Original Article

Rescue of failing or failed trabeculectomy blebs with slit-lamp needling and adjunctive mitomycin C in Indian eyes

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Purpose: The aim of this study is to investigate the efficacy and safety of needling-revision augmented with a high dose of mitomycin C (MMC) in failing or failed blebs after trabeculectomy in Indian eyes. **Methods:** Prospective, noncomparative, interventional study. All patients (>18 years) who had raised intraocular pressure (IOP) following trabeculectomy (>6 weeks and <2 years), who had a flat bleb, bleb encapsulation, and/or required antiglaucoma medication (AGM) for IOP control were eligible for inclusion. MMC was injected subconjunctivally at least ½ hour before the needling procedure was carried out at the slit lamp in the outpatient's clinic. **Results:** Thirty-nine eyes of 38 patients were included. The median follow-up was 20 months and time interval between trabeculectomy and needle revision was 113 days. Initially, in all cases, aqueous flow was re-established with a raised bleb; 7 eyes required repeat needling. IOP decreased from median 24 mmHg (Q1 21, Q3 27, interquartile range [IQR] 6, range 18–35) preneedling to median 14 mmHg (Q1 10, Q3 16, IQR 6, range 6–18) postneedling at last follow-up ($P < 0.0001$, 95% confidence interval [CI]: 8.2–13.0). The use of AGM reduced from median 1 (Q1 0, Q3 3, IQR 3, range 0–4) preneedling to median 0 postneedling ($P < 0.0001$, 95% CI: 1–2). Complete success was seen in 28 eyes (71.8%, 95% CI: 71.1%–96.4%); another 5 eyes (12.8%) were controlled with AGM (qualified success) with overall success of 84.6%. Most complications were transient in nature with resolution within 1 week. One patient developed hypotony, and another developed a late bleb leak. **Conclusion:** Needling revision augmented with high-dose MMC, at the slit lamp, effectively rescues failing or failed filtration, and appears to be safe.

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Trabeculectomy, creating a subconjunctival filtration channel, is the surgical procedure of choice in most countries when it comes to treatment of chronic glaucoma. Since its first description in 1968 by Cairns,[1] the operation has survived challenges from newer procedures, especially in the management of advanced glaucoma.

Trabeculectomy, however, is not without its pitfalls as the bleb is known to remodel indefinitely. Subconjunctival (episcleral) fibrosis is the most common cause of failure; it is also a significant cause of late failure in eyes that were initially successful.[2,3] Furthermore, sub-Tenon's encapsulation of blebs, which presents as raised, often angry-looking blebs with elevated intraocular pressure (IOP), usually occurs in 1–6 months after surgery and is seen in 10%–20% of patients after trabeculectomy.[4]

In an attempt to control the fibrotic response, anti-inflammatory agents, such as steroids,[5] and anti-fibrotics, such as mitomycin C (MMC)[6] and 5-fluorouracil (5-FU), have been used. They have increased the success rate of trabeculectomy operations to 80% to 95% at 1 year.[7-9] Five-year success rates are still around 50% to 60% despite the use of antimetabolites.[10] Thus, increasing IOP with failing blebs continues to be an issue after glaucoma surgery. Options at the disposal of the treating ophthalmologist at this stage include reintroduction of antiglaucoma medications (AGM), with incumbent quality of life and compliance and adherence issues and financial implications; other options include re-do filtration surgery which has yet lower success rates,[11] and needling of the bleb.

Needling of the bleb helps to cut through the fibrous tissue, with a needle, which engulfs the bleb and shuts the filtration channel, leading to failure; antifibrotics are used as an adjuvant to prevent or retard closure by decreasing the production of fibroblasts and scar tissue.

5-FU was the choice of antifibrotics for needling by most glaucoma specialists in the past, but recent comparative studies with MMC, have shown better success rates with the latter, without any significant difference in safety.[12,13]

All reported studies have involved predominantly Caucasian populations; very few, if any, involve South Asian eyes who are presumed to scar relatively easily. The authors thus propose to investigate the efficacy and safety of this procedure, performed on the slit lamp, especially with the adjuvant use of high-dose MMC in Indian eyes.

