

## Trabeculectomy with subconjunctival collagen implant in Indian eyes: Long-term results

Kirti Singh, Mainak Bhattacharyya, Ankush Mutreja, Sonal Dangda

**Purpose:** To report long-term safety and efficacy of trabeculectomy with collagen implant in Indian population. **Methods:** All cases of trabeculectomy with Ologen® Collagen Matrix implant performed over a 7-year period from May 2008 through April 2015 at a tertiary referral institute were reviewed. A total of 30 eyes of 28 patients were included in the study with two patients undergoing bilateral trabeculectomy. Outcomes measured included intraocular pressure (IOP) control, number of antiglaucoma medications used, bleb morphology, and complications/reoperations. **Results:** Trabeculectomy resulted in reduction in IOP from 36.46 to 11.65 mm Hg in the immediate postoperative period (day 1), a 68% decrease to 15.18 mm Hg at 84 months (58% decrease). The mean IOP reduction decreased over time from 63% in the first year to 55% after 5 years of follow-up. Fourteen eyes attained a follow-up of 5 years and eight eyes a follow-up of  $\geq 7$  years. No sight-threatening complication such as hypotony, bleb leak, and bleb-related endophthalmitis was observed in our series, and only intervention required was 5-fluorouracil needling in one case. **Conclusion:** Ologen-augmented trabeculectomy is effective in controlling IOP over a long-term follow up from minimal 3 to maximal 7 years. No untoward events jeopardizing bleb safety were noted at any time. This modality is a viable alternative for patients with contraindications to use of antimetabolites.

**Key words:** Bleb morphology, bleb safety, collagen implant, mitomycin-C, Ologen, trabeculectomy

The use of antimetabolites, such as mitomycin-C (MMC) and 5-fluorouracil (5-FU), has significantly enhanced trabeculectomy success rates by preventing episcleral fibrosis and scarring of bleb.<sup>[1,2]</sup> However, the use of these relatively toxic agents is fraught with the risk of corneal toxicity, wound leak, overfiltration, and hypotony during the immediate postoperative period. The long-term follow-up in blebs treated with antimetabolites is associated with a higher risk of thin-walled avascular blebs, bleb leak, blebitis, and endophthalmitis subsequent to impaired surface healing.<sup>[3-10]</sup>

Complications ensuing after use of antifibrotics is due to impaired healing, resulting in irregular epithelialization, fibroblast destruction, and absence of basement membrane,<sup>[11]</sup> all of which endanger bleb safety.<sup>[12]</sup> The quest for safer antifibrotics for bleb modulation which modify healing response more safely and prevent activation of fibroblasts has led to use of amniotic membrane, antivascular endothelial growth factor agents and lately biodegradable implants.<sup>[13,14]</sup> One such implant is the Ologen® Collagen Matrix (Aeon Astron Europe B. V., Leiden, the Netherlands) a porous implant comprising >90% Type I atelocollagen and <10% lyophilized glycosaminoglycan with a pore size of 10–300  $\mu$ m which permits controlled resistance to aqueous outflow coupled with a random, relatively loose orientation of regenerating myofibroblasts, fibroblasts, and secreted extracellular matrix yielding reduction of scarring.<sup>[15-17]</sup> Its porous structure forces conjunctival fibroblasts and myofibroblasts to grow into the pores and impair connective

tissue lay down reducing scar formation and wound contraction. After implantation, the device is believed to degrade within 90–180 days.<sup>[17,18]</sup>

Ologen (Olo) implant may be placed over the scleral flap (subconjunctival) or subsclerally during the operation, theoretically serving as a reservoir for bleb formation while optimizing wound-healing.<sup>[19]</sup> Olo has also been used in combination with low doses of MMC and for treating hypotony after trabeculectomy.<sup>[20-22]</sup> Short-term results of Olo use in infantile glaucoma and as a patch graft in lieu of human sclera in tube shunt surgery have also shown encouraging results.<sup>[23-25]</sup>

Olo-treated blebs developed a prominent vasculature without thinning compared with thin avascular blebs seen with MMC augmentation.<sup>[17,26]</sup> This could be extrapolated to imply long-term safety of this implant in trabeculectomy eyes, but this aspect has not been adequately explored in previous studies.<sup>[18,27,28]</sup> Another study has reported that efficacy and safety of trabeculectomy with 5-FU were similar to that with Olo over short-term follow-up.<sup>[29]</sup> Our study presents a long-term follow-up of Olo implanted eyes and evaluates success (both functional and anatomical) in patients of Asian ethnicity with a minimum 5-year follow-up.

