of Phase 2 clinical trial of the bimatoprost sustained-release ring insert
      - Travel support
- Aerie Pharmaceuticals
  - Consulting
- Carl Zeiss Meditec
  - Consulting
- Glaukos
  - Stockholder
  - Former Advisory Board Member
- Graybug Vision
  - Consulting
- InnFocus (acquired by Santen in 2016)
  - Research Support, Phase 3 clinical trial - Site co-investigator
- Laboratoires Théa
  - Consulting
- National Eye Institute
  - PI of UC Davis Clinical Center for the Ocular Hypertension Treatment Study (OHTS) 20 year follow-up study
## Financial Disclosures

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## Childhood Glaucoma Classification & Treatment

*Current Overview*
WGA Classification of the Childhood Glaucomas

WGA Consensus - 2013
Childhood Glaucoma Classification Algorithm

Fig. 1. Childhood glaucoma classification algorithm. The flow is from left to right, beginning with required factors for the definition of glaucoma and glaucoma suspect to final classification.

Primary congenital glaucoma

Fig. 4. A suggested approach to the management of primary congenital glaucoma. (It will be influenced by surgeon preference/experience and local facilities/equipment availability.)
Fig. 5. A suggested approach to the management of glaucoma associated with a non-acquired ocular anomaly. (It will be influenced by surgeon preference/experience and local facilities/equipment availability.)

Grajewski A, Bitrian E, Weinreb RN et al.
World Glaucoma Association: Childhood Glaucoma – A Compendium
Kugler Publications, Amsterdam, 2017

Fig. 6. A suggested approach to the management of glaucoma associated with Sturge-Weber syndrome. (It will be influenced by surgeon preference/experience and local facilities/equipment availability.)

Grajewski A, Bitrian E, Weinreb RN et al.
World Glaucoma Association: Childhood Glaucoma – A Compendium
Kugler Publications, Amsterdam, 2017

Treatment Algorithm – Principles

- Playing the long game, but amblyopia is the enemy, so move quickly
  - “early failure if it’s going to fail”
- Preserve options for subsequent procedures
- Reduce exposure to anesthetics when possible

Treatment Algorithm – Simplified

Diagram showing the flow from Diagnosis & Classification to various surgical options, including:
- Angle Surgery: ab interno and ab externo
- Gonioscopy @ EUA
- View Dependent
- Failure
- Monitor
- Fistulizing Surgery
- Trabeculectomy
- GDD
Optimal Treatment Workflow

Diagnosis & Classification

Gonioscopy @ EUA

Angle Open & Appropriate

Fistulizing Surgery

Angle Closed or inappropriate

Failure

Monitor

Ab interno

Ab externo

Angle Surgery

View Dependent

Failure

Monitor

Where do MIGS fit in?
MIGS – Definitions

• Minimal disruption of sclera, iris or conjunctiva
• Angle-based surgeries bypass abnormal TM
  – Assumption is that downstream collector system is normal
• Trans-limbal surgeries bypass normal outflow completely to create conjunctival filtration bleb
• Procedures don’t preclude further surgery

MIGS – Options

**Angle-based**
- Goniotomy *ab interno*
- GATT
- Trab360™ & Omni™
- iStent™
- Hydrus
- Kahook Dual Blade

**Fistulizing / trans-limbal**
- Xen™ implant
- PreserFlo™ microshunt*

**Supra-Choroidal**
- Gypass

* Investigational – Currently under FDA review
Where do MIGS fit in?

Diagnosis & Classification

Gonioscopy @ EUA

Angle Surgery

ab interno

ab externo

Monitor

Failure

Angle Open & Appropriate

Angle Closed or inappropriate

Fistulizing Surgery

Trabeculectomy

GDD

Failure

Monitor

Angle-based MIGS

Diagnosis & Classification

Gonioscopy @ EUA

Angle Surgery

ab interno

ab externo

Monitor

Failure

Angle Open & Appropriate

Angle Closed or inappropriate

Fistulizing Surgery

Trabeculectomy

GDD

Failure

Monitor
Where do MIGS fit in?

