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Long term outcome of 5-Fluorouracil (5-FU) augmented bleb needling revision of failed and failing filtration blebs

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Abstract

Purpose: *To evaluate the long term outcome of 5-Fluorouracil (5-FU) augmented bleb needling revision of failed and failing filtration blebs based on survival analysis and to identify risk factors for failure, indicators for success and complications.*

Methods: *This was a prospective, interventional case series with survival analysis. 32 eyes of 32 patients underwent bleb needling augmented with 5-FU and were then followed up. Statistical analysis was done to assess the association between study factors and time to failure. Main outcome measures were reduction in IOP (<21 mm of Hg), number of antiglaucoma medications (AGM's), complications and factors associated with outcome including indicators for success.*

Results: *At one year followup 9 (28. 13%) eyes had IOP <21 mmHg without the use of any antiglaucoma medications. 13 eyes (40. 63%) had qualified success with mean IOP <21 mm Hg after 1 or multiple needlings but with the help of one or more AGM's (1. 2±0. 4). 10 cases (31. 25%) failed and had to undergo repeat Trabeculectomy or shunt surgery. In the cases which achieved overall success, complete and qualified together (n = 22) the baseline IOP pre needling was 26. 7±8. 2 mmHg which was reduced to 13. 6±4. 6 mmHg at the end of the minimum follow up period of 1 year. The median interval between the "index" filtration surgery and the first (or only) needling procedure was 7. 5 months (Range 3 months to 4 years). Overall reduction in mean number of topical AGM's was from 2. 68±0. 82 to 0. 82±0. 34. Overall cross sectional success rate at 1 year follow up (complete and qualified) was 68. 76%(n=32) and the overall cross-sectional success rate (complete and qualified) at the 3 year follow up period was 66. 91%(n=24) and 65. 82%(n=16) at 5 year follow up. Strong evidence was found for association between pre needling IOP >28 mm of Hg and failure and immediate attainment of low IOP <11 mmHg and longer survival. None of the other proposed factors were identified as having statistically significant effect.*

Conclusions: *This long term study shows that bleb needling augmented with 5-FU is a safe and effective method by which a significant number of failed or failing filtration blebs can be rescued. Attaining an immediate reduction in IOP <11 mmHg seems to be a favorable factor with respect to reasonably long-term efficacy.*

Keywords: *5 Fluorouracil, Antiglaucoma medication, Bleb Needling, Failed bleb, Trabeculectomy.*

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Introduction

Trabeculectomy is presently the surgical treatment of choice for many patients with glaucoma, and, overall, the success rate of the procedure is reasonably high.[1,2] The introduction of intraoperative and postoperative antimetabolite application for the manipulation of wound healing have greatly enhanced the success rates of surgery.[3,4] However, a proportion of the procedures fail, both in the early postoperative period and, in a smaller proportion of patients, after a number of years. In a 20 year follow up study on trabeculectomy done by Landers *et al.* the authors noted that 13% of the eyes failed to achieve complete success during the first year (6% in the first 2 months and 7% in the subsequent 10 months). Thereafter, 1. 6% of eyes failed to achieve the criteria of complete success per year for the next 19 years.[5] If qualified success was taken as the criteria of success then the authors noted that seven percent of eyes failed the definition of qualified success during the first 5 years, with 0. 3% of eyes failing per year for the next 15 years thereafter. The failure rate of trabeculectomy with 5-fluorouracil in the Fluorouracil Filtering Surgery Study (FFSS) was 16% at 1 year, 29% at 3 years, and 51% at 5 years.[6] In the Tube versus Trabeculectomy study, which was designed to evaluate the safety and efficacy of Baerveldt-350 tube shunt implant compared to trabeculectomy with MMC in eyes with prior cataract or trabeculectomy surgery, the failure rates in the trabeculectomy group were 13. 5% at 1 year, 28. 2% at 2 years, 30. 7% at 3 years and 46. 9% at 5 years.[7] Failure is usually the result of scarring in the subconjunctival space with resultant intrableb fibrosis and the development of a failed bleb, instead of a functioning, filtering bleb.[8,9,10,11]

In addition to the use of antimetabolites, there have also been developments in the manipulation of flow resistance after surgery. Traditionally, the triangular or rectangular flap was closed with fixed sutures, which allowed no postoperative manipulation apart from massage.[12] Subsequently, laser suturelysis came into being and a single or multiple sutures could be cut to manipulate the flow.[13,14] This was followed by the development of releasable sutures, which when removed at the slit lamp could alter the outflow facility and, most recently, the development of adjustable sutures where the tension can be altered by suture loosening with a specially designed pair of forceps has come into being.[15,16,17]

Many approaches for managing dysfunctional filtration blebs have been proposed.[18] Several reports have advocated needling revision with adjunctive 5-Fluorouracil (5-FU) or Mitomycin-C (MMC) as an effective and relatively simple method of re-establishing filtration in eyes with failed filtering blebs.[18,19,20,21,22,23] Some studies however indicate that successful outcome may require multiple needling revisions.[23,24,25,26] We wanted to study the outcome of postoperative needle revision of failing or failed trabeculectomy blebs performed with the use of adjunctive 5-fluorouracil (5-FU) to inhibit postneedling fibrosis in a south Indian population and evaluate the results based on survival analysis.