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## Methods

This study adhered to the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of our institution. In all our patients as a routine protocol, an informed consent was taken explaining clearly the nature and benefits/risks of Olo keeping well in mind that the porcine nature of Olo discs may be unacceptable to some of our Muslim patients due to their religious beliefs. The case logs of all patients subjected to trabeculectomy with implant of Ologen Collagen Matrix from May 2008 through April 2015 and completing a minimum follow-up of 3 years were reviewed. Case logs were excluded in case of the following conditions: absence of postsurgical follow-up data, prior retinal/glaucoma/other anterior segment surgery except cataract surgery, and patients with ocular surface disease or diabetes (as factors additionally confounding bleb healing). Parameters evaluated included types of glaucoma, number of glaucoma medications, control of intraocular pressure (IOP), bleb morphology, and postoperative complications/reoperations. All patients had their prostaglandin analog/pilocarpine stopped 2 weeks before surgery to avoid prevent conjunctival hyperemia/inflammation associated with their use. We did not routinely use any topical steroids in preoperative period for ocular surface priming in our patients.

### Surgical technique

All operations were carried out under local peribulbar anesthesia by the same surgeon (KS). Standard trabeculectomy with fornix-based conjunctival flap of 8-mm linear dimension, 4.5 × 4.0 mm rectangular scleral flap and suturing with *two loose fixed* (Olo placement requires sutures to be kept loose) and *two releasable sutures* (Wilson's modification) using 10-0 monofilament nylon, was done. A cylindrical Olo implant with dimensions of 6 mm height and 2 mm diameter (Model 830601; Aeon Astron Europe B. V.) was placed straddling the posterior edge of scleral flap. Conjunctival flap was anchored to limbus with bleb forming horizontal mattress sutures (9-0 monofilament nylon) and bleb titration was performed at the end of surgery through the side port to ensure water tight suturing.

Postoperatively, all eyes were treated with topical antibiotic-steroid combination (gatifloxacin 0.5% eye and prednisolone acetate 1%) eye drops six times daily for 1 week, four times daily for 2 weeks, twice daily for 2 weeks, and once daily for a final week, as well as homatropine eye drops twice daily for 1 week and once daily for 1 week. Atropine as a cycloplegic was used in cases with a shallow anterior chamber during first 2 weeks. Releasable sutures were sequentially released on either noting a reduction in bleb height or observing IOP beyond single digits after the first week. In the absence of these two criteria, the releasables were removed only after a 4-week period. All patients were assessed postoperatively on days 1 and 7 and weeks 2, 4, 6, and 12 followed by an annual visit.

The primary outcome variable was mean postoperative IOP with *complete success* being defined as IOP <20 mm Hg without use of any antiglaucoma medications and *qualified success* as attaining this IOP level with additional use of ≥1 anti-glaucoma medication(s). Secondary outcome measures included reduction in the number of antiglaucomatous medications, complication rate, and bleb morphology.

Descriptive statistics were performed and differences between preoperative and postoperative IOP were tested for significance using paired *t*-test ( $P < 0.05$ ). Trabeculectomy performed before 2010 were imaged by ultrasound biomicroscopy (UBM) and those performed later with anterior segment optical coherence tomography (AS-OCT). Blebs with a thickened wall (when compared with conjunctivoepiscleral space) and discrete hyporeflexive microcystic spaces were classified as successful. Blebs with absence of bleb wall thickening/microcystic spaces and/or presence of dense linear collagen scars were categorized as "failed."

