

Bleb needling outcomes for failed trabeculectomy blebs in Asian eyes: a 2-year follow up

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Abstract

• **AIM:** To describe the outcomes of bleb needling in primary glaucoma in an Asian tertiary eye centre over a 2y period. To compare the success rates between primary angle-closure glaucoma (PACG) and primary open angle glaucoma (POAG). Lastly, to identify factors associated with success of bleb needling.

• **METHODS:** This was a retrospective review of 227 patients who underwent bleb needling between June 2009 and June 2011 in Singapore National Eye Centre. The 5-fluorouracil (5-FU) augmented bleb needling was performed either at the slit lamp or in the operating theatre. Repeat bleb needlings were performed as necessary. Complete success was defined as maintenance of intraocular pressure (IOP) ≥ 6 mm Hg and ≤ 21 mm Hg, in the absence of further surgery or use of antiglaucoma medication. Qualified success met the above criteria with or without use of antiglaucoma medications.

• **RESULTS:** One hundred and seventy-five eyes completed the two-year follow up. Sixty-nine percent of participants had POAG and 31% had PACG. The mean interval between filtering surgery and bleb needling was 299.9 ± 616.4 d for POAG and 167.1 ± 272.2 d for PACG. Mean needling attempts were 1.9 ± 1.4 and 2 ± 1.6 for POAG and PACG respectively. In general, there was a statistically significant reduction of IOP ranging from 21.9% to 26.8% from month 1 through to month 24. The complete success rates at month 6 were 70.0% for POAG and 65.7% for PACG. At month 12, this decreased to 62.2% for POAG and PACG and at month 24, 57.9% for POAG and 63.0% for PACG respectively. The qualified success rates at month 6 for POAG and PACG were 23.8% and 29.9% respectively, 32.2% and 29.2% at month 12, and 34.7% and 29.6% at month 24. The success rates

between POAG and PACG were not significantly different ($P > 0.05$ for complete and qualified success at months 6, 12 and 24). An increased number of needlings and higher pre-needling IOP were associated with failure.

• **CONCLUSION:** The 5-FU augmented bleb needling within one year of trabeculectomy in Asian eyes can provide clinically significant IOP lowering of more than 20% for 2y. POAG and PACG had similar complete success rates (58% and 63% respectively). Factors associated with greater risk of procedure failure included increased number of needlings and higher pre-needling IOP. Asian eyes have a greater propensity for scarring but bleb needling, if performed in a timely manner can rescue bleb function.

• **KEYWORDS:** 5-fluorouracil bleb needling; trabeculectomy; Asian eyes

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INTRODUCTION

Trabeculectomy remains the mainstay of treatment in medically uncontrolled glaucoma. The use of anti-metabolites to inhibit wound healing has improved the success rates of trabeculectomy^[1].

However, failure of the trabeculectomy bleb can occur due to fibrotic proliferation as part of the wound healing response. Surgical failure is reported more frequently in Asian and Afrocaribbean eyes compared to Caucasian eyes, where the fibrotic responses from the former may be exuberant^[2,3]. The 5-fluorouracil (5-FU) augmented bleb needling, first described in 1990, is a relatively simple method which can rescue failing blebs^[4]. It specifically targets the episcleral and intrascleral fibrosis which occurs in late failing blebs. The procedure can be performed in an office setting at the slit lamp or in the operating theatre. There are varying surgical techniques but the aim of the procedure is to re-open and maintain the filtering site and to free the scar tissue that is adherent between the conjunctiva and sclera^[5]. Bleb needling has been reported to be successfully performed up to 30y after trabeculectomy^[6]. Various studies have reported bleb needling in failed trabeculectomy with success rates ranging

from 33% to more than 90%^[4,7-9]. However, the heterogenous nature of these studies precludes meaningful comparison. The aim of this study is to describe the outcomes of bleb needling in an Asian tertiary eye centre over a 2y period, and to compare the success rates between primary angle closure glaucoma (PACG) and primary open angle glaucoma (POAG). Factors that indicate better outcomes following the needling procedure will also be identified.