Purpose

The aim of this study was to evaluate the long term outcome of 5-Fluorouracil (5-FU) augmented bleb needling revision of failed and failing filtration blebs based on survival analysis and to identify risk factors for failure, indicators for success and complications.

Materials and Methods

This was a prospective, noncomparative, interventional case series. The study population included patients who satisfied the inclusion criteria, had undergone a Trabeculectomy and then subsequently presented for follow up at the Glaucoma clinic.

Thirty two eyes of 32 patients were included and analyzed. At the time of entry into the study, a past ophthalmic history was obtained, with all previous surgery, laser and topical therapy being documented. Visual acuity was recorded using the Snellen's chart. The failed blebs were assessed and the bleb characteristics noted. In addition, it was documented whether part of the bleb or surrounding conjunctiva was injected and whether conjunctival microcysts were evident. A routine anterior segment examination was performed at the slit lamp. Applanation tonometry was performed and the intraocular pressure (IOP) recorded.

After failure of a releasable suture (if a releaseable suture had been placed) or suture lysis (if non releaseable sutures had been placed), bleb massage, or a combination thereof, any patient with a failed or failing trabeculectomy bleb was included in the study. Gonioscopy was performed to confirm that the internal ostium of the trabeculectomy was patent. The posterior pole of the eye was examined at the slit lamp using a 90-diopter lens.

The target IOP set for each patient was based on the severity as well as the history of progression of glaucomatous optic nerve damage. If the IOP did not reach its goal and the filtration bleb showed signs of failure, such as a flat bleb inspite of suturelysis and bleb massage and a highly vascular bleb inspite of a patent internal ostium on gonioscopy, then a decision for needling revision was taken. After approval of the ethics committee the needling procedure was performed. Only patients unwilling to give consent for the procedure were excluded.

Bleb Needle Revision Technique

After obtaining informed consent an antibiotic (Ofloxacin 2%) was instilled in the eye. A drop of povidone-iodine was used before the procedure and anaesthesia was obtained by a topical anaesthetic (Proparacaine 0. 5%). A sterile lid speculum was inserted for separation of the eyelids. Using sterile technique and viewing the infraducted eye with an operating microscope, the subconjunctival space was entered with a with a 26-gauge needle, with an attached syringe containing Xylocaine 1%, 0.1 ml, at approximately 10 to 12mm distal to the site of the failed filtration bleb. The Xylocaine was delivered and the subconjunctival drug spread out with a cotton tip applicator. A 30-gauge needle attached to an insulin syringe was used for needling. The needle was introduced subconjunctivally about 10 mm away from

the bleb or 5 to 6 mm temporal to the site of the scleral flap in the supero-temporal quadrant. The needle was then advanced subconjunctivally toward the failed filtration bleb site, then over the trabeculectomy scleral flap, repeatedly if necessary, until local elevation of the conjunctiva due to egress of the aqueous humor was observed. Using a sweeping motion, the cutting edges of the needle tip were used to disrupt any episcleral fibrosis. If local elevation of the conjunctiva did not occur, the needle tip was deliberately introduced underneath the scleral flap and, if still not successful, into the anterior chamber underneath or through the scleral flap in an attempt to reestablish the fistula. Another 30 gauge needle attached to a 1cc syringe containing 0. 2 ml of 5 Fluorouracil (25 mg/ml) was taken. The needle was pushed through the subconjunctival space in a zigzag manner to reduce the risk of subsequent antimetabolite leakage. The needle tip of this syringe was placed as distally as possible from the reestablished filtration fistula and the puncture site, and the 5-FU solution was injected subconjunctivally, with the bevel of the needle directed away from the reestablished filtration fistula. Care was taken throughout the procedure not to buttonhole the conjunctiva. (Figs: 1–6)

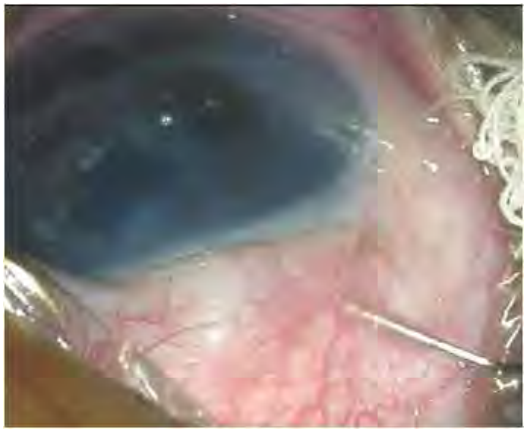


Fig 1: A 30 G needle attached to a syringe being used to dusrupt the episcleral fibrosis.

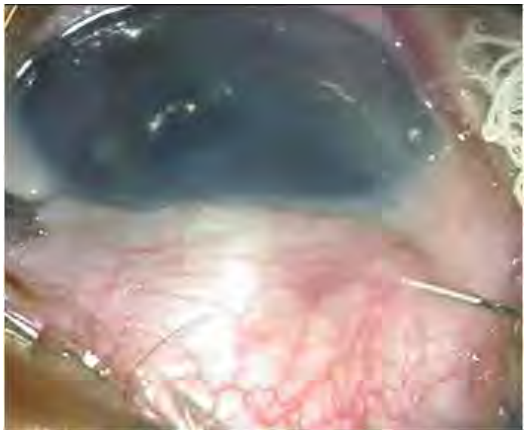


Fig 2: A sweeping motion being used and the cutting edges of the needle tip being utilized to disrupt the fibrotic tissue.