## Results

A total of 30 eyes of 28 patients were included in the study with two patients undergoing bilateral trabeculectomy with Olo implantation. The median follow-up was 36 months. Fourteen eyes attained a follow-up of 5 years and eight eyes a follow-up of >7 years.

The mean preoperative IOP was 36.46 mm Hg, on two or more topical antiglaucoma medications with all patients requiring systemic acetazolamide over 5–8 days for control of IOP before trabeculectomy.

Trabeculectomy resulted in reduction in IOP from 36.46 to 11.65 mm Hg in the immediate postoperative period (say 1), a 68% decrease [Table 1]. The mean IOP reduction decreased over time from 63% in the first year to 55% at 5 years.

Complete success was attained in 100% cases till 24 months following which six eyes (20%) required addition of ≥1 topical medication (Timolol) to maintain IOP of below 20 mm Hg and were classified as "qualified success." Of the eight patients completing 7-year follow-up, five cases attained "complete success" and one patient required bleb resuscitation after 2 years with one event of 5-FU needling.

IOP reduction was not gender-specific with males achieving a 52% fall and females a 57% decrease in IOP at 5 years of follow-up. The efficacy of trabeculectomy was evaluated in young adults (≤30 years) versus older individuals and IOP control was found to be similar in both age ranges until 1 year of follow-up. A longer follow-up of 5 and 7 years documented slightly enhanced IOP control in younger subjects [Table 2], but the difference in IOP control did not attain statistical significance at any time (Wilcoxon test).

Imaging revealed implant eyes develop diffuse, low bleb at each follow-up even after 5 years of surgery [Fig. 1]. UBM and AS-OCT documented gradual degradation of implant with establishment of low reflectivity in subconjunctival space during follow-up visits. The implant was visible at 6 months in all cases and up to 9 months in five cases but became completely disintegrated by 12 months [Figs. 2 and 3]. All Olo blebs had hyporeflexive microcystic spaces except the one case which required 5-FU needling and were classified as successful. No bleb demonstrated a thin bleb wall.

Complications noted were shallow anterior chamber with hypotony (four eyes), overfiltering blebs (three eyes), and conjunctival wound leak requiring resuturing during the initial week (one eye). One eye developed Tenon's cyst requiring needling at 24 months with the AS-OCT showing hyperreflective bleb wall with reduced microcystic spaces suggestive of failing

**Table 1: Control of intraocular pressure with time**

Stage	IOP values		P*	Percentage of IOP reduction	
	Mean (SD)	Median (IQR)		Mean (SD)	Median (IQR)
Preoperative	36.46 (8.80)	34.5 (11.6)	-	-	-
1 Week	11.65 (2.55)	12.2 (2.2)	<0.001	0.66 (0.12)	0.67 (0.14)
1 Month	12.86 (2.18)	12.2 (2.0)	<0.001	0.62 (0.14)	0.65 (0.12)
6 Months	13.33 (3.07)	14.0 (2.6)	<0.001	0.62 (0.14)	0.65 (0.19)
1 Year	13.31 (2.69)	12.2 (2.6)	<0.001	0.62 (0.13)	0.65 (0.17)
15 Months	14.39 (2.87)	14.6 (4.8)	<0.001	0.59 (0.15)	0.60 (0.18)
2 Years	15.48 (2.97)	14.6 (3.3)	<0.001	0.55 (0.14)	0.60 (0.17)
3 Years	16.10 (2.25)	17.3 (2.7)	<0.001	0.53 (0.13)	0.52 (0.23)
4 Years	16.12 (2.16)	15.9 (2.7)	<0.001	0.50 (0.13)	0.48 (0.14)
5 Years	16.36 (2.87)	16.6 (2.7)	<0.001	0.51 (0.16)	0.52 (0.21)
6 Years	15.82 (2.58)	15.9 (3.3)	<0.001	0.51 (0.19)	0.52 (0.30)
7 Years	15.18 (2.78)	14.6 (3.5)	0.002	0.57 (0.18)	0.65 (0.28)

\*P-values were calculated by paired t-test. IOP: Intraocular pressure; SD: Standard deviation; IQR: Interquartile range