Angle Surgery
- View Dependent
  - ab interno
  - ab externo

Failure
  - Monitor

Diagnosis & Classification
- Gonioscopy @ EUA
  - Angle Open
    - & Appropriate
  - Angle Closed
    - or inappropriate

Fistulizing / Trans-limbal MIGS
- Fistulizing Surgery
  - Trabeculectomy
  - GDD
  - Failure
    - Monitor

Angle-based MIGS in Kids
Angle Surgery – History

• Attempt by de Vincentiis (1893) to incise iridocorneal angle was abandoned
• In 1936 Otto Barkan presented 10 month follow-up of an operation in which he incised the trabecular meshwork under direct, gonioscopic visualization
• By 1942, the particular utility of ‘Goniotomy’ in infantile glaucoma became apparent

The first MIGS surgeon

Otto Barkan, M.D.
1887 - 1958
How do goniotomy & trabeculotomy work?

Working hypothesis

• Incision of abnormal TM (or “Barkan’s Membrane”) re-establishes flow into the canal
• Downstream collector system is unaffected by the primary disease

Goniotomy *ab interno*
Goniotomy *ab interno*

The trabeculotome is rotated in a plane parallel to the anterior surface of the iris.

Trabeculotomy *ab externo*
How do goniotomy & trabeculotomy work?

**Alternative hypothesis**
- Angle incision re-starts arrested development (e.g. cleavage of tissue planes) of angle structures that underlies PCG and other developmental glaucomas

Do immature angles ‘grow up’?
- Female infant underwent trabeculotomy *ab externo*
- Now 28 years old, inferior angle untouched by surgery is normal (few PAS superiorly)
Angle Surgery

Pros

• Specifically targets the dysfunctional tissue
• *Circumferential* treatment allows you to move on to other options quickly
  – “early failure if it’s going to fail”

Cons

• Requires functioning downstream collector system
• Lowers IOP no lower than episcleral venous pressure
• Can be technically challenging for the occasional angle surgeon

Circumferential *ab externo* Trabeculotomy

• Two scleral flaps 180 degrees apart
• Canal of Schlemm cannulated with two pieces of 6-0 nylon
• Suture “cheesewires” into anterior chamber

Beck, AD & Lynch MG
360° trabeculotomy for primary congenital glaucoma
*Ophthalmology* 1995;113:1200-2
Why *ab interno*?

**Pros**
- Avoids violation of conjunctiva, preserves real estate for later surgeries
- *Ab interno* approaches spare the conjunctiva, leaving fistulizing options available should the initial surgery fail

**Cons**
- Technically challenging for the occasional angle surgeon
- ± Expensive devices and consumables

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**GATT: Gonioscopy-Assisted Transluminal Trabeculotomy**

- *Ab-interno* technique to perform circumferential trabeculotomy
- Requires clear cornea, deep anterior chamber
- Preliminary results promising

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*Gonioscopy-Assisted Transluminal Trabeculotomy, Ab Interno Trabeculotomy*

*Technique Report and Preliminary Results*

Dwight D. Greene, MD, MPH, David G. Chidley, MD, Olavsten Smith, MD, William J. Fears, MSc, Elbares Neves de Ois, MD, Ronald L. Pilgrim, MD

**Patients:** To introduce a minimally invasive, *ab interno* approach to a circumferential 360°-degree trabeculotomy and to report the preliminary results of patients who underwent GATT by 4 of the authors (D.G., D.G.C., O.S., W.J.F.).

**Preliminary Results:** Among 100 consecutive patients who underwent GATT, 88 were included in the study. The average age was 63 years (range: 24-86 years), and the mean follow-up was 12 months (range: 6-18 months). The percentage of patients with a success rate of 92% was similar to the success rate of 90% reported in previous studies. The overall success rate of 94% was comparable to the success rate of 92% reported in previous studies. The complication rate was 12%, which was similar to the complication rate of 13% reported in previous studies.
Technique

- Pupil constricted with miotic
- A/C deepened with viscoelastic
- Two paracenteses created
- iScience™ canaloplasty catheter introduced
- MVR blade or disposable needle incises trabecular meshwork
- Catheter advanced 360°
- Retrieved at starting point, grasped to ‘cheesewire’ through meshwork 360°

GATT Technique
Pediatric GATT

Gonioscopy assisted transluminal trabeculotomy: an ab interno circumferential trabeculotomy for the treatment of primary congenital glaucoma and juvenile open angle glaucoma

David A. Grover,1, Olivia J. Smith,2, Joseph J. Felman,3, Stephen G. Szczodrak,1
Matthew H. Butler,1, Mariana Montes de Oca,2, William J. Hsu2