Because of the oblique nature of needle entry, no suturing of the conjunctiva was required. Only a brief tamponade with a cotton applicator soaked with topical anaesthetic solution was required to close the conjunctival puncture wound. After additional antibiotic drops, antibiotic-corticosteroid and atropine 1%eye drops were instilled. The eye was examined approximately 1 hour later with a slit-lamp. The patient was then discharged with antibiotic-corticosteroid eye drops and Homatropine eye drops to be gradually tapered as the ocular inflammation subsided.

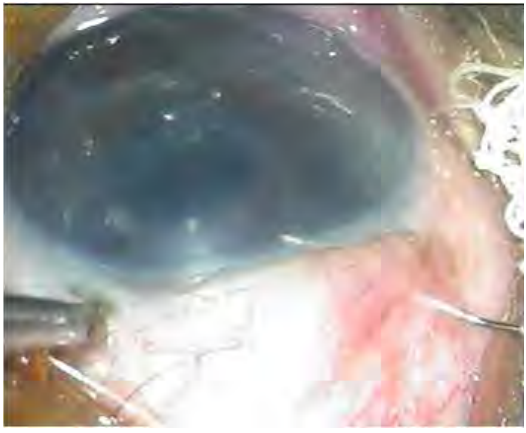


Fig 3: If local elevation of the conjunctiva was not achieved even after disrupting fibrosis underneath the scleral flap then the needle is advanced into the anterior chamber underneath the flap in an attempt to reestablish the fistula

The patients were seen routinely at 1, 2, 4, 8 and 16 weeks, with subsequent follow-up visits at 3 monthly intervals. The dosage of topical antibiotic-steroid was tapered as clinically indicated. Depending on the IOP control achieved as well as the appearance of the filtration bleb further steps were taken. The successful cases showed varying degrees of improvement of the appearance of their blebs. If signs of failure appeared in the bleb or if the IOP rose, digital massage or focal pressure was applied to the globe. On the basis of bleb morphologic features and IOP the examining ophthalmologist decided whether an additional subconjunctival 5-FU injection was clinically indicated.

At each postneedling clinic visit, visual acuity was recorded using the Snellens's chart and the needled bleb was reassessed and categorized. A routine anterior segment examination was performed at the slit lamp, IOP was recorded, and the posterior pole of the eye was examined using a 90-D lens. All complications considered to be a direct consequence of the needling procedure were recorded. If additional needling of the bleb was considered necessary, the procedure was carried out in the same manner as the initial procedure. The decision regarding whether to proceed with a subsequent bleb needling was based on the response to the previous procedure, together with the morphologic features of the bleb, gonioscopy findings and intraocular pressure.

When recommencing medical therapy, patients were initially prescribed a topical β-blocker (unless contraindicated). If β-blocker therapy was contraindicated or ineffective, therapy was switched to a prostaglandin analog. If β-blocker therapy

was effective, but inadequately so, a combination therapy of β blocker and Dorzolamide was started. Subsequent changes in therapy were based on clinical need.

Success was defined on the basis of IOP and morphological features of the bleb. For a procedure to be considered successful, the IOP had to be reduced to <21 mmHg with no antiglaucoma therapy, or less therapy than had been used before the needling. In the cases where the preneedling IOP (on antiglaucoma therapy) was <21 mmHg, success was defined as an IOP <21 mmHg with less or no antiglaucoma therapy. Complete success was defined as IOP > 5 and <21 mm of Hg without the use of antiglaucoma medications. Qualified success was defined as IOP <21 mmHg with the use of anti glaucoma medication and failure was defined as IOP> 21 mmHg even with the use of medication.

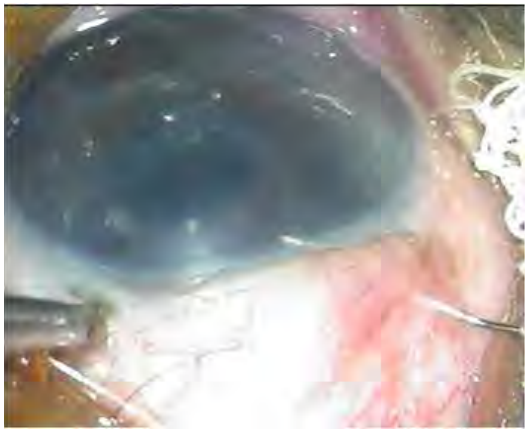


Fig 4: This figure clearly shows the needle inside the anterior chamber after dispruption of the fibrosis of the flap.