**Table 2: Comparison of IOP control in young adults (≤30 years) versus older adults (> 30 years)**

Stage	Median IOP value (IQR)		Median percentage of IOP reduction (IQR)	
	Age ≤30	Age ≥30	Age ≤30	Age ≥30
Pre OP	40.00 (10.00)	33.00 (10.80)	-	-
1 week	12.20 (4.40)	12.10 (3.90)	0.66 (0.16)	0.67 (0.16)
1 Month	13.10 (3.40)	12.20 (2.00)	0.67 (0.11)	0.62 (0.14)
6 month	12.20 (4.40)	14.00 (2.60)	0.69 (0.12)	0.60 (0.18)
1 Year	12.20 (2.40)	14.00 (4.60)	0.65 (0.12)	0.61 (0.24)
15 month	15.25 (4.55)	15.25 (4.45)	0.68 (0.17)	0.56 (0.16)
2 Year	14.60 (4.90)	14.60 (2.15)	0.64 (0.05)	0.50 (0.19)
3 Year	17.30 (3.40)	15.45 (2.70)	0.62 (0.08)	0.43 (0.15)
4 Year	15.95 (3.40)	15.90 (2.70)	0.57 (0.17)	0.43 (0.12)
5 Year	14.60 (5.85)	17.30 (1.40)	0.63 (0.09)	0.37 (0.20)
6 Year	14.30 (5.10)	17.30 (2.10)	0.65 (0.12)	0.40 (0.16)
7 Year	14.00 (2.40)	15.90 (2.70)	0.67 (0.05)	0.39 (0.16)

bleb. By 36 months, four eyes had developed visually significant cataract and three patients underwent clear corneal temporal phacoemulsification with maintained bleb function over a minimal follow-up of 12 months after the surgery. No case of late-onset leakage, bleb-related endophthalmitis, or thinning of bleb was observed in our series.

### Discussion

Prevalence of glaucoma is increasing globally partly as a result of increased life span and partly improved healthcare facility. The disease impact is more in developing countries where inadequate resources and poor and variable access to healthcare ensure late diagnosis often resulting in blindness. Extrapolating these same factors coupled with long-term feasibility and affordability of medical therapy makes trabeculectomy the favored option to treat blinding glaucoma.<sup>[30]</sup>

For these people of developing countries (eastern and central hemisphere), adjunctive use of MMC is almost

mandatory keeping in mind the genetic propensity for these brown-eyed individuals to exhibit enhanced subconjunctival fibrosis. However, use of MMC is a double-edged sword and is documented to cause hypotony, avascular filtering blebs, late leakage, and endophthalmitis subsequent to impaired healing.<sup>[31-33]</sup> These vision-disabling complications have been reported in almost 23% cases over 5 years of functioning trabeculectomy thereby putting a question mark of use of antifibrotics jeopardizing bleb safety.<sup>[12]</sup> The search for effective wound modulation ensuring trabeculectomy survival while ensuring safety by generating healthy, vascular yet vital blebs is the need of the hour for all and especially for dark-eyed children of these developing countries who often reside in rural environment, putting their blebs at a higher risk for trauma-induced infection.

Histologically, the bleb wall consists of an outer, cellular, vascular connective tissue layer composed primarily of collagen, elastin fibres (fibroproliferative layer) merging with deeper avascular, relatively acellular layer of hyaline degeneration of collagen covering aqueous-filled space (fibrodegenerative layer). Fibroblasts and macrophages in bleb capsules undergo cycle of cell death and replacement, with a fibroproliferative response occurring in the vicinity of aqueous permeated well-oxygenated tissue and fibrodegenerative response in the vicinity of poorly oxygenated tissue.<sup>[34]</sup> Aqueous percolation is thus the best way to prevent occurrence of subconjunctival fibrosis, and an ideal augmented trabeculectomy ensures this by modified wound-healing without killing the fibroblasts. Ologen (Aeon Astron Europe B. V.) is one such strategy which creates such a physiological aqueous percolated environment by preventing compressed collagen lamellae generation, using a biodegradable porous material comprising 90% lyophilized atelocollagen (pepsin-treated type I porcine collagen) and 10% lyophilized porcine glycosaminoglycan and pore size (20–300 µm) designed to permit loose, random, nonlinear organization of regenerating fibroblasts and extracellular matrix.<sup>[15]</sup>