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Methods

Design

Prospective, nonrandomized, noncomparative, interventional case series with survival analysis.

Setting

Tertiary level academic eye care center in India.

The Institutional Review Board of the Institute approved the protocol and the accumulation of data. The study was performed per the tenets of the Declaration of Helsinki.

Informed consent was obtained from each consecutive patient who fulfilled the inclusion criteria and was enrolled in the study.

All adult patients (>18 years) who had raised IOP following trabeculectomy (>6 weeks and <2-year postoperative) with a patent internal ostium on gonioscopy, who had a flat bleb with visible scleral flap, bleb encapsulation, and/or required AGM for IOP control were eligible for inclusion. Eyes, which had undergone trabeculectomy more than 2 years ago, multiple trabeculectomies and previous needling procedures, were excluded from the study.

Procedure

Preneedling

Relevant history for all individuals was recorded, and each subject underwent a comprehensive ophthalmic examination, including best-corrected visual acuity (BCVA) assessment (ETDRS chart, Precision Vision, IL, USA), slit-lamp biomicroscopy and photography of the bleb, IOP assessment with Goldmann applanation tonometry (Zeiss SL 130 slit lamp with Goldmann style applanation tonometer AT 030), gonioscopy with Sussman 4-mirror to check for open ostium, stereo fundoscopy with + 66D Volk lens (Volk Instruments, OH, USA).

Needling procedure

All needling procedures were performed in the outpatient clinic by one fellowship-trained surgeon. Pre-preparation with topical anaesthetic (Paracaine 0.5%, Sunways, India), topical phenylephrine (Aurophenyl 2.5%, Aurolabs, India) to constrict blood vessels and Betadine (Aurodone 5%, Aurolabs, India) eye drops were instilled three times, 10 min apart. Strict aseptic precautions were maintained for all cases.

0.15 ml of a 0.4 mg/ml solution of MMC (Biochem, India) was drawn in an insulin syringe after 0.05 ml of lignocaine 2% was drawn, for a final concentration of 0.3 mg/ml of MMC or a total dose of 60 micrograms. This was injected subconjunctivally with a 29- or 30-gauge needle at least 30 min before the revision procedure in the clinic. The site of the injection was superior and was at least 8–10 mm away from the bleb.

At the slit lamp, the patient was instructed to look down so that the entire bleb was exposed.

The slit lamp was set at the lowest magnification facilitating visualization of the bleb, even if the eye moved during the procedure.

Needling was performed with a 29-gauge needle on a tuberculin syringe. The needle was bent 45° using the sheath (to keep the tip sterile), to facilitate easier entry. It was introduced into the subconjunctival space, at least 2 mm from the edge of the bleb, and advanced into the bleb. The subconjunctival fibrosis was cut with a firm back-and-forth motion, and the direction of the needle was changed, as required. The scar tissue was cut with sweeping motions in all directions around the scleral flap, till a diffuse bleb was lifted. If a bleb did not lift adequately, then subscleral flap needling was done, and the AC was entered. The endpoint was determined when there was change in the appearance of the bleb, with the bleb size increasing, and the needle was then withdrawn.

Seidel test was performed immediately after the procedure, and postneedling IOP was recorded.

Patients were instructed to use topical antibiotics ofloxacin hydrochloride 0.3% (Exocin, Allergan, Irvine, CA) 4 times daily for 1 week with topical steroid drops (prednisolone acetate 1%) for 8 weeks in tapering dose and topical cycloplegic eye drops (Cyclopentolate Hydrochloride 1%, Cyclogik, FDC, India); they were advised to commence gentle digital massage from day 7 after explanation and demonstration.

