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Use of a Novel Microshunt in Refractory Childhood Glaucoma: Initial Experience in a Compassionate Use/Early Access Cohort

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• PURPOSE: **In patients with refractory childhood glaucoma, treatment options include trabeculectomy or large glaucoma drainage devices (GDDs) with attendant short- and long-term risks. A novel polymer-based microshunt is under review by the US Food and Drug Administration (FDA) for use in adults. The device is attractive for children given the long-term stability of the polymer and the small conjunctival incision required for implantation. This early clinical series explores the safety and efficacy of this device in patients with refractory childhood glaucoma who would otherwise undergo trabeculectomy or implantation of a GDD.**

• DESIGN: **Prospective single-center case series under FDA compassionate use investigational device exemption.**

• METHODS: **FDA and institutional review board approvals were obtained to treat ≤20 children using this investigational device under the compassionate use pathway. Single eyes in patients with refractory childhood glaucoma were treated surgically with the microshunt. Patients with ≥1 year of follow-up are reported.**

• RESULTS: **Twelve eyes of 12 children (15 months to 14 years if age) with mean preoperative intraocular pressure of 22.72 ± 4.8 mm Hg on 3.3 ± 0.65 medications were treated beginning in December 2019. No intraoperative complications occurred. Among eyes with ≥1 year of follow-up (range 12-23 months), 9 were successfully controlled. In this group, preoperative intraocular pressure 21.6 ± 4.9 mm Hg dropped 45% to 11.9 ± 3.8 mm Hg at 1 year; 7 patients were taking no medications at 12 months, and 2 required 2 medications (fixed-combination dorzolamide-timolol). Three eyes failed, requiring additional surgery.**

• CONCLUSION: **These early data suggest that the device is safe and appears effective in patients with refractory childhood glaucoma. A prospective, multicenter pivotal trial is planned.** (Am J Ophthalmol 2022;239: 223–229. © 2022 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/))

Glaucoma in children comprises a spectrum of genetic and acquired syndromes in which the outflow system of the eye is maldeveloped or damaged. Failure of the outflow system leads to elevated intraocular pressure (IOP) and damage to the eye. Untreated, childhood glaucoma is uniformly and irreversibly blinding. The widespread adoption in the mid-20th century of goniotomy[1] and trabeculotomy,[2] during which the internal structures of the outflow system are incised, led to highly effective and sight-saving treatments. Childhood glaucoma is no longer a sentence of blindness.

Despite the efficacy and safety of angle surgery, in 15% to 25% of these children, angle surgery eventually fails or is impossible to perform, requiring an escalation to more invasive interventions.[3] The surgical options for this smaller group of patients with refractory childhood glaucoma include conventional filtration surgery (trabeculectomy) with mitomycin-C (MMC) or implantation of a glaucoma drainage device (GDD).[4,5] Both have significant short- and long-term disadvantages. Furthermore, although implantation of currently available GDD designs into the pediatric eye is within the standard of care, they have not been specifically designed for, nor rigorously evaluated in, this special patient population. Indeed, GDDs designed for adult eyes frequently must be shortened with scissors during surgery to prevent the posterior edge of the device plate from impinging on the optic nerve in pediatric eyes.[6]

Bleb-forming minimally invasive glaucoma surgery (MIGS) devices might be an attractive interim step for refractory childhood glaucoma before moving on to the more extensive surgical dissection and risk associated with trabeculectomy with MMC or plate-based GDDs. Small-lumen tubes that shunt aqueous humor to a subconjunctival space treated with MMC are marketed or in development for glaucoma in adults. We have limited data about the porcine-collagen Xen (Allergan) implant in pediatric patients,[7] but the observation that the device may

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degrade over time[8] should give pause when considering its use in children.

A novel ab externo microshunt (PRESERFLO MicroShunt, Santen USA) currently under investigation in the United States and approved outside the United States[9] is fabricated from a polymer (SIBS [styrene-block-isobutylene-block-styrene]) with a multidecade history of stability when used in coronary stents.[10] The long-term stability of the material and the efficacy and safety profile of the device in adults[9,11] suggest that this approach may be particularly suitable in children with refractory glaucoma. This article discusses implantation of the MicroShunt in 16 of 16 children under a US Food and Drug Administration (FDA) investigational device exemption (IDE) supplement that permitted compassionate use/early access use of this device in a pediatric cohort and reports outcomes of the 12 eyes that have reached ≥1 year of follow-up.