Literature on use of Olo implant in trabeculectomy survival is ambivalent with comparable outcomes compared with



conventional MMC-augmented trabeculectomy<sup>[15,18,35,36]</sup> and others reporting suboptimal results.<sup>[17,35,36]</sup> A meta-analysis with a 2-year follow-up concluded Olo implant to be equivalent to MMC trabeculectomy in IOP-lowering efficacy, reduction in number of glaucoma medications, success rates, and tolerability.<sup>[28,30]</sup>

The aspect of Ologen Collagen Matrix being primarily a wound modulator which generates a more loosely organized bleb tissue and not manifesting antifibrotic properties is borne out by morphology of filtering bleb in our patients where neither avascularity nor wall thinning was noted in any patient at any follow-up interval. This aspect has been confirmed by previous studies comparing Olo-treated eyes with MMC-treated eyes.<sup>[4,5,7,17]</sup>

The mean IOP reduction by 54% or almost 20 mm Hg decrease at 5 years reiterates the effectivity of Olo-augmented trabeculectomy. No case required repeat surgery except one event of needling over 5–7 years which underscores the long-lasting bleb modulation. To the best of our knowledge, this is the first study reporting a long-term follow-up of Olo trabs.

Trabeculectomy in younger age is known to scar more rapidly and become less efficacious but our series did not observe this. Good long-term IOP control in younger patients of our series demonstrates efficacy of implant-induced bleb modulation over a span of ages. The documented trend for improved control

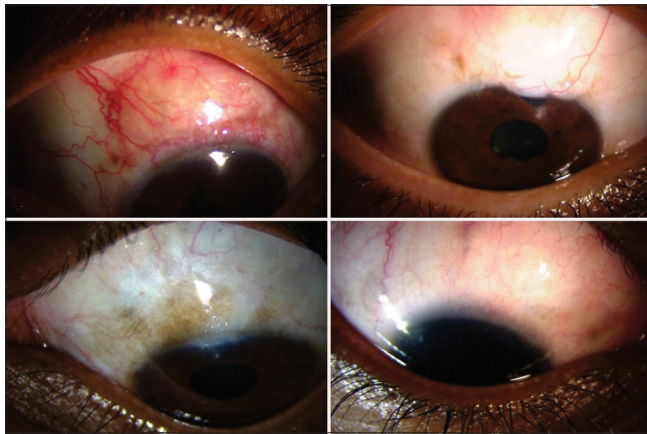
in younger age could be attributed to higher initial pressures (40 vs. 33 mm Hg) in the younger age group which translated into greater reduction in IOP (63%: 37% at 5 years,  $P = 0.004$ ).

Wound closure after implant application was not onerous unlike to that reported by Narayanswamy *et al.* and meticulous wound closure could be achieved in all cases with no incidence of bleb leak.<sup>[35]</sup> This could be explained partly by our technique of performing bleb titration on table, at end of surgery, to confirm a water tight section.