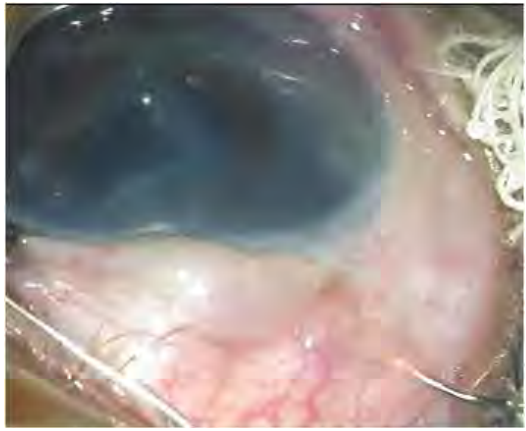


Fig 5: Figure showing clearly the elevation of the bleb after the withdrawal of the needle from the anterior chamber.

Potential risk factors for failure considered were age, gender, laterality, glaucoma diagnosis, previous topical therapy, previous exposure to antifibrotic agent, the interval between the index operation and the bleb needling procedure, preneedling IOP, immediate postneedling IOP, and number of needling procedures performed.

The data were duty noted into the case sheets and then collected and analysed.

Kaplan–Meier plots were constructed to estimate the probability of IOP "survival" over time after treatment with respect to the arbitrarily set level of 21 mmHg. For the purpose of the Kaplan– Meier plots, failure of treatment was defined to have occurred if IOP was more than 21 mmHg on 2 successive visits, having initially been at or below these levels on 2 successive visits after the most recently performed bleb needling procedure. The IOP after needle revision was compared with the preneedle revision IOP using the paired Student's *t* test. The Wilcoxon signed-rank test was used to compare the use of ocular hypotensive agents before and after needle revision and the Fisher's exact test was used to show the outcome in relation to type of bleb. Cox proportional hazards regression analysis was used to assess the association between each study factor and the time to IOP failure. Statistical analyses were performed using an established software package (SPSS v9. 0. 0; SPSS Inc., Chicago, IL).

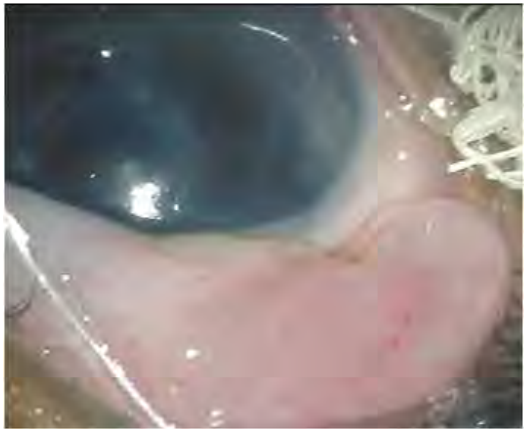


Fig 6: 5 FU being injected subconjunctivally with the needle tip being placed as distally as possible from the reestablished filtration fistula and the puncture site.

Results

Thirty two eyes of 32 patients underwent the postoperative bleb needle revision with adjunctive 5-FU. Patient demography is shown in Table 1. The mean age ± standard deviation (SD) of the patients was 67. 2±11. 4 years (Range 38–89 years). The blebs undergoing rescue related to 32 trabeculectomies of which 8 were repeat procedures. The trabeculectomy after which the needling procedure was done will henceforth be referred to as the index procedure. Thirty of these index procedures had been augmented with adjunctive antifibrotic therapy. In 6 cases (18. 75%) MMC 0. 02%had been used for 2 minutes while in the rest 24 cases (75%) MMC 0. 04% had been used for 2 minutes. In 2 cases (6. 25%) no antifibrotic agents had been used during the index procedure. Some of the cases had high risk characteristics for bleb failure. 8 cases (25%) were repeat trabeculectomies, 1 case (3. 1%) was a case of uveitic glaucoma, 1 case (3. 1%) was a patient with age <40 years and 2 cases (6. 25%) had multiple risk factors.

Management before the index procedure varied between eyes as expected and is summarized in Table 1. After the index procedure, 26 eyes had been restarted on topical antiglaucoma therapy, and 12 were still receiving some postoperative topical steroid therapy.

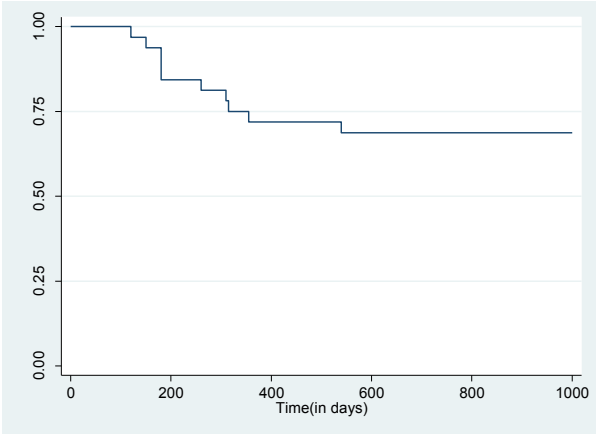
Table 1: Patient demographics and details of Glaucoma variables

	n (%)	Mean	SD
Gender **Male** **Female**			
	17 (53. 125)		
	15(46. 875)		
Age (Years)		67. 2	11. 4
Eyes **Right** **Left**			
	18(56. 25)		
	14(43. 75)		
Diagnosis **POAG** **PACG** **PXF Glaucoma** **Pseudophakic Glaucoma** **Uveitic Glaucoma**			
	14 (43. 75)		
	13 (40. 63)		
	2 (6. 25)		
	2 (6. 25)		
	1 (3. 13)		
Pre operative MD (29/32)		-15. 3	8. 1
Pre operative PSD (29/32)		8. 6	3. 4
Pre needling IOP		28. 2	7. 6
Filtering procedure **First Trabeculectomy** **Repeat Trabeculectomy**			
	24(75)		

	n (%)	Mean	SD
	8(25)		
Previous therapy **Topical** **SLT** **Laser PI** **Iridoplasty**			
	26(81. 25)		
	2 (6. 25)		
	13(40. 63)		
	1 (3. 13)		