Primary outcome measure was IOP with complete success being defined as an IOP >5 and ≤18 mmHg without medication; if the preoperative IOP was ≤21 mmHg, an IOP reduction of >20% without medication, was also considered as a success. Qualified success was defined as meeting these criteria with medication. Failure to meet these criteria and/or requirement for more than three needle revision procedures and or reoperation (trabeculectomy or glaucoma drainage device or transscleralcyclophotocoagulation) was defined as failure of the needling procedure.

Secondary outcome measures included LogMAR best corrected visual acuity (LogMAR BCVA), AGM and major complications.

Data are presented in the median to account for outliers, as it is nonnormally distributed and as quartiles, that divides these data into quarters. The first quartile or Q1 is the number between the smallest number and median of the data; the third quartile (Q3) is the number between median and highest value. Interquartile range (IQR) is calculated by deducting Q1 from Q3 (Q3-Q1= IQR) and represents the distribution of data in the central 50% of the dataset.

Pre- and post-needling IOP, BCVA, and AGM were analyzed using the Wilcoxon signed rank test; confidence interval (CI) has been used at 95% and represents a range within which a parameter lies. A multivariate Cox regression model with stepwise elimination using Akaike information criteria was performed to assess the association between study factors and time to failure.

All statistical analyses were performed using the R software (version 2.12, The R Foundation for Statistical Computing). R is available as Free Software under the terms of the Free Software Foundation's GNU General Public License in source code form.

Results

Thirty-nine eyes of 38 patients were included in the study. Twenty-seven patients were male; median age was 59 years (Q1 47, Q3 65, IQR 18, range 22–79). Median interval between trabeculectomy and needle revision was 113 days (Q1 73, Q3 387,

IQR 314, range 45–750 days). Median follow-up was available for 20 months (Q1 12, Q3 24, IQR 12, range 4–48 months). The demographics of the study population are listed in Table 1.

The IOP decreased from median 24 mmHg (Q1 21, Q3 27, IQR 6, range 18–35) preneedling to median 14 mmHg (Q1 10, Q3 16, IQR 6, range 6–18) postneedling at last follow-up ($P < 0.0001$, 95% CI: 8.2–13.0). IOP was significantly less at all time points during the follow-up period (immediate postneedling, 1 week, 1 month, 3 months, 6 months, 12 months, and at last follow-up) [Fig. 1]

The use of topical AGM reduced from median 1 (Q1 0, Q3 3, IQR 3, range 0–4) preneedling to median 0 postneedling ($P < 0.0001$, 95% CI: 1–2). Nearly 50% of patients required Diamox preneedling; none required Diamox postneedling.

LogMAR BCVA improved marginally from median 0.3 (Q1 0.175, Q3 0.525, IQR 0.35) to median 0.2 (Q1 0.1, Q3 0.325, IQR 0.125) and was statistically significant ($P = 0.03$). Two eyes had decreased BCVA at last follow-up one eye with hypotony and corneal decompensation lost 2 lines following endothelial grafting and one eye which developed a cataract, is awaiting surgery but was subsequently lost to follow-up.

The procedure achieved complete success in 28 eyes (71.8%, 95% CI: 71.1%–96.4%) (defined as reduction of IOP by two criteria; ≤18 mmHg or >20% from baseline if IOP ≤21 mmHg); additionally, another five eyes (12.8%) achieved the above criteria with AGM (qualified success). The total success rate at the end of the 2nd year was thus 84.6%.

Initially, in all cases, aqueous flow was re-established with a raised bleb; however, 7 (17.9%) eyes needed repeat needling, at a rate of 1.2 procedures per eye. Two procedures were required in 5 of these eyes while two eyes needed a third procedure.

In multivariate analysis, the risk factors for failure to achieve success in our series, as defined earlier, included multiple needle revisions as well as needling done post combined phacotrabeculectomy [Table 2].

Needling failed in six eyes (15.4%); two of these failed within the 1st 3 weeks of the procedure. Two eyes failed following cataract surgery, (phacoemulsification with posterior chamber implant-phaco+ posterior chamber intraocular lens [PCIOL]), at 8- and 12-month postprocedure, respectively, after initially being successful. One eye failed after two needling procedures and one after three needling procedures. Five of these failed eyes subsequently underwent glaucoma drainage device surgery and the sixth one underwent transscleral cyclophotocoagulation through diode laser.