SUBJECTS AND METHODS

This was a retrospective case note review of 227 consecutive patients who underwent 5-FU augmented bleb needling between June 2009 and June 2011 at the Singapore National Eye Centre. The study had the approval of the local Institutional Review Board for waiver of consent and adhered to the tenets of the Declaration of Helsinki. The patients had previously undergone either trabeculectomy with mitomycin C (MMC) or combined phacotrabeculectomy with MMC. Demographic information obtained included age, gender, race, co-morbidities, glaucoma diagnoses, visual acuity, number of needlings and intraocular pressure (IOP). At various time points (months 1, 3, 6, 12 and 24 post needling), IOP, any repeat needlings, restarting of IOP medications and any further surgical intervention were recorded.

Exclusion criteria include age < 21y, patients who were pregnant or breast-feeding, patients who were unable to give informed consent and those who had subconjunctival injection of 5-FU without bleb needling.

The 5-FU augmented bleb needling was performed either at the slit lamp or in the operating theatre under aseptic technique. The patient's eyelid and periorbital skin were cleaned with 10% providone iodine followed by instillation of tetracaine eye drops and a drop of 5% providone iodine. Needling of the bleb was performed using a 27-gauge needle. The aim was to perform sweeping motions to cut episcleral scarring and to release scarring that was obstructing the intrascleral pathway. This was followed by an injection of 0.1 mL of 5-FU solution (50 mg/mL) along the far posterior margins of the bleb area. Topical 1% prednisolone acetate eye drops and 0.5% levofloxacin every 3h were prescribed postoperatively. At subsequent follow up, repeat bleb needlings were performed as necessary. Only right eye data were used.

IOP was measured using Goldmann applanation tonometry. Complete success was defined as maintenance of IOP \geq 6 mm Hg and \leq 21 mm Hg, in absence of further surgery or use of antiglaucoma medication. Qualified success refers to meeting the above criteria with or without use of antiglaucoma medications. The need for repeat trabeculectomy or glaucoma drainage device would constitute surgical failure.

Statistical Analysis Basic statistical analyses were performed using IBM SPSS statistic version 19.0 (IBM corp,

Armonk, NY, USA). Mean with standard deviation (SD) were calculated for continuous variables and frequency with percentage were tabulated for categorical variables. Student's *t*-test was used for continuous variables and χ^2 test or Fisher's exact test for categorical variables. Logistic regression was used to compare the success rates between POAG and PACG at each time point.

Kaplan-Meier survival analysis comparisons of the two glaucoma groups was conducted for the repeated failure events based on failure rates at 6, 12 and 24mo, and Cox regression analysis was performed to calculate the hazard ratios of possible factors that may lead to bleb failure using Stata version 11.1. All reported *P* values were compared at a significance level of 0.05.

RESULTS

One hundred and seventy-five eyes completed the two year follow up. Sixty-nine percent of participants had POAG and 31% had PACG. The mean interval between filtering surgery and bleb needling was 299.9 \pm 616.4d for POAG and 167.1 \pm 272.2d for PACG. Mean number of needling procedures were 1.9 \pm 1.4 and 2.0 \pm 1.6 for POAG and PACG respectively.

The baseline characteristics of the study patients are summarized in Table 1. The POAG group had a male preponderance and more hypertensives compared to the PACG group. There was no statistically significant difference in number of medications pre-needling, pre-needling IOP and total number of needlings between the 2 groups.