The median duration of topical steroid therapy for the 28 eyes after the index procedure and before bleb needling was 3 months (range, 3 month–6 months). The duration of topical antiglaucoma therapy for the 26 treated eyes after the index operation and before bleb needling was 4. 6±1. 2 months. The median interval between the index filtration surgery and the first (or only) needling procedure was 7. 5 months with a range of 3 months to 4 years.

Twenty-one eyes (65. 63%) underwent only a single 5-FU needling revision; 9 eyes (28. 13%) required two revisions and 2 eyes (6. 25%) underwent three revisions with an overall mean of 1. 41 needling revisions with adjunctive 5-FU. At the minimum follow up period of 1 year complete success was noted in 9 cases (28. 13%) and qualified success was seen in 13 cases (40. 63%) thus the total overall success was achieved in 22 cases (68. 75%). In 10 cases (31. 25%) either the IOP was not controlled even with medications or the patient had to undergo a repeat filtering procedure and thus they were considered as failure. The Kaplan–Meier survival analysis success rates were 68. 76% at 1 year and 66. 91% after 3 years of follow-up (Graph 1).



Graph 1: Kaplan Meier Analysis showing the survival rate.

The statistical analysis comparing the number of needling procedures and comparing it to the success rates showed that the cases which underwent a single needling procedure (n=21) had the highest percentage of success with complete success being noted in 8 cases (38. 1%) and qualified success in 9 cases (28. 1%). In cases which underwent 3needling procedures (n=2) none of the cases achieved complete success while qualified success was seen in one case (50%). (Table 2)

Table 2: Table showing the number of needling procedures compared to success rates

Number of needlings	Complete Success	Qualified success	Failiure
1 (n =21)	8	9	4
2 (n = 9)	1	3	5
3 (n = 2)	0	1	1

In 11 cases an IOP of <11 mmHg was achieved immediately post needling. This group noted the highest percentage of success with complete success being seen in 7 cases (63. 64%) and qualified success in 4cases (36. 36%). There were no cases which showed failure in the group which achieved an immediate post needling IOP of <11 mmHg. In the group which achieved an immediate post needling IOP between 14 and 16 mmHg (n = 9) there was a high percentage of failure noted (7 cases, 77. 78%). A low immediate post needling IOP (<11 mm Hg) was associated with a higher success rate (P< 0. 001). (Table 3)

Table 3: Table showing the number of cases with pre needling IOP > 28 mm Hg and those with immediate IOP <11 mm of Hg and the percentage of success and failure in each group.

IOP	n (number)	Complete success (n/%)	Qualified success (n/%)	Failiure (n/%)	P value
Pre needling IOP Pre needling IOP > 28 Pre needling IOP < 28	 14 18	 1 8	 6 7	 7 3	<0. 001
IOP immediate post needling <11 mm Hg 11 – 13 14 - 16	 11 12 9	 7 1 1	 4 8 1	 0 3 7	<0. 001

For all 32 eyes, the overall mean±SD pre-needling IOP was 27. 7±7. 5 mmHg, with a range of 18 to 48mmHg. In the cases which achieved overall success, complete and qualified together (n = 22) the baseline IOP pre needling was 26. 7±8. 2 mmHg which was reduced to 13. 6±4. 6 mmHg at the end of the minimum follow up period of 1 year. When these cases were further followed up this IOP was 13. 4±4. 3 mmHg (n=24) at the end of a follow up of three years and 13. 6±4. 7 mm Hg (n=16) at the end of five years of follow up.

A pre needling IOP of <28 mmHg (n=18) was associated with a higher success rate with complete success seen in 8 cases (44. 44%) and qualified success in 7 cases (38. 89%) whereas cases which had a pre needling IOP of >28mmHg (n = 14) achieved complete success in 1 case (7. 14%) and qualified success in 6 cases (42. 86%)(P<0. 001)(Table 3)

The mean age ±SD of those patients in whom bleb needling was successful was 65. 34±8. 21years (range, 38– 87 years), whereas for the failures the mean age ±SD was 68. 22±7. 44 years (range, 42–89 years)(P=0. 36). As a continuous variable, younger age was not identified as a significant risk factor for failure. There was no significant difference with respect to gender or laterality. (Table 4)

Table 4: Hazard Ratios for Failure of Bleb Needling relating to potential risk factors for failure