Table 1: Patient demographics (*n*=38), eyes (*n*=39)

Demographics	*n*	Percentage
Age, median (IQR)	59 (18)	-
Gender	27 males	71.0
Etiology of glaucoma		
Primary angle closure glaucoma	21	53.8
Primary open angle glaucoma	9	23.1
Pseudoexfoliation glaucoma	6	15.4
Other secondary glaucoma	3	7.7
Lens status		
Phakic	13	33.3
Pseudophakic	26	66.6

IQR: Interquartile range

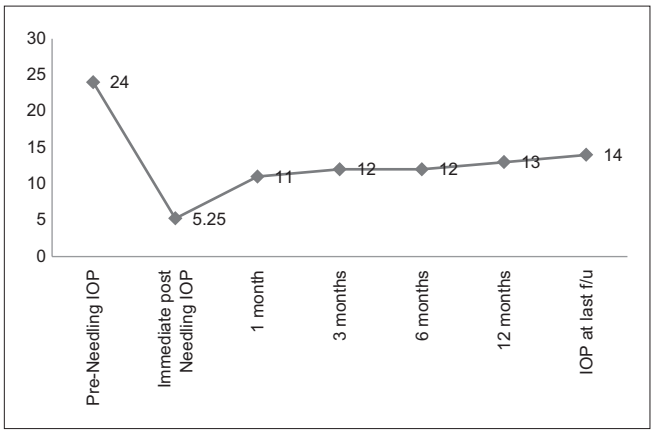

Figure 1: Median intraocular pressure (mmHg) pre- and post-needling with Mitomycin C at all time intervals after procedure

Table 2: Cox proportional hazard model to evaluate the factors affecting success of needling

Variable	Univariate regression		Multivariate regression	
	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
Age	0.9944 (0.9429-1.0487)	0.84	-	
Gender	1.86 (0.22-15.89)	0.57	-	
Duration from trabeculectomy	0.999 (0.9949-1.0031)	0.63		
Preneedling IOP	0.96 (0.79-1.16)	0.65	-	
Number of preneedling AGM	1.2 (0.64-2.24)	0.57		
Phakic status: Pseudo versus phakic	0.94 (0.17-5.16)	0.948	10.99 (0.85-141.8)	0.06
Needling postcombined surgery	0.32 (0.06-1.72)	0.183	0.01 (0.0004-0.7)	0.03
Use of MMC in index trabeculectomy	1.02 (0.19-5.59)	0.98		
Immediate post needling IOP	1.08 (0.9-1.3)	0.418		
Postneedling SCH	0.29 (0.06-1.46)	0.13	0.13 (0.01-1.14)	0.06
Number of needling procedures	5.21 (1.04-25.97)	0.044	16.13 (1.22-211.71)	0.03

IOP: Intraocular pressure, MMC: Mitomycin C, AGM: Anti-glaucoma medication, SCH: Subconjunctival haemorrhage, CI: Confidence interval

Kaplan–Meier survival analysis was used to evaluate the survival of bleb postneedling and was 82% at the end of the 2nd year (95% CI 0.71–0.96) [Fig. 2].

Most complications were transient with resolution within 1 week - subconjunctival hemorrhage (SCH) (n = 27) and superficial punctate keratitis (n = 4). Even though SCH was common, the outcome of the procedure in eyes with or without subconjunctival hemorrhage did not differ [P = 0.12, Fisher's exact test]. Fig. 3 illustrates the long-term appearance of the bleb of one such subject who had SCH during needling. If the bleb were to be evaluated with the Wuerzburg bleb classification system,[14] it would score the desired 11 out of 12.

Other relatively more serious complications occurred in 10 eyes (25.6%). However, the majority settled on conservative management and these included – button holing of conjunctiva (n = 1, 2.5%), hyphema (n = 1, 2.5%) and choroidal effusion (n = 2, 5%).