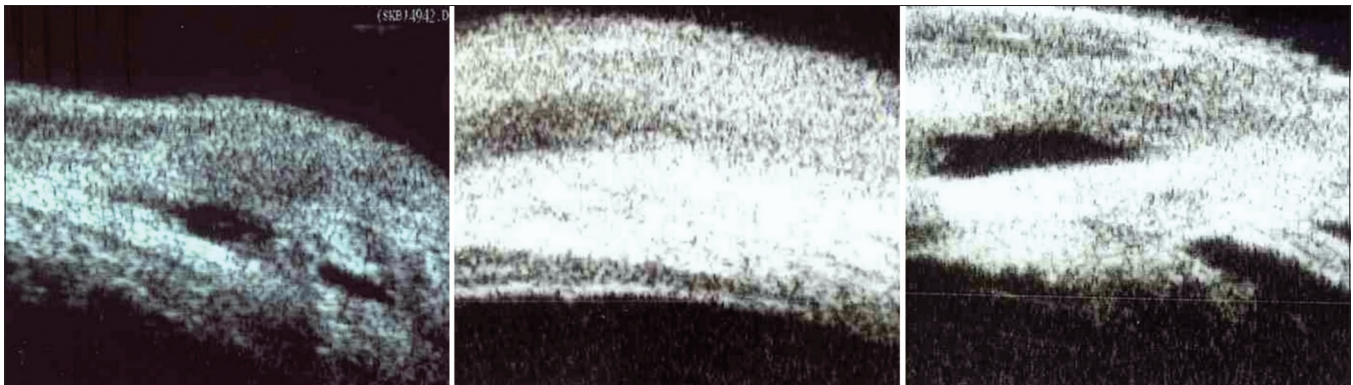
Ethnicity plays a key role in determining fibroblast proliferation and pigmented races have been documented to exhibit a more rapid wound-healing process and subsequent scarring.<sup>[37,38]</sup> Epidemiologic studies on skin healing have shown that dark-skinned patients are 15 times likely to develop an abnormal fibroproliferating healing process leading to keloids compared with White races.<sup>[39]</sup> This tendency for rapid and aggressive wound healing in dark pigmented races is also applicable to people of north Indian ethnicity. There is paucity of data on Olo blebs in Asian community of North Indian ethnicity, but studies on the more darker skinned South Indian community have reported similar success profile with trab adjunctives of Olo and MMC groups.<sup>[18]</sup> A combined approach such as Olo implant with low-dose MMC has been suggested for races with aggressive healing.<sup>[40]</sup> More studies are needed to ascertain whether Indian ethnicity is an independent risk for increased filtering failure, and whether combined MMC with Olo implant would offer added benefits in aggressive healing patients.

There is theoretical risk of increased inflammation in eyes with Olo implant due to non-human (porcine) origin of the implant. The antigenicity conferred by the amino acid sequence of telopeptide collagen at both N and C terminals has been reduced by use of telopeptide-free atelocollagen and we did not document any increased inflammation in our cases either in the form of increased anterior chamber reaction or bleb hyperemia/granuloma at any time during the entire follow-up.