Study Factor	Category	Hazard ratio	95% CI
Gender	Male	1	(0. 53 , 1. 56)
	Female	0. 9	
Eye	Right	0. 94	(0. 74, 2. 78)
	Left	1	
Diagnosis	POAG	1	(0. 46, 1. 64)
	Non-POAG	1. 54	
Previous exposure to antimetabolites	Yes	1	(0. 81 , 2. 44)
	No	1. 44	
Pre needling IOP	>28 mm Hg	1. 65	(0. 60 , 2. 71)
	<28 mm Hg	1	
Previous filtering procedures	Single index procedure	1	(0. 44 , 1. 48)
	Repeat Trabeculectomy	1. 36	
Immediate post needling IOP	<11 mm Hg	0. 5	(0. 26 , 0. 92)
	>11 mm Hg	1	

The success rate was greater for eyes with primary open-angle glaucoma (POAG) compared with eyes with other diagnoses, however it did not reach statistical significance (p=0. 173). (Table 5)

Previous exposure to MMC, 0.04% for 2minutes, n=24, during the index procedure was associated with a higher success rate post needling (20/24 cases, 83. 33%)

compared to an MMC concentration of 0. 02% for 2 minutes, n=6 (2/6 cases, 33. 33%) and this was statistically significant (p=0. 005)(Table 5)

Table 5: Showing the diagnosis and the concentration of MMC in relation to success and failure

Parameter	Number (n)	Complete success	Qualified success	Failiure	P value
Diagnosis					
POAG	14	8	4	2	0. 173
PACG	13	1	7	5	
PXF Glaucoma	2	0	1	1	
Psedophakic Glaucoma	2	0	1	1	
Uveitic Glaucoma	1	0	0	1	
Conc of MMC					
0. 04%	24	8	12	4	0. 005
0. 02%	6	1	1	4	
Nil	2	0	0	2	

The use of topical antiglaucoma therapy, or topical steroid, immediately before the needling procedure had no apparent effect on the outcome, and there was little difference between the types of antiglaucoma agent being administered at the time of needling, although exposure to pilocarpine had occurred in more of the failures (14%) compared with successes (8%) and vice versa with topical carbonic anhydrase inhibitors (6% vs. 16%).

The interval between the index operation and bleb needling had no significant effect on the outcome but the mean cumulative duration of antiglaucoma therapy administered between the index procedure and bleb needling was more for the failed cases (3. 2 ±1. 1 months) in comparison with successes (2. 8±0. 8 months), but not to a degree to reach statistical significance (P=0. 23)

The blebs which were characterized as being flat (n =8) at the time of the needling procedure had the highest failure rate at 62. 5%. Blebs which were characterized as encapsulated (n=6) and those which were fibrotic and cystic in part (n=6) had a much lower failure rate at 16. 67% each (Table 6).

Table 6: Outcome in relation to the type of bleb

		Complete success	Qualified success	Failure	P value
Flat blebs	8	2(25%)	1(12. 5%)	5(62. 5%)	0. 363
Low diffuse blebs with high vascularity	7	1(14. 26%)	4(57. 14%)	2(28. 57%)	
Cystic+Fibrotic	6	2(33. 33%)	3(50%)	1(16. 67%)	
Cystic+Thick Conjunctiva Tenons complex	5	1(20%)	3(60%)	1(20%)	
Encapsulated	6	3(50%)	2(33. 33%)	1(16. 67%)	

No serious complications were encountered with the procedure. However, transient complications were encountered in 5 eyes. Two eyes had corneal epithelial defects post procedure (6. 25%), 2 eyes (6. 25%) had hyphaema and one eye (3. 13%) had bleb leak post needling. None of the complications that occurred in eyes that had an unsuccessful needling procedure were considered to have been directly causative of the failure and all the cases were managed conservatively. In most cases, there was no significant change in visual acuity after bleb needling. Visual acuity decreased by 2 or more Snellen lines in 4 patients, but increased by 2 or more lines in 3 patients.

Discussion

Failure of filtration surgery may be managed in a number of ways, but if a revision or repeat surgical treatment is chosen, the clinician has to accept a technically more difficult procedure with an increased risk of failure.

Since 1941, many authors have described bleb-needling procedures and although a variety of methods have been described, the principle remains the same, which is to disrupt subconjunctival and scleral scar tissue and to restore bleb function.[20,21,22,23]

Needles used have ranged from 25 gauge, 28 gauge or Saunder's needle to 30gauge. Other, more complicated, methods described have involved the use of a 30-gauge needle with a small needle knife or a Zeigler knife with Vannas scissors.[21,23,24,25,26] The latter method required conjunctival suturing, but probably allowed more extensive disruption of the fibrous tissue. Some authors have advocated the additional use of subconjunctival 5-FU or MMC.[23,24,25,27]