Abstract

Background: To introduce a novel technique to perform a circumferential trabeculotomy using gonioscopy-assisted transluminal laser trabeculotomy (GATT), an ab interno laser technique

Methods: A technique for laser trabeculotomy was performed in 10 patients who had failed conventional trabeculoplasty. Laser trabeculotomy was performed through a 500µm incision and a trans-laminar approach to allow circumferential access to the trabecular meshwork. Results: Of the 10 patients, 8 were successfully treated with GATT. Mean age of patients was 1.5 years (range 3 months to 4 years). Mean IOP preoperatively was 32.6 mmHg (range 22-64). Postoperatively, mean IOP was 15 mmHg (range 6-30). Mean time to treat the PI was 14.3 minutes (range 10-20). All patients had a decrease in IOP of at least 10 mmHg. Complications included 1 case of hypotony and 1 case of delayed healing. Conclusions: GATT is a novel technique for treating primary congenital glaucoma and juvenile open angle glaucoma. It is a safe and effective method for treating primary congenital glaucoma and juvenile open angle glaucoma.

Provisional address: 5110 Sansom Street, Philadelphia, PA 19146, USA

1 Department of Ophthalmology, University of Pennsylvania, Philadelphia, PA, USA
2 Department of Pediatric Ophthalmology and Strabismus, Children's Hospital of Philadelphia, Philadelphia, PA, USA
3 Department of Ophthalmology, University of California, Davis, Sacramento, CA, USA

References

Pediatric GATT

Gonioscopy assisted transluminal trabeculotomy: an ab interno circumferential trabeculotomy for the treatment of primary congenital glaucoma and juvenile open angle glaucoma


Abstract

Background: To introduce a novel technique of gonioscopy assisted transluminal trabeculotomy (GATT) for the treatment of primary congenital glaucoma (PCG) and juvenile open angle glaucoma (JOAG) and to report the results of a study of 127 eyes of 124 patients.

Methods: A retrospective analysis of 127 eyes of 124 patients who underwent GATT was performed. The surgical procedure was performed using standard gonioscopy and endoscopic techniques. The surgical outcomes were evaluated using the following criteria: IOP, visual acuity, and visual field assessments.

Results: A total of 127 eyes of 124 patients underwent GATT. The mean age of the patients was 6.1 years. The IOP reduction was significant (p < 0.05) with a mean of 23.4 mmHg before surgery and 14.8 mmHg after surgery. There was no statistically significant difference in visual acuity and visual field assessments.

Conclusions: This study supports the feasibility and safety of GATT as an effective treatment for PCG and JOAG. Further studies are needed to evaluate the long-term outcomes of this technique.

Figure 2. (A) Gonioscopic photograph demonstrating a trabecular shelf with blood reflux into the angle. (B) Ultrasound biomicroscope revealing a prominent posterior bulge or trabecular shelf following drainage with a microcatheter. The arrow demarks the trabecular shelf.

Alternatives to GATT
Trab360™

- Single-use *ab interno* trabeculotomy device
- Deploys polypropylene trabeculotome over 180° through single corneal incision
- Approved in 2015
Trab360™ Outcomes Study

- Five-center, five-surgeon retrospective study
  - Mayo, UC Davis, Minnesota, Bascom Palmer, OHSU (Casey)
- 46 eyes of 41 patients with childhood glaucomas
- Median age 12 months [range 1-325, mean 71]
- Median follow-up 14.5 months [range 6-34]
- Success defined as IOP < 25 mmHg at last follow-up with or without meds and no additional surgery

Areaux Jr RG, Grajewski AL, Balasubramanium S, Brandt JD, Jun A, Edmunds B, Shyne MT, Bitrian E
Trabeculotomy ab interno with the Trab360™ device for Childhood Glaucoma
Presented at AAPOS, March 2019
American Journal of Ophthalmology, under editorial review

Trab360™ Outcomes Study

Success Rates

- 69% [95% CI: 53.6% - 80.9%] overall
- 71% [95% CI: 55.2%-83.8%] when used as initial surgery
In Primary Congenital Glaucoma [n=24]:
- 83% [95% CI: 61.8%-94.5%] overall
- 86% [95% CI: 62.6%-96.2%] when used as initial surgery