Table 2 depicts the visual acuity, mean IOP, IOP reduction from baseline and the percentage of patients who required IOP lowering medications and repeat needlings at the various time points. The mean IOP pre-needling was 20.7 \pm 7.4 mm Hg and there was a statistically significant reduction of IOP ranging from 21.9% to 26.8% from month 1 through to month 24. Of note, the mean visual acuity was maintained at least 0.5 (Snellen decimal) at all times. The percentage of patients requiring additional IOP lowering medications increased from 10.7% at month 1 to 38.3% at month 24. The highest percentage of patients requiring repeat needlings was at months 1 and 3 and this decreased from month 6 through to month 24. Figure 1 depicts the reduction in IOP over time.

The complete, qualified and total success rates between POAG and PACG at months 6, 12 and 24 were compared (Table 3). The complete success rates at month 6 were 70.0% for POAG and 65.7% for PACG. At month 12, this decreased to 62.2% for POAG and 61.5% for PACG and at month 24, 57.9% for POAG and 63.0% for PACG respectively. The qualified success rates at month 6 for POAG and PACG were 23.8% and 29.9% respectively, 32.2% and 29.2% at month 12, and 34.7% and 29.6% at month 24. The success rates between POAG and PACG were not statistically significant at all time points. Table 4 shows the logistic regression analysis for success rate at each time point.

Bleb needling outcomes in Asian eyes

Table 1 Demographics

Parameters	POAG (n=157)	PACG (n=70)	P
Age (SD)	66.9 (10.8)	66.8 (12.2)	0.925
Gender (M; F) (%)	106 (67.5); 51 (32.5)	32 (45.7); 38 (54.3)	0.002
Chinese (%)	113 (72)	57 (81.4)	0.129
Other races (%)	44 (28)	13 (18.6)	
Diabetes mellitus	63 (40.1)	24 (34.3)	0.403
Hypertension	83 (52.9)	28 (40)	0.010
Hyperlipidemia	24 (15.3)	13 (18.6)	0.536
Ischemic heart disease	19 (12.1)	5 (7.1)	0.262
Asthma	5 (3.2)	6 (8.6)	0.098
Time interval to needling (d)	299 (616)	167 (272)	0.025
No. of pre-needling eyedrops	0.3 (0.72)	0.16 (0.53)	0.098
IOP pre-needling (mm Hg)	21.1 (7.5)	19.9 (7.2)	0.240
Total No. of bleb needlings	1.9 (1.4)	2.0 (1.6)	0.686

χ^2 & Fisher's exact test for categorical groups and independent *t* test for age.

Table 2 IOP before and after needling at different time points

Parameters	No. of eyes	Visual acuity mean (SD) Snellen decimal	IOP mean (SD, range)	^a <i>P</i>	IOP reduction (%) from preneedling baseline	% requiring IOP lowering medications	% requiring repeat needling
Pre-needling	227	0.58 (0.3)	20.7 (7.4)				
Post needling							
Month 1	223	0.56 (0.3)	14.2 (5.8)	<0.001	26.8 (31.3)	10.7	21.0
Month 3	218	0.61 (0.3)	15.2 (5.7)	<0.001	21.9 (30.9)	17.9	23.9
Month 6	214	0.63 (0.3)	14.7 (4.9)	<0.001	22.8 (31.0)	29.0	17.3
Month 12	208	0.63 (0.3)	14.5 (4.8)	<0.001	23.2 (32.5)	35.1	10.1
Month 24	175	0.62 (0.3)	13.9 (4.4)	<0.001	25.1 (37.3)	38.3	8.6

^aAdjusted *P* values comparing preneedling IOP and postneedling at each time point (Bonferonni). Paired *t* test for baseline comparisons with IOP each time point (Bonferonni adjusted *P* values for the multiple comparisons).