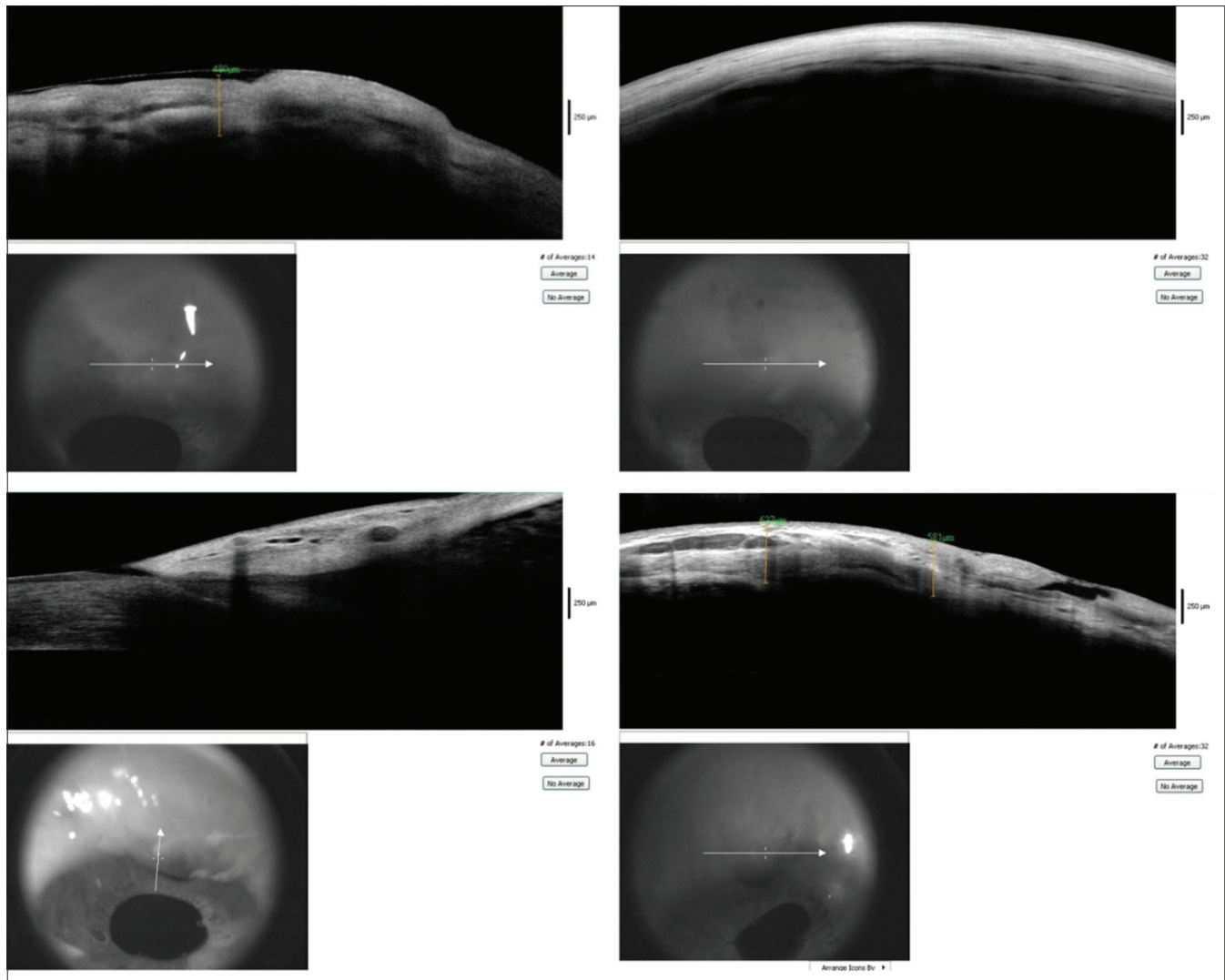
No sight-threatening complication was documented and early postop complications of hypotony (four eyes) with overfiltering blebs (three eyes) could be managed conservatively. One eye with bleb leak required resuturing at fourth postoperative day. The long-term efficacy of Olo trabeculectomy over 5 years in 14 eyes and 7 years in 8 eyes indicates this modality can be tried as an alternative antifibrotic



**Figure 1:** (Clockwise from top L–R) Posttrabeculectomy with Ologen implant (week 1, 2 months, 1 year, 5 years)



**Figure 2:** (Left to right) Ultrasound biomicroscopic appearance of Ologen implant in posttrabeculectomy bleb (6 months, 9 months, 1 year)



**Figure 3:** Anterior segment optical coherence tomography appearance of bleb showing hyporeflexive microcystic spaces in all except top right showing scarred bleb

especially in secondary/developmental glaucomas afflicting young adults, where use of MMC with its propensity to generate unsafe blebs raises concern about maintenance of good vision over remaining life years. The concern raised as to the efficacy of the more robust bleb tissue being able to maintain target IOP over a long-term follow-up has been adequately redressed by our study findings.<sup>[26]</sup>

It should be noted that our study has its limitations. First, the data presented here come from a retrospective case logs and could reflect a selection bias in using Olo implant for low-risk patients. Second, no control group was evaluated with similar profiling for direct comparison. Moreover, the data come from a single center and the sample size is not large enough to reflect pooled findings from multiple hospitals. A randomized controlled study is warranted to address ideal patient selection for Olo implant and long-term follow-up.

**Conclusion**

Our data demonstrated that Olo-augmented trabeculectomy uses physics and physiology to generate a vascular,

thicker-walled, and healthier bleb with no evidence of avascularity, bleb ooze, or leak over a minimum follow-up of 5 years and maximum follow-up of 7 years. This tissue bioengineering device could be considered a viable alternative for patients with contraindications to use of antimetabolites.

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Nil.

**Conflicts of interest**

There are no conflicts of interest.

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