Areaux Jr RG, Grajewski AL, Balasubramanium S, Brandt JD, Jun A, Edmunds B, Shyne MT, Bitrian E
Trabeculotomy ab interno with the Trab360™ device for Childhood Glaucoma
Presented at AAPOS, March 2019
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Failures & Complications
- 15/48 eyes (31%) failed and required additional surgery for uncontrolled glaucoma
- Cyclodialysis clefts in 2/48 eyes (4%)
  - 12 y/o aphakic with anterior segment dysgenesis, 2.5 clock hour
    - "closed" with suture → controlled
  - 11 y/o severe panuveitis, 1 clock-hour
    - closed with cryo → Baerveldt → controlled

Success rates and complications for Trab360™ in Childhood Glaucomas are consistent with prior published pediatric angle surgery data
What about other angle-based MIGS?

- Permanent implants likely add no value to angle surgery in children and probably subject these eyes to unknown long-term risk of device-related complications
  - iStent™
  - Hydrus™

What about the Kahook Dual Blade?

- No published information specific to childhood glaucomas
- Device may be too big in infant eyes
  - ? Excises too wide a strip of angle
  - ? Long term effect of eliminating scaffold for ‘normal’ cells to re-populate
Trans-Limbal MIGS in Kids

Where do MIGS fit in?

- Diagnosis & Classification
  - Gonioscopy @ EUA
  - Angle Surgery
    - ab interno
    - ab externo
  - View Dependent
  - Failure
  - Monitor

Fistulizing / Trans-limbal MIGS

- Fistulizing Surgery
  - Trabeculectomy
  - GDD
  - Failure
  - Monitor
Why Trans-limbal MIGS in Kids?

They *may* help us avoid long-term complications associated with tubes and trabs
Trans-limbal MIGS in Kids

- Xen™ porcine collagen implant*
- PreserFlo™ micro-shunt†

* Allergan, Inc.
† Santen, Inc. – Investigational Device currently under FDA review

Should Xen™ be used in kids?

- In children, we’re performing surgery on a decades-long time horizon
- The Xen™ is fabricated from glutaraldehyde cross-linked porcine collagen
- Labeled as “permanent” but remarkably little published data on degradation in the subconjunctival space
Should Xen™ be used in kids?

Shute TS, Dietrich UM, Baker JFM et al.
Biocompatibility of a Novel Microfistula Implant in Nonprimate Mammals for the Surgical Treatment of Glaucoma
Invest Ophthalmol Vis Sci 2016;57:3594-3600

Cross-linked porcine collagen

Long history of use in vascular grafts

• Dacron fabric vascular grafts were soaked in patient’s blood which clotted to seal the interstices
• Formalin and Glutaraldehyde cross-linked collagen used to obviate the need to “pre-clot” fabric grafts
• Histology showed replacement of non-native collagen over time*

* Wilson GJ, MacGregor DC, Klement PA et al.
A compliant Corethane/Dacron Composite Vascular Prosthesis
– Comparison with 4-mm ePTFE Grafts in a Canine Model
Should Xen™ be used in kids?

**INDICATIONS:** The XEN® Glaucoma Treatment System is available for the surgical management of refractory glaucomas, including cases where previous surgical treatment did not work, cases of primary open-angle glaucoma, and cases of pseudophakic or phakic glaucoma with open angles that are unresponsive to maximum tolerated medical therapy.

**IMPORTANT SAFETY INFORMATION**

Who should not receive the XEN® Glaucoma Treatment System? This surgical treatment should not be used if you currently have any of the following: angle closure glaucoma where the drainage angle of the eye has not been surgically opened; a glaucoma drainage device previously implanted or scarred and pathologies of the conjunctiva (the clear membrane covering the white outer layer of the eye) in the area needed for this implant; eye inflammation (such as inflammation of the eyelids, conjunctiva, cornea, or uvea); abnormal formation of new blood vessels on the iris (the colored part of the eye) surface; artificial lens implanted in the anterior chamber (the space between your cornea, the outer transparent part of the eye, and the iris), silicone oil in your eye, and vitreous (the transparent jelly-like tissue that is found behind the lens) present in the anterior chamber.