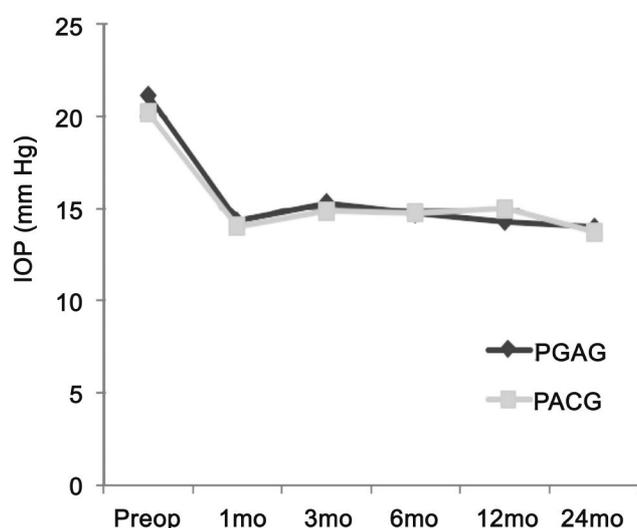


Figure 1 IOP reduction over time for POAG and PACG
Preop: Pre-needling.

The total number of needlings showed a significant odds ratio (OR) of 0.599 (95%CI 0.451-0.795; $P<0.001$) at 12mo and OR of 0.684 (95%CI 0.500-0.936) at month 24 ($P=0.018$), after adjusting for age, gender, race, time interval to bleb needling, number of pre-needling eyedrops and IOP pre-needling. This showed that increasing number of needlings was negatively associated with bleb success.

Furthermore, Cox regression analysis on bleb failure rates showed statistically significant hazard ratios of 1.03 (95%CI 1.01-1.06; $P=0.025$) for pre-needling IOP and 1.35 (95%CI 1.19-1.54; $P<0.001$) for total number of bleb needlings (Table 5).

The repeated event failure Kaplan Meier survival analysis was used to compare the two glaucoma groups and found that POAG had a cumulative probability survival of 94% (95%CI 89.3-96.9) at 6mo, 89.5% (95%CI 83.6-93.3) at 12mo, and 84.3% (95% CI 84.3-89.1) at 24mo. In the PACG group the cumulative probability survival was 95.7% (95% CI 87.3-98.6) at 6mo, 87.5% (95%CI 77.4-93.3) at 12mo, and 82.5% (95% CI 71.8-89.4) at 24 mo. The restricted estimated mean survival for POAG was 22.39mo (95%CI 21.7-23.1) and PACG was 22.2mo (95% CI 21.1-23.3). Log rank test among the two glaucoma groups for survival over 24mo did not show statistical significance ($P=0.729$, Figure 2).

DISCUSSION

In this study, we reported the bleb needling outcomes in Asian eyes, and compared the success rates of bleb needling between POAG and PACG. We also reported on factors associated with greater bleb failure. We found that the total success rates were generally high for POAG and PACG, and there was no statistical significance between the two types of glaucoma. Survival analysis over the two year period also

Table 3 Comparison of success rates between different glaucomas %

Months	POAG				PACG				P
	Complete success rate	Qualified success rate	Success rate	Fail	Complete success rate	Qualified success rate	Success rate	Fail	
6	70.0	23.8	93.9	6.1	65.7	29.9	95.5	4.5	0.757
12	62.2	32.2	94.4	5.6	61.5	29.2	90.8	9.2	0.375
24	57.9	34.7	92.6	7.4	63.0	29.6	92.6	7.4	1.0

χ^2 & Fisher's exact test for comparing success rate by diagnosis at each time point.

Table 4 Multivariate logistic regression analyses for success rate at each time point

Parameters	Month 6			Month 12			Month 24		
	P	OR	95%CI for (OR)	P	OR	95%CI for (OR)	P	OR	95%CI for (OR)
Time interval to bleb needling	0.593	1.001	(0.998, 1.003)	0.388	1.000	(0.999, 1.00)	0.407	0.999	(0.998, 1.001)
No. of pre-needling eyedrops	0.604	1.592	(0.275, 9.218)	0.456	0.689	(0.259, 1.835)	0.404	2.215	(0.343, 14.31)
IOP pre-needling	0.306	0.961	(0.891, 1.037)	0.313	0.964	(0.898, 1.035)	0.483	0.972	(0.896, 1.053)
Total No. of needlings	0.317	0.836	(0.588, 1.188)	<0.001	0.599	(0.451, 0.795)	0.018	0.684	(0.500, 0.936)

OR: Odds ratio.