METHODS

This a prospective, single-center case series of the use of an unapproved device (the PRESERFLO MicroShunt) in the management of refractory childhood glaucoma. A request for an early access/compassionate use supplement to the existing IDE was filed with the FDA to permit use of the unapproved device in 1 eye of children 3 months to 18 years of age who had refractory childhood glaucoma. The FDA approved this request in 2019 and approval to proceed with implantation of an unapproved device in ≤10 patients was then obtained from the University of California, Davis institutional review board. Written informed consent was obtained from a parent of each patient, and the case series adhered to the tenets of the Declaration of Helsinki and US FDA regulations related to IDEs. After treatment of the initial cohort of 10 patients, the FDA and the local institutional review board granted permission to implant devices in an additional 10 eyes; at the time this article was published, 6 more devices have been implanted (follow-up 1-12 months). Data reported here are limited to the 12 of these 16 eyes that have reached 1 year of follow-up.

For this series, eyes with refractory childhood glaucoma were defined as those in which ≥1 conventional surgery (ab interno or ab externo angle surgery, eg, goniotomy or trabeculotomy; trabeculectomy; GDD) with or without topical medications had failed to control IOP or in which there was evidence of progression (eg, progressive axial length increase, corneal enlargement or clouding, or progressive cupping on disc photography). In eyes with previous angle surgery alone, gonioscopy demonstrating complete circumferential angle treatment was confirmed before proceeding to microshunt implantation. As agreed with the FDA and the local institutional review board, all cases were approved as being appropriate by an independent medical monitor, Alana Grajewski of the Bascom Palmer Eye Institute, University of Miami.

The device and the surgical technique for implantation of the microshunt as performed in the US adult pivotal trial under this IDE have been described elsewhere[12] and are briefly reviewed here. A narrated video of the surgical technique is available on AJO.com (Video 1).

The microshunt is fabricated from SIBS polymer and measures 8.5 mm in length and 0.35 mm in diameter with a 70-μm lumen. Two anchoring wings are positioned 4.5 mm posterior to the beveled tip of the device. In all cases in this series, the microshunts were implanted in the superior nasal quadrant, either because a conventional GDD was present in the superior temporal quadrant or because the superior temporal quadrant was left untouched should it become necessary to implant a conventional GDD later. In no case was surgery performed in a previously operated quadrant nor was a previous GDD removed.

In all cases, 40 μg of MMC was injected into the subconjunctival/intra-Tenon's space of the superior nasal quadrant approximately 6 mm posterior to the limbus, the area targeted for aqueous drainage. A small (<2 clock hour) peritomy was performed and the Tenon's capsule was elevated from the sclera. A location 3 mm posterior to the limbus centered on the peritomy was marked and a 1-mm double-step knife was used to create both a narrow scleral track into the anterior chamber and a shallow scleral pocket to provide accept the anchoring wings of the device to prevent inward migration of the device into the eye. Flow of aqueous humor from the posterior lumen of the device is typically seen immediately upon entry of the device into the anterior chamber; little if any aqueous humor flows around the device. An iris sweep or cyclodialysis spatula is used to lift the Tenon's capsule and overlying conjunctiva up from the device to prevent tissue from obstructing the posterior tip of the device as the Tenon's capsule and conjunctiva are drawn forward and sutured to the limbus with monofilament 9-0 polyglactin suture.

Modifications from the adult IDE protocol for use in children included general anesthesia, a smaller limbal incision in the superior-nasal quadrant of the affected eye, and the preincision injection of 40 μg of MMC in the superior-nasal quadrant rather than the use of sponges which requires a much larger incision.

Patients were treated postoperatively with ofloxacin 3% 4 times daily for 1 week; prednisolone acetate 1% drops were used 4 times daily for ≥1 month then tapered off based on conjunctival appearance, usually within 2 to 3 months. Patients were examined at regular postoperative intervals. IOP was measured using the tonometry technique tolerated by the child, most frequently the iCare IC200 rebound tonometer (iCare Finland OY) in young children and Goldmann applanation tonometry in some older children. Glaucoma medications were reintroduced and examinations under anesthesia performed as needed. Slit-lamp photography, optic disc photography, and optical coherence

tomography were acquired in children who were able to cooperate.