Reported success rates for bleb needling procedures have been variable. Cohen *et al.* reported success (IOP< 22 mmHg) in 9 of 15 cases (60%) with or without additional therapy (complete and qualified success) at 1 year follow up.[20] A slightly

higher success rate, using similar criteria (9/13; 69%), was reported by Pederson and Smith, with 3 patients requiring 2 needlings. However, of their 13 cases, only 3 (23%) achieved complete success (IOP<22 mmHg, no antiglaucoma therapy, and no bleb dysesthesia).[22] Ewing and Stamper reported success in 11 of 12 patients (91. 6%; complete in 58. 3% and qualified success in 33. 3%), 7 of whom had undergone multiple post needling inferior subconjunctival 5-FU injections.[23] The authors had a clinical impression that the use of 5-FU was advantageous, but some of the patients had a follow-up of only 2 months. The range of follow up in the study by Ewing and Stamper was from 2 months to 31 months with a mean follow up of 9 months. Gilles and Brooks reported success in 12 of 16 patients (75%), who were administered additional 5-FU injections with follow up ranging between 9 and 15 months, but their criteria for success were not specified.[24] Hodge *et al.* reported success (IOP <21 mmHg) in 16 of 17 patients (94%; complete in 47% and qualified in 47%) using a technique involving an intrableb injection of 5-FU at 1 year follow up.[25] In their series, 12 patients underwent between 2 and 4 needling procedures each. Of the 5 patients in whom a single procedure was performed, complete success was achieved in only 2 patients.

In a study done by Shin *et al.* 24 of 30 procedures (80%) augmented with intrableb 5-FU were reported as complete or qualified successes (the latter patients being on less medication than before the needling) after a mean number of 2. 6 needlings at 1 year of follow up.[26] In the study by Shin *et al.* the success rate for a single needling procedure was considerably lower (9/30; 30%) and the authors emphasized the importance of considering bleb rescue as a potential course of needlings, rather than a one-off procedure. Allen *et al.* reported a 100% success rate in achieving an IOP <22 mmHg after a mean number of 2 needlings of encapsulated blebs after a mean interval ±SD between surgery and needling of 9. 7 ±26. 9 weeks and a follow-up period of 10. 7± 2. 9 months.[28]

In our study, however, we noted that the results were better in the group which underwent a single needling procedure. Our results are similar to those of Greenfield *et al.* who reported that success was more likely after 1 needling procedure rather than multiple procedures. They reported a successful outcome in 46 (73%) of 63 eyes at a minimum follow-up of 3 months after needling revisions of failing filtration blebs following trabeculectomy with MMC.

Our overall cross sectional success rate (complete and qualified) was 68. 76%(n=32) at 1 year, 66. 91%(n=24) at 3 year and 65. 82%(n=16) at 5 year follow up. The success rates of previous studies have been variable and range from 52% to 95%.[22, 23, 24, 25,26,27,28,29] Our results are comparable to a lot of the mentioned studies and the percentage of success over a long term follow up shows that single or multiple needlings can be used to save a lot of failed or failing blebs.

One of the reasons for the results being so variable could be that the various studies have taken different types of blebs for manipulation and thus since the types of blebs needled are different the results vary greatly between the studies. The study done by Allen *et al.* included only those blebs with Tenon's capsule cysts and not those with other morphologic appearances.[28] Another reason could be that

even though studies show that 5-FU needling revision is an effective and safe way of restoring patency to previously fibrosed passageways of aqueous flow within failed or failing filtration blebs, it may need to be repeated more than once and it may not be successful in some patients even with repeated needling revisions.[26] Thus some patients may not respond even to multiple needling procedures because there may be other factors responsible for failure and unless those are addressed the needling will not be successful. Therefore, it is important to identify the risk factors for failure of the initial trabeculectomy and the subsequent 5-FU needling revision procedure.

The comparison of success rates between studies are not always meaningful, considering the fact that the techniques used for needling are different, the bleb morphologies are different and the studies are being done in different ethnic groups. Since the different techniques applied in the various studies poses a problem when it comes to comparison between studies, we used a standard technique in our study but it may not be comparable to a few studies who have used slightly different techniques.

As mentioned previously the morphology of the blebs undergoing needling are different in different studies and thus since the types of blebs needled are different the results vary greatly between the studies. Most previous studies have related to Tenon's cysts or encapsulated blebs alone.[22,25] In the study by Gilles *et al,* half of the needled blebs were encapsulated.[24] Very few studies have considered other specific types of blebs. The studies by Ewing *et al.* and Shin *et al.* considered nonencapsulated failed blebs and the study by Cohen at al included blebs which were flat, small, or thick-walled.[20,23,26]

In our study we included various types of blebs like flat blebs, low diffuse blebs with high vascularity, small cystic blebs with fibrotic regions, encapsulated blebs and partly cystic blebs with thick conjunctiva-tenons complex. It has generally been accepted that encapsulated blebs respond to needling better than flat, scarred blebs. High success rates for surgical revision of encapsulated blebs have been reported, but it has been proposed that the results for scarred-down blebs is poor, even when the procedure is augmented with antimetabolites. Hawkins *et al.* classified blebs using 5 characteristics (encapsulation, thickness, vascularity, elevation, and microcysts), but reported that these had no effect on outcome.[30] Our study results showed that needling was least successful with blebs which were flat and the best post needling results were achieved for encapsulated blebs but this did not reach statistical significance.

Many authors have advocated initial massage or laser suture lysis in nonencapsulated, failed blebs, and others have suggested initial medical therapy or massage before needling, particularly with encapsulated blebs.[20,22,25] The Advanced Glaucoma Intervention Study results reported that digital massage and topical steroid therapy (without needle revision) led to similar outcomes with respect to IOP for encapsulated blebs compared with nonencapsulated blebs, albeit on additional medical therapy.[32] However massage and suture removal or lysis, although useful in the early postoperative period, usually becomes less effective with increasing time after surgery.