Table 5 Cox regression analysis of long term survival

Parameters	HR	Lower HR 95%CI	Upper HR 95%CI	P
Pre needling IOP	1.03	1.01	1.06	0.025
Total No. of needlings	1.35	1.19	1.54	<0.001

HR: Hazard ratio. HR adjusted for diagnosis (PACG/POAG).

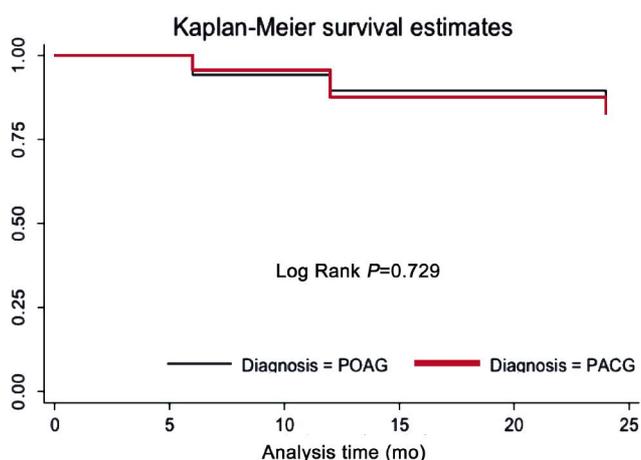


Figure 2 Kaplan Meier survival plot of POAG and PACG.

showed comparable rates between POAG and PACG. This report is the largest cohort of 5-FU augmented bleb needlings performed in Asian eyes to date.

Bleb failure is most commonly caused by scarring. Early rise in IOP after surgery is usually managed by ocular massage or release of scleral flap sutures. Once fibrosis occurs, options include restarting topical IOP lowering medications, laser trabeculoplasty, repeat trabeculectomy, glaucoma drainage device or bleb needling^[10]. Bleb needling is a relatively safe procedure. Complications are mostly minor and consist of conjunctival wound leak, transient shallowing of the anterior chamber, small hyphemas and corneal epithelial toxicity^[11]. Vision threatening complications such as significant hypotony, suprachoroidal hemorrhage, malignant glaucoma and endophthalmitis can occur but are rare^[11].

Variable success rates have been reported in the literature. It is difficult to make comparisons across studies due to different study lengths, sample size, definition of success and antimetabolites used. Ewing and Stamper first reported 91.7% overall success (target IOP achieved with or without use of topical medications) in a small sample of 12 cases using 5-FU augmented bleb needling^[4]. The mean follow up was 9mo. Greenfield *et al*^[7] analysed 441 eyes that had bleb needling without antimetabolites and reported 73% overall success at 3mo. A retrospective study by Shin *et al*^[9] used 5-FU as an antimetabolite in 64 eyes; they reported an overall success of 33% at 2y. In this study, the reported low success rate is probably because this study population consisted primarily of African Americans, who have been shown to have a greater tendency for poorer pressure control following surgery^[11]. Rotchford and King^[8] performed survival analysis of 81 blebs after 5-FU needling. In this prospective cohort study, there was a preponderance of nonpigmented races (86.4%). They reported survival rates of 64.2%, 54.3% and 45.7% at 6, 12 and 24mo respectively. In their study, they calculated survival rate based on a definition of total success (complete and qualified) which was similar to ours.

It is important to note that bleb needling without adjunct antimetabolites has been shown to be associated with a higher chance of failure. In a study by Costa *et al*^[12], the authors found that needling resulted in a higher chance of failure compared to medical treatment in encapsulated blebs. The authors opined that the needling might have induced a strong fibroblastic proliferation which scars the openings of the capsule wall, hindering the development of a functioning bleb, especially when 5-FU or MMC were not used. In another study by Ewing and Stamper^[4], approximately half of their patients received transconjunctival needling with 5-FU. Although they did not find any difference in outcomes between the two groups, the authors commented that patients

who received 5-FU were those who were pre-determined to be at higher risk of surgical failure to start with.