In cases where IOP rose despite the resumption of topical medications and there was sufficient concern about possible progression, needling was attempted under anesthesia. A second dose of MMC (40 μg) was injected posterior to the distal end of the microshunt and a 25-g needle was used to disrupt the bleb if it appeared encapsulated and when possible to also sweep away any Tenon's capsule that might be blocking the microshunt. Care was taken to avoid engaging or dislodging the device.

Failure was defined a priori as the need for additional surgery to control IOP or failure to prevent evidence of progression despite the addition of topical medications. Because IOP measurement in children is highly variable at best, success required not only a measured drop in IOP but other evidence of clinical response as well. Unqualified success was defined as a clinically significant (≥25%) drop in IOP from preoperative levels without the need for glaucoma medications along with additional evidence of clinical response, eg, corneal clearing, axial shortening, hyperopic shift, or cupping reversal[13] documented on serial disc photographs. Qualified success was similarly defined but topical glaucoma medications were allowed.

RESULTS

Twelve eyes of 12 children 15 months to 14 years of age (7 girls, 5 boys) with refractory childhood glaucoma were treated between December 2019 and February 2021. Follow-up ranged from 12 to 23 months. Three more children have undergone surgery as part of this case series and are doing well but have <1 year of follow-up (1-9 months; data not reported).

Table 1 lists the clinical characteristics of the 12 eyes reaching 1 year of follow-up, including diagnoses, previous surgical interventions, IOP measurements and medication burden at time of surgery, interventions if any during the first year, and outcomes at the 12 month follow-up visit. Diagnoses included primary congenital glaucoma (n = 6, including 1 neonatal-onset and 2 late-diagnosed), Sturge-Weber syndrome (n = 3), aniridia (n = 1), and Axenfeld-Rieger syndrome (n = 2). Previous surgery included angle surgery with subsequent GDD (n = 5), GDD alone (n = 3), and ab interno angle surgery only (n = 4).

No intraoperative complications occurred. In patient 11, a 7-year-old with Sturge-Weber syndrome, a shallow anterior chamber and low-lying choroidal effusions were observed; after cycloplegia, the anterior chamber deepened within a week and the choroidals resolved in <1 month. No corneal or lens related opacities developed during the first year in any patient.

The IOPs of the 12 eyes (9 successful, 3 failed) at 1, 3, 6, and 12 months are shown in Figure 1, A; a Kaplan–Meier survival curve for the entire cohort is shown in Figure 1, B.

The clinical appearance of the implanted microshunts and associated blebs among the 5 children who cooperated with slit-lamp photography are shown in Figure 2, along with an example of cupping reversal observed in patient 10.

Three of the successful patients (7, 8, and 10) had IOPs <10 mm Hg at various times during follow-up. Clinical dilated examination along with macular imaging by optical coherence tomography detected no evidence of hypotony maculopathy in these eyes.

Of this initial cohort of 12 eyes, 9 patients (75%) were deemed successful at last follow-up with a reduction in IOP (preoperative IOP 20.9 ± 4.4 mm Hg; IOP at 1 year 11.0 ± 2.5 mm Hg), medication burden (preoperative medications 3.4 ± 0.8, medications at 1 year 0.3 ± 0.8), and additional evidence of clinical improvement. Of the 2 children considered a qualified success, 1 (patient 2, with aniridia) remains on fixed-combination timolol-dorzolamide out of an abundance of caution as the child tolerates the medication, this is the child's better-sighted eye, and the family is now unable to return for follow-up more than a few times a year. In the second child (patient 11, with Sturge-Weber syndrome), the same fixed-combination medication was initiated during a hypertensive phase and she has remained on the medication.

The most granular IOP data are available in patient 10, whose father purchased an iCare tonometer and captured IOP data multiple times, sometimes daily, between clinic visits. A plot of the child's preoperative and postoperative IOP course is shown in Figure 3. In this child IOPs have been consistently in the upper single digits. Hypotony maculopathy has never been observed in this patient; beginning at about 9 months postsurgery he began to cooperate with macular optical coherence tomography and at that time and subsequently no choroidal or macular folds have been observed.