In our study the success rates were greater for the POAG patients, with a complete success 57. 14% and qualified success 28. 57% thus having an overall success rate of 85. 71% compared with eyes with other diagnoses which together had a complete success rate of 5. 56% and a qualified success rate of 50% thus having an overall success rate of 55. 56%. This is similar to the study done by Broadway *et al.* where the success rate was greater for eyes with primary open-angle glaucoma compared with eyes with other diagnoses (49% vs. 37%).[33]

In our study we found that the overall success rates were greater for the eyes where a higher concentration of MMC (0. 04%) was used during the index procedure , 83. 33%, compared to a lower concentration of MMC (0. 02%) which achieved an overall success rate of 33. 33%. There were two cases where no anti fibrotic agent had been used during the index procedure and both of them went into failure after the needling procedure. This is in contrast to the study done by Broadway *et al.* where the authors noted that previous exposure to 5-FU, MMC, or β-irradiation was associated with a lower success rate (54% vs. 39%).[33] The authors explained that this perhaps reflected only the fact that such antifibrotic agents had been used in eyes that may have been considered to be at a greater risk of failure of their index procedure. However our results are similar to the study done by Shin *et al.* where the authors found that the use of MMC during the original glaucoma filtration surgery seemed to be a beneficial factor in the future success of 5-FU needling revision.[34] They found that only 20% (7 of 35 cases) of the initial 5-FU needling revisions were successful in the group that had not received MMC during the filtration surgery. In contrast, 51% (15 of 29 cases) were successful in those who had received MMC during the previous filtration surgery. The authors stated that this significant difference seemed to support the findings that the effects of MMC on local fibroblasts may be long lasting, if not irreversible.[35]

A further factor of potential importance is the interval between initial surgery and needling. In some reports, some blebs have been needled as early as 3 days after surgery.[20,26] In another study, the needlings were performed within a 6-week postoperative period, whereas in others, the interval was a number of years in a proportion of the cases.[20,22,23,24] A short interval between the initial surgery and needling has been associated with success, although, in 1 report, an interval of more than 1 month was found to be advantageous.[21,24] In the present study, massage and suture removal were tried before needling, but a period of intensive medical therapy was not attempted as we felt that the time delay would reduce the chances of success post needling. In the present study, the interval between initial surgery and needling seemed to make no difference to the outcome. Our results are similar to the studies done by Cohen *et al.*, Ewing *et al.* and Greenfield *et al.* in which the authors also could not find any correlation between the time interval of needling and the outcome.[20,23,29]

Other factors identified to be associated with needling failure have included young age, aphakia or pseudophakia, fornix-based conjunctival flap trabeculectomy, previous surgery involving a conjunctival incision, lack of MMC use during the previous filtration surgery, long-term previous exposure to topical

sympathomimetics, and higher preneedling IOP. In the present study, however, none of these risk factors were identified as having a statistically significant effect on outcome. It would seem, therefore, from the results of the present study, that bleb needling is worth attempting in any eye with apparent bleb failure associated with inadequate IOP control, if not otherwise contraindicated. Thus we recommend attempting at least one needling procedure for these patients.

The most significant factor identified in the present study to have an effect on success was the immediate attainment of a low IOP of <11 mm Hg, a finding that was also reported by Shin *et al.*[26] Thus attaining a low IOP of <11 mm Hg immediately after needling seems increase the chance of success and in this study 7/11(63. 63%) cases achieved complete success, 4/11(36. 36%) cases achieved qualified success and there were no failures at the 1 year follow up period. Although none of the other proposed factors that may have affected outcome were identified as having a statistically significant effect, this may have been the result of low statistical power for some of the proposed factors; a larger study would be required to identify such factors.

Very few serious complications have been reported after bleb needling. Some studies which have mentioned some serious complications include significant hypotony, malignant glaucoma, suprachoroidal haemorrhage and a case of endophthalmitis has also been reported.[29,32,36] Most of the reported complications are usually minor and include temporary conjunctival wound leaks, small hyphaemas, transient shallowing of the anterior chamber and corneal epithelial 5-FU toxicity.[22,23,25,26] The incidence of minor complications has been reported to lie between 20% and 38%.[25,26]

The complications encountered in the present study were corneal epithelial defects, hyphaema and a case of bleb leak. The overall percentage of complications was 15. 63% which is lower than the quoted studies but the potential for complications should never be underestimated.

This present study identified three independent risk factors for failure of the initial 5-FU needling revisions: preneedling IOP >28 mmHg, lack of MMC use during previous filtration surgery, and immediate post-needling IOP >11 mmHg. In patients with one or more of these three risk factors, it is especially important to monitor IOP closely following the initial needling revision. They are more likely to require additional therapeutic intervention, including repeat needling revision.

Thus bleb needling should be considered in the management of failing or failed filtration blebs. Bleb needling has a number of advantages compared to repeat surgery. The procedure is simple and repeatable, and has the potential to be equally effective as initial filtration surgery. The method is safe, is performed at the original site, carries no additional theoretical complications over trabeculectomy, and does not preclude resorting to other methods for IOP control if it fails.

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