There is currently no consensus regarding the choice of antimetabolite. When MMC was used to augment bleb needling, the overall success rates ranged from 59% to 92%^[13-16]. Palejwala *et al*^[17] performed a direct comparison of bleb needling with 5-FU and MMC and found no difference, whilst another found that 5-FU bleb needlings were associated with a higher rate of repeat needlings^[18]. MMC is known to have a greater potency, lower risk of bleb encapsulation and better IOP control^[13]. However, its use has to be balanced with the associated higher rate of complications such as bleb leaks, blebitis, and endophthalmitis compared with 5-FU^[19].

In our centre, we routinely augment our bleb needling with 5-FU. We report more than 90% success rate in two years in primary glaucoma. This is despite a higher propensity of scarring in Asian eyes^[2]. Our study also reported a consistent reduction in IOP of more than 20% over a 2y period. This is achievable with reinstating topical medications and performing repeat needlings in a timely manner, which is usually early within the first 4mo when post op inflammation is most active. This reflects a pragmatic effort to rescue bleb function at the earliest possible time to ensure long term bleb survival as much as possible.

The mean interval between trabeculectomy and first needling also varies among different studies. Bleb needling has been reportedly successful up to 30y after filtration surgery^[6]. Shin *et al*^[9] reported a mean interval of 13.6mo in a group of black subjects. In another study from United Kingdom, the mean interval was 63mo. In another group of White patients, the mean time from filtering surgery to first needling was 141wk^[20]. Broadway *et al*^[11] reported only a 3.1mo mean interval. In contrast, our study reported a mean interval of 8mo. Despite augmenting our trabeculectomy surgeries with MMC, the tendency for scarring in Asian eyes could account for the short interval between filtration surgery and first bleb needling. However, other studies have shown that mean interval does not seem to be a factor in eventual failure of 5-FU bleb revision. Shin *et al*^[9] found that risk factors for failure include pre-needling IOP>30 mm Hg, the lack of MMC use in trabeculectomy, and an immediate post needling IOP of >10 mm Hg.

In our study, we found that increased number of needlings was associated with failure. This is similar to a previous study by Wong *et al*^[21] which also studied Asian eyes. Asian eyes are prone to scarring, and bleb needling is performed when there are early signs of scarring. It is not surprising that an increased number of needlings suggests that these eyes have a greater propensity to scar. Moreover, an invasive procedure such as bleb needling can in itself induce

inflammation and fibroblastic proliferation, with further needlings exacerbating this scarring process. We also found that a higher pre-needling IOP is associated with failure, which is in agreement with Shin *et al*^[9].

We have demonstrated that bleb needling is a useful adjunct as subconjunctival scarring occurs. In accordance with our findings, bleb needling is a useful method to rescue failing blebs to delay repeat filtration surgery or the need for implanting glaucoma drainage devices.

Our study has some limitations. It is a retrospective study with no control group. Moreover, the bleb needling was performed by different surgeons. However, we believe that this reflects current clinical practice and the realistic setting allows for generalization of our outcome. Finally, 52 patients did not complete the follow-up and that might introduce bias. Finally, our study did not compare the bleb needling success for subjects who underwent trabeculectomy alone versus phacotrabeculectomy. Although no difference between these groups were found in a previous study, further research is required to clarify this^[9].

In conclusion, 5-FU augmented bleb needling is a useful adjunct for managing failing trabeculectomies in Asian eyes with primary glaucoma. We provided evidence that increased number of needlings and higher pre-needling IOP were associated with bleb failure. Asian eyes have a greater propensity for scarring, but bleb needling if performed in a timely manner can rescue bleb function.

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