The 3 eyes deemed treatment failures (patients 1, 4, and 6) are instructive. In these 3 cases, IOP measurements began to rise about 3 months after surgery and medications were reintroduced during the first year of follow-up (at 29, 8, and 10 weeks, respectively). Office-based examinations and subsequent examinations under anesthesia suggested stability until failure was confirmed during an examination under anesthesia when needling or further surgery was carried out at 59, 70, and 55 weeks, respectively. Two of the eyes (patients 1 and 6) had undergone GDD surgery in the superior temporal quadrant using a limbal-based conjunctival flap before implantation of the microshunt in the superior nasal quadrant.

In patient 1, the bleb failed slowly after 6 months and medications were reintroduced; an attempt to excise the scar directly with the application of additional MMC at 59 weeks resulted in a late dehiscence of the conjunctival wound as has since been described in adults[14]; the device

TABLE 1. Clinical Characteristics of the 12 Eyes Reaching 1 Year of Follow-Up

Case No.	Diagnosis	Indications for Surgery	Previous Surgeries	Age at Surgery (Yrs)	Preop Meds	IOP (mm Hg)							Meds at 1 Year	Success / Failure	Clinical Evidence of Success/Failure
							Postoperative								
						Preop	D1	W1	M1	M3	M6	M12			
1	PCG (late diagnosed)	IOP, progressive cupping, medication burden	Ab externo trabeculotomy, BGI	9.0	4	22	10	8	12	13	23	26	2	Failure	IOP rose despite medications beginning at 6 months; open revision with injection of more MMC at 14 months. Conjunctival dehiscence and exposed device, microshunt removed at 18 months after several revisions
2	Aniridia	IOP, medication burden, worsening cupping and corneal edema	AGV	3.9	3	26	10	16	27	11	16	13	2	Qualified Success	IOP, corneal clearing, cupping reversal
3	Sturge-Weber syndrome	IOP, progressive cupping, medication burden	GATT	1.6	3	28	20	20	19	24.7	19	26	2	Failure	Needling with MMC at 12 months. Increased axial length and cupping at 18 months, BGI placed
4	Axenfeld-Rieger syndrome	Progressive cupping, corneal edema	BGI	14.6	5	26	7	7	7	10	12	11	0	Success	IOP, corneal clearing, cupping reversal, hyperopic shift in refraction
5	Sturge-Weber syndrome	Progressive RNFL thinning, progressive cupping, IOP	Trab360, goniotomy	9.4	3	18	14	13	10	12	13	13	0	Success	IOP, medication burden, possible cupping reversal
6	PCG of neonate	IOP, medication burden, corneal clouding	GATT, AGV	1.3	3	28	13	8	10	30	30		2	Failure	Needling with MMC at 4.5 months. Inferior-nasal AGV placed at 10 months
7	PCG	IOP, cupping progression, axial length increase	GATT	5.6	3	21	8	8	6	7.3	4	9	0	Success	IOP, medication burden, 1 D hyperopic shift
8	PCG	IOP, medication burden, worsening cupping and myopia	Goniotomy, trabeculotomy, AGV	12.2	4	15	9.8	6.5	6	7	10	10	0	Success	IOP, medication burden, possible cupping reversal
9	PCG	IOP, medication burden, worsening cupping and myopia	Goniotomy, AGV	6.5	3	17	8.5	9.6	8.5	9	7.8	14	0	Success	IOP, medication burden, possible cupping reversal
10	PCG	IOP, increasing axial length, myopia, intermittent corneal clouding, Haab striae	GATT	4.0	3	23	5.5	3.9	5.4	9	7	7	0	Success	IOP, cupping reversal
11	Sturge-Weber syndrome	IOP, progressive cupping, OCT changes	Goniotomy, Trab360	7.6	3	19	13	11	15	21	21	20	2	Qualified Success	Cupping reversal
12	Axenfeld-Rieger syndrome	Progressive cupping, axial length increase, OCT changes	AGV	5.5	3	29.6	8	7	10	9	10	10	0	Success	IOP, cupping reversal, medication burden

AGV = Ahmed glaucoma valve; BGI = Baerveldt glaucoma implant; D = diopter; GATT = gonioscopy-assisted transluminal trabeculotomy; IOP = intraocular pressure; M = month; MMC = mitomycin-C; PCG = primary congenital glaucoma; RNFL = retinal nerve fiber layer; Trab360 = ab interno trabeculotomy using the Trab360 Omni device (Sight Sciences); W = week.