The development of cataract was seen in three eyes (n = 3, 7.5%), two of which failed following phaco + PCIOL.

One (2.5%) pseudoexfoliation glaucoma eye developed an ischemic bleb with late leakage at 6 months; this resolved with amniotic membrane grafting.

One phakic angle closure subject developed nonresolving hypotony and flat anterior chamber (n = 1, 2.5%) and subsequent endothelial decompensation, which required an endothelium graft, performed along with phaco + PCIOL; IOP remained well controlled for this eye after latter procedures, without AGM, even after 4 years of follow-up. Another pseudophakic angle closure glaucoma eye developed an encysted bleb (n = 1, 2.5%), requiring repeat needling – this eye eventually failed.

The outcome of eyes with and without an adverse event did not differ (P = 0.33, Fisher exact test).

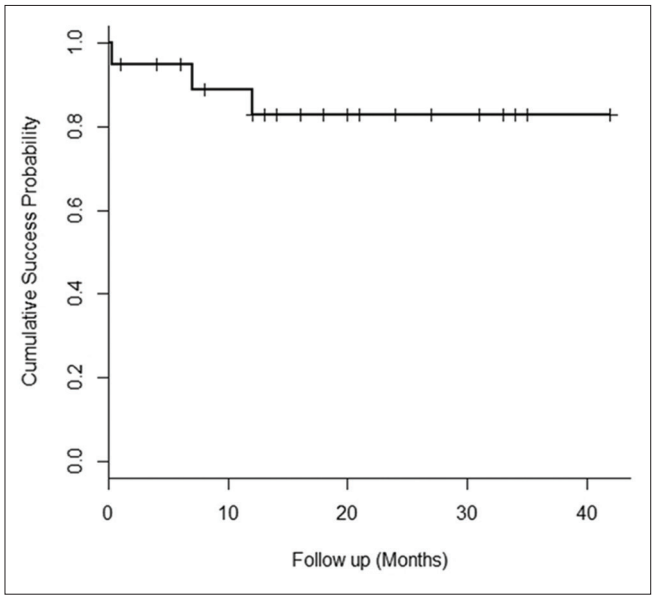

Figure 2: Kaplan–Meier cumulative survival curve for all needling procedures

Two subjects had a vasovagal episode during the procedure at the slit lamp; both were males.

Other very serious sight-threatening complications, namely, blebitis or bleb induced endophthalmitis, supra choroidal hemorrhage, and aqueous misdirection did not occur in this cohort.

Discussion

Blebs in the Indian population are prone for failing due to scarring of subconjunctival tissues. Needling is meant to tackle this scarring process, and our study showed that in above 80% of patients, with the concurrent use of MMC, filtration can be restored, provided the internal sclerostomy is patent. Success rates of approximately 60%–70%,[15] have been reported in literature, with the adjunctive use of MMC; results obtained when blebs were needled with 5FU are somewhat lower (30%–65%).[16-19] A recent report from Singapore comparing outcomes of bleb needling with 5-FU in primary glaucomas (open and closed angle) in an Asian tertiary eye center over a 2-year period, also reported a total success rate of approximately 60%.[17] However, comparison between various studies, as reported in literature, is counter-intuitive as there are differences in the parameters studied. These include and are not restricted to patient demographics, type and severity of glaucoma, original filtration with or without antifibrotics, multiple filtration surgery, timing of needle revision, type of blebs needled, amount and type of antifibrotic agent used, definition of success criteria, follow-up period among others.

Nonetheless, bleb needling with MMC has been moderately successful in the intermediate term, even when performed with a relatively low dose of MMC (10–25 µg),[12,20,21] including transconjunctival sponge application of 0.05 mg/ml MMC.[22] Most authors prefer this low dose of MMC, though there is very little agreement between authors, on the standard dose that should be used.