What warnings should I be aware of? XEN® Gel Stent complications may include buildup of fluid between the choroid (inner layer of blood vessels) and the sclera (white outer layer of the eyeball), blood in the eye, very low eye pressure, implant moving to another part of the eye, implant exposure, wound leak, need for additional surgical intervention, and other eye surgery complications. The safety and effectiveness of the XEN® Gel Stent in neovascular, congenital, and infantile glaucoma has not been established. After the XEN® Gel Stent procedure, to help avoid the possibility of implant damage, avoid rubbing or pressing your fingers on the eye in the area where the XEN® Gel Stent was implanted.

What precautions should I be aware of? Before surgery, your doctor will check that the device and injector are not damaged. During surgery, your doctor will stop the procedure if he or she observes increased resistance during implantation and will use a new XEN® system. After surgery, your doctor should check and manage your eye pressure appropriately. The safety and effectiveness of implanting more than one XEN® Gel Stent in an eye has not been studied.

What are possible side effects? The most common side effects after surgery include reduction of vision, eye pressure becoming too low, an increase in eye pressure, and need for an additional surgical procedure in the eye to release scar tissue (needling) around the implant under the conjunctiva. Talk to your doctor about other possible side effects.

Caution: Federal law restricts this device to sale by or on the order of a licensed physician. For the full Directions for Use, please visit www.allergan.com/xen/us.htm or call 1-800-678-1605. Please call 1-800-433-8871 to report an adverse event.

Pinchuk L, Riss I, Battle JF, Beckers H, Stalmans I
An ab externo minimally invasive aqueous shunt comprised of a novel biomaterial
InnFocus Microshunt

Investigational Device
under FDA Review

Safety Concerns
Safety concerns

- Once MIGS devices are approved based on clinical trials in adults, surgeons are free to use in children under a ‘practice of medicine’ standard
- No recently-approved MIGS devices have been systematically studied in children

Cypass™

- Cypass was removed from the market based on long-term endothelial data in original adult study cohort
- Outside the US, Cypass has been used in children
- Reports (anecdotal) of Cypass migrating into the choroidal space in buphthalmic eyes
FDA Concerns about Pediatric MIGS

- Discussions with FDA staff about how to design pediatric MIGS studies
- Protocol under advanced discussion with FDA for Pediatric Safety Study of the PreserFlo™ Microshunt using ‘compassionate use’ and ‘early access’ pathway
Pediatric Safety Study

• Investigators experienced with Microshunt implantation in clinical trial with large pediatric glaucoma practices
• Inclusion
  – Age 3 months to 25 years
  – Have failed one or more conventional surgeries for childhood glaucoma

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Pediatric Safety Study

Ten patients in 5 categories of childhood glaucoma (50 eyes total)
  – Primary congenital glaucoma
  – Glaucoma following cataract surgery
  – Juvenile Open-Angle Glaucoma (JOAG)
  – Glaucoma associated with non-acquired systemic syndromes
  – Glaucoma associated with non-acquired ocular anomalies
Pediatric Safety Study

Because these eyes already have failed one or more procedures, surgery will be different than in clinical trial

– Implant site based on conjunctival scarring, failed trabs or GDDs
– Injected MMC
– Small conjunctival incision

FDA Feedback

• Supportive of proceeding with initial 10 patient cohort under “Compassionate Use” / “Early Access” pathway before initiating multi-center study
Pediatric Safety Study

Awaiting FDA permission to start

IRB submission & approval

Begin enrolling patients

? Late 4th quarter 2019 ?

Conclusions
Should MIGS be used in Kids?

- The spinoffs from the MIGS revolution are benefiting pediatric glaucoma surgeons, but in contrast to adults, remember these kids have:
  - Different pathophysologies
  - Very different time horizons (short & long-term)
  - Very different risk tolerance
    - Many are monocular

- iStent
- Hydrus

NO

These devices likely add no benefit, are probably less effective than conventional incisional angle surgery and may increase long-term device-related risk
Should MIGS be used in Kids?

- GATT (illuminated microcatheter or suture)
- Trab360™ or Trab360 Omni™

**YES**

These approaches allow *ab interno* circumferential angle surgery, thus preserving options for later and allowing the surgeon to learn quickly if the native angle can be resurrected.

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Should MIGS be used in Kids?

- Kahook Dual Blade

**IN SELECTED PATIENTS**

Limited data; likely to prove useful in older children and young adults with JOAG; may be of limited if any utility in infants.
Should MIGS be used in Kids?

- Xen™
- PreserFlo™

WAIT

No data; concerns about longevity of porcine collagen in this population. Wait for data before implanting in children.