Note: If multiple IOP measurements were acquired during a 3-month window surrounding the 6-month and 1 year follow-up date, the highest value is reported. Fixed-combination formulations were considered 2 medications. IOPs recorded to 1 decimal point were acquired with the iCare 200 Rebound Tonometer

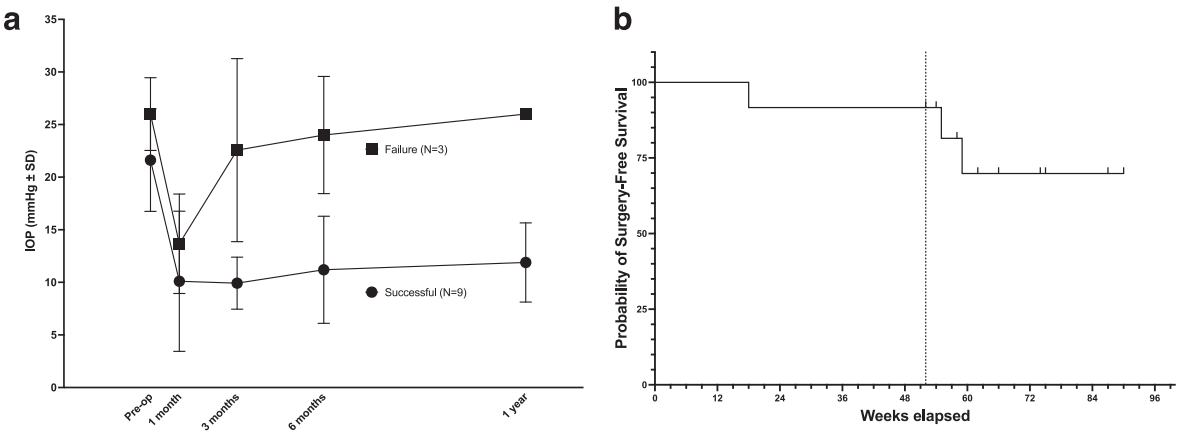

FIGURE 1. A. Preoperative and postoperative intraocular pressure (IOP) at 1, 3, 6, and 12 months (mm Hg ± standard deviation [SD]) for the successful eyes (n = 9) and eyes that failed (n = 3) in this small series. B. Kaplan–Meier survival curve of the 12 eyes described in this report. The vertical line indicates 1 year of follow-up.