In 2005, Shetty *et al*.,[15] reported 64% total success rate, achieving a higher target IOP ≤21 mmHg, at a relatively higher dose of 40 µg of MMC (0.2 ml of 0.2 mg/ml MMC), though this dosage was lower than that used in our study. Even with this relatively high-dose MMC, they found success rates to be lower in African-Americans (though not statistically significant), females and phakic patients. The gender ratio in our study was almost the reverse of that seen in the study conducted by Shetty *et al*.

In a study by Groth and Sponsel[23] which comprised of predominantly Hispanic population, 76% achieved a target IOP of ≤18 mmHg at 6 months, when a novel lavage technique of 0.6 ml of 0.4 mg/ml MMC application through needling wound followed by thorough wash, was used.

In the only reported study of needling in South Asian eyes,[24] target IOP of <20 mmHg was achieved in 57% eyes with a lower dose of MMC (20 micrograms) than used in our study. They too found female gender to be a risk factor for failure to achieve target IOP; additionally, they found pseudophakia and needling done within 1 month of original filtration surgery as risk factors for failure.

We did not find pseudophakic status *per se* to be a risk factor for failure. In our study, 26 eyes were pseudophakic, but 23 of these had undergone original filtration as part

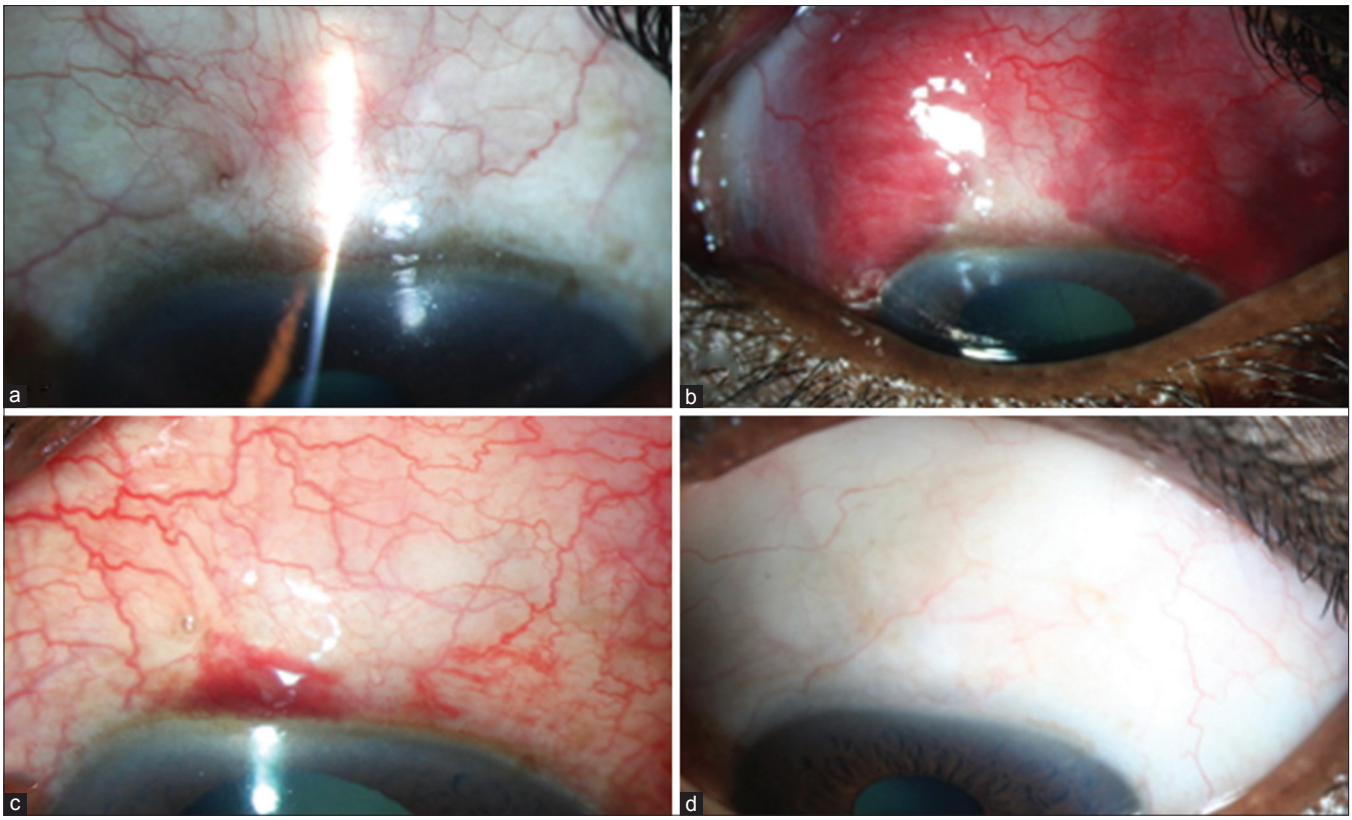

Figure 3: Appearance of bleb. (a) Preneedling; intraocular pressure 34 mmHg on 3 antiglaucoma medication. (b) Immediate postneedling diffuse bleb; intraocular pressure 10 mmHg with subconjunctival hemorrhage. (c) Postneedling 1 week resolution of subconjunctival hemorrhage; intraocular pressure 16 mmHg. (d) Postneedling 1 year; intraocular pressure 10 mmHg, no antiglaucoma medication

of combined surgery. Contrary to the finding in South Asian eyes by Mahar *et al*.,[24] needling in the latter group appeared to be more successful [Fig. 2] in our study. This may be counter-intuitive as it is known that breakdown of blood aqueous barrier occurs post phacoemulsification, with prolonged presence (up to 3 months) of flare in the anterior chamber.[25] A relatively small sample size appears to be the most likely explanation for this as the median interval between combined surgery and needling was 67 days in this subgroup, when compared to the entire cohort (median 113 days). Median interval between filtration surgery and needling of the remainder of the pseudophakic eyes, who had staged procedures, was much longer at 104 days.