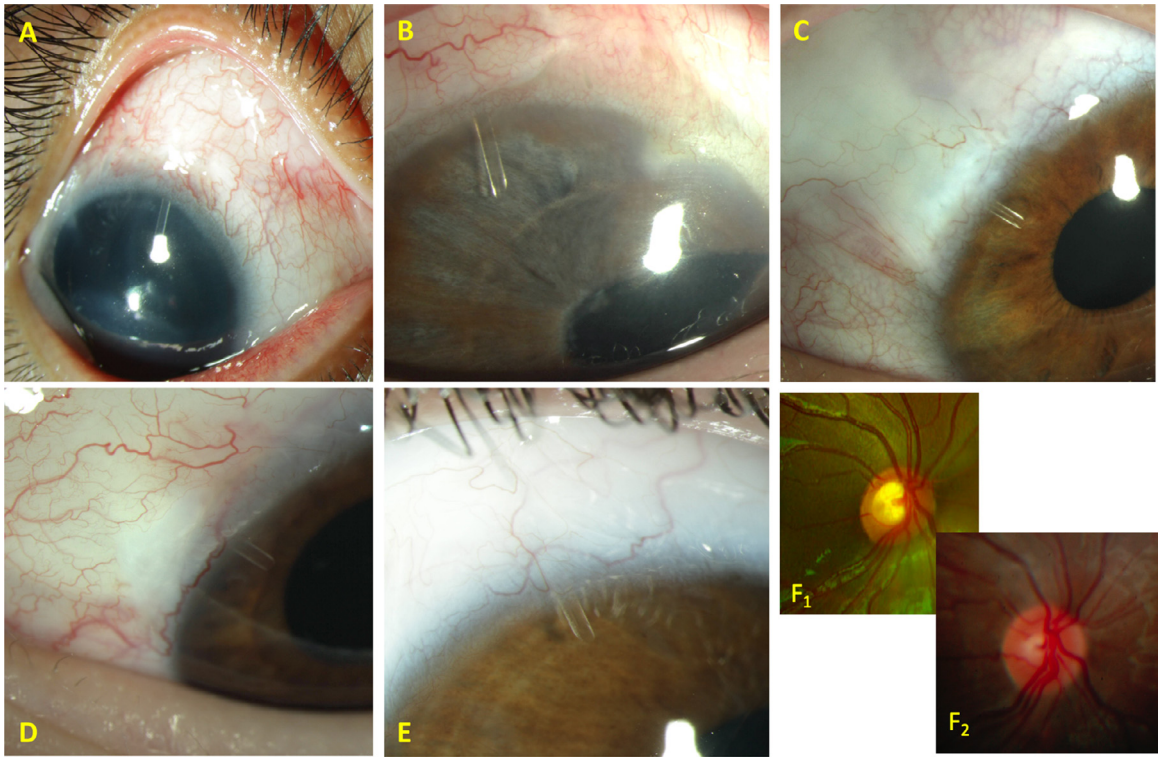

FIGURE 2. Slit-lamp images of microshunts with adjacent blebs at various lengths of follow-up. A. Patient 2 at 3 months. B. Patient 4 at 14 months. C. Patient 5 at 14 months. D. Patient 7 at 4 months. E. Patient 9 at 14 months. Images F_1 and F_2 are optic disc images of patient 10 immediately before (false color wide-field scanning laser ophthalmoscope; intraocular pressure, 23 mm Hg) and 4 months after surgery (digital fundus camera; intraocular pressure, 8 mm Hg), demonstrating significant cupping reversal.

was explanted and the conjunctival wound was allowed to heal.

The other 2 eyes that failed underwent bleb needling and injection of MMC under general anesthesia. In both cases, the IOP response to needling was temporary but their blebs scarred down, and based on evidence of progression confirmed during subsequent examinations under anesthesia, conventional GDDs were placed (inferior nasally in patient 4, superior temporally in patient 6) under the same general anesthetic. In these 2 cases, because the effect of needling was temporary, the date of needling was used as the time point of failure. In this

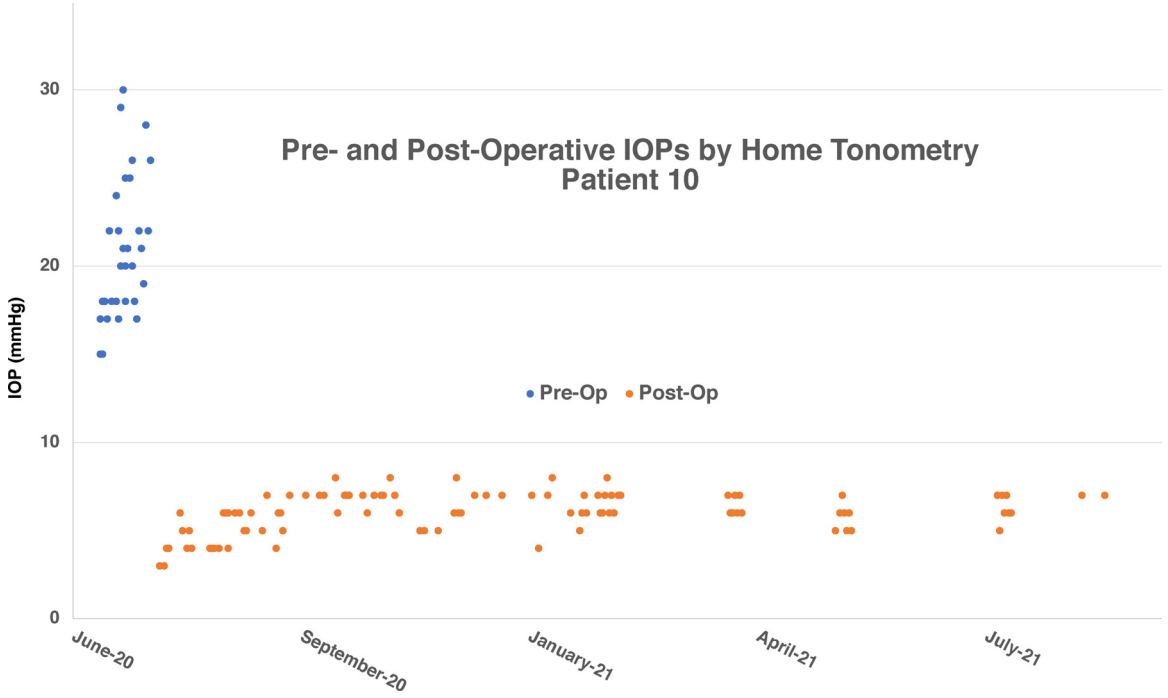

FIGURE 3. Home tonometry data acquired in the operative eye by patient 10's parents using an iCare rebound tonometer before and after surgery in July 2020 through 1 year of follow-up. IOP = intraocular pressure.

small case series, no case where needling was attempted was successful.

DISCUSSION

Data from this cohort of 12 eyes suggest that the novel microshunt is effective in refractory childhood glaucoma, with success in 9 eyes (75%) at last follow-up (12-18 months). The published 1-year success rates of larger GDDs such as the Ahmed and Baerveldt devices in pediatric glaucoma vary widely between 54% and 90% depending upon patient age, underlying diagnosis, surgical technique, primary or secondary use, and varying definitions of success.[5] This initial evaluation of the microshunt was limited to eyes with refractory disease among which higher failure rates of conventional GDDs are commonly observed along with nontrivial complications such as flat anterior chambers and tube-corneal touch. The microshunt device requires a much smaller conjunctival incision and dissection than the alternatives (trabeculectomy or GDD) and does not preclude the subsequent use of either should the device fail to control IOP. The device may therefore prove especially useful as an interim approach after ab interno angle surgery has failed before moving on to more invasive and possibly higher-risk alternatives that use up valuable conjunctival real estate. Longer-term data should help clarify the microshunt's utility in this clinical setting.

In the 3 eyes in which the surgery failed, needling or bleb revision were attempted without success. It remains to be seen whether failure because of external scarring and/or Tenon's capsule incarceration can be mitigated in children with needling and MMC injection as is commonly done in adults. In children, rising IOP and the loss of a posterior bleb may indicate that it is time to move on to more invasive options. Given that one must return to the operating room for a general anesthetic in pediatric patients, moving on may be the best approach to protect vision and avoid amblyopia. Only a larger and longer-term clinical trial will help determine the optimal management of this scenario.

This clinical series has significant limitations. It is too small and too heterogeneous in terms of age, diagnosis, and previous surgery from which to generalize to all children, and one of the more common forms of childhood glaucoma (glaucoma after cataract surgery) was not encountered in this initial cohort. IOP measurement in children is always challenging and the need to measure IOP by whatever technique a child would allow on a given day leads to noisy IOP data. As seen in Figure 1, A, the preoperative IOP in the successful and failure groups overlapped. The data are too sparse to evaluate the role of starting IOP in long-term outcomes. Finally, although I placed the microshunt in adult eyes as a surgeon in the pivotal trial,[12] I observed a significant learning curve when performing the procedure in pediatric eyes—the device is designed for an entry site 3 mm posterior to the limbus to assure proper scleral seating of the

microshunt and a short 1.5 mm length of the implant in the anterior chamber. The limbus can be challenging to identify in children, particularly in eyes with significant buphthalmos and/or anterior segment dysgenesis where limbal landmarks are smeared or indistinct.

Pediatricians often remind us that children are not just little adults. The same goes for children's eyes. It is not surprising that formal pivotal trials have yet to be attempted in childhood glaucoma—it is neither feasible to do large clinical trials for this rare group of disorders nor to expect clean IOP data given that measuring IOP in a child is challenging at best. Those of us treating childhood glaucoma should nonetheless insist on the same high level of evidence we expect when evaluating new surgical approaches and implants for adults. A multicenter, prospective clinical trial of this novel microshunt is planned.

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