We used an even higher concentration of MMC of 0.3 mg/ml (total drug dose 60 micrograms) as all our patients were exclusively of South Asian origin and were presumed to be at higher risk for failure due to scarring in subconjunctival tissues. This concentration is well below the dose-response effect of toxicity of MMC on corneal endothelium as published by Nuyts *et al*. in 1992.[26] None of our patients had corneal edema after the procedure, except one who had corneal decompensation after hypotony related flat anterior chamber, which unlike the case reported by Darian-Smith and Toh[27] did not resolve and underwent endothelial keratoplasty.

Meticulous technique and strict, standard asepsis protocol adopted by a single fellowship-trained surgeon ensured minimal serious complications. Most importantly, for the survival of the bleb, it is critical for digital massage to be instituted early and continued into the long term because it ensures long-term functioning of blebs.

Thus, it is possible to avoid a second filtration surgery in a significant number of patients with primary bleb failure and/or avoid reintroduction of topical AGMs, which have quality-of-life, social and financial implications.

Our prospective study managed to eliminate selection bias but was limited by the fact that it was unmasked and there were no controls, with or without the use of antifibrotics. Furthermore, identification of risk factors for failure following bleb revision using high-dose MMC was limited by the relatively small sample size. Nonetheless, this study has established several firsts in South Asian eyes – needling is efficacious and high-dose MMC is relatively safe and that it can be performed in an outpatient setting, eliminating the risk, and expense of more invasive procedures in the operating room in approximately 8 out of 10 cases of failed or failing filter.

Conclusion

In conclusion, needle revision of bleb with high-dose MMC can be successfully accomplished at the slit lamp in Indian eyes as it effectively rescues failing or failed filtration by reestablishing aqueous flow without compromising safety. This inexpensive, simple and safe intervention is thus a viable alternative, with less surgical trauma, compared to re-do filtration in failed trabs.

To the best of the authors' knowledge, there has been no

study on the efficacy and safety of the procedure, at the slit lamp, with higher dose MMC in Indian eyes of South Asian descent.

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Conflicts of interest

There are no conflicts of interest.

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