Bleb needling revision with 5-fluorouracil in filtering blebs with chronic failure for over 6 months post-trabeculectomy: a 12-month prospective study

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Purpose: To evaluate the results of bleb needling revision with adjunctive 5-fluorouracil (5-FU) in chronic filtering bleb failure over 6 months post-trabeculectomy.

Method: A prospective study of failed trabeculectomies in a glaucoma clinic between November 2017 and April 2019 were treated with bleb needling revision with 5-FU injection by the same glaucoma specialist and technique. A 27 gauge needle was used to achieve multiple punctures of subconjunctival fibrosis or encystment to attempted elevation of the scleral flap. In all cases, 0.1 ml of 50 mg/ml of 5-FU was then injected subconjunctivally superior to the re-formed bleb, and topical prednisolone acetate and moxifloxacin were prescribed. Success was defined as target IOP achieved and maintained less than 21 mmHg without anti-glaucoma medication at 12 months after first needling. Patients were followed up and re-needled as required.

Results: Needling was attempted on 51 eyes (30 eyes of POAG, 18 eyes of PACG and 3 eyes of secondary glaucoma). The mean number of needling procedures was 1.88 (range 1-10). Needling was successful in 41 (80.4 %) eyes. The average pre-needling IOP was 24.8 ± 12.6 mmHg and the average post needling IOP was 13.5 ± 7.4 mmHg ($P < 0.001$) at 12 months after first needling. The mean number of medications pre-needling was 2.6 ± 1.4 and post-needing was 0.3 ± 0.5 ($P < 0.001$). The mean time post trabeculectomy was 68 months (range 6- 120 months). Prognostic factors for failure of needling revision was pre- needling IOP > 25 mmHg (HR = 3.1, $P = 0.0003$), needling revision ≥ 3 times (HR = 2.6, $P = 0.0012$) and history of repeated filtration surgery before performed this procedure (HR = 1.8, $P = 0.011$). Ten eyes (19.6 %) did not respond to needling; 6 eyes of POAG, 3 eyes of PACG and and 1 eye of secondary glaucoma which required revised trabeculectomy, glaucoma drainage device implantation and anti-glaucoma medication. Three eyes had complications; 2 hyphema and 1 hypotony and no other procedures were required.

Conclusion: Late bleb needling revision with 5-FU injection is still an effective and lasting treatment for the majority of failed trabeculectomy and avoid further surgery included Thai patients. More than one needling is frequently necessary to achieve target IOP. The procedure is relatively safe, with a short operating time and is minimally invasive with less complications.

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Key Words: 5-fluorouracil, needling revision, trabeculectomy bleb

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Introduction

The reduction of intraocular pressure (IOP) is aimed at treatment to delay or stop glaucoma progression. Trabeculectomy remains the mainstay of treatment in

medically uncontrolled glaucoma. The use of antifibrotic agents to inhibit wound healing has improved the success rates of trabeculectomy. Despite the advent of antifibrotics, there are significant early and late complications including late failures.[2] Failure of trabeculectomy blebs 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.[3,4] Proper postoperative management is essential for success during the follow up period.[5] Patients with early postoperative failing blebs typically need maneuvers such as digital massage and release of sutures to maintain adequate pressure control. The 5-fluorouracil (5-FU) when given as repeated subconjunctival injection was shown to improved surgical success in patients with high-risk characteristics when given in the early postoperative period.[6] Patients whose bleb fail later usually restart anti-glaucoma medications in an attempt to keep their intraocular pressure (IOP) under control, otherwise a second surgical procedure becomes necessary such as repeat/revise trabeculectomy, the placement of glaucoma drainage device implant or cyclodestructive procedures.[7]

The 5-fluorouracil (5-FU) augmented bleb needling, first described in 1990, is a relatively simple method which can rescue failing blebs.[8] 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, most are aimed toward re-opening and maintaining the filtering site and to free scar tissue that is adherent between the conjunctiva and sclera.[9] Bleb needling has been reported to be successfully performed up to 30 years after Trabeculectomy.[10] Some studies have reported results of bleb needling revision in late failed trabeculectomy, however, there is still no data for Thai patients.[3,11] In this prospective study we aim to evaluate the results of bleb needling with adjunctive 5-fluorouracil (5-FU) in chronic filtering bleb failure 6 months post trabeculectomy. Results at 1 year, as well as risk factors of needle revision failure in Thai patients.

Method

The prospective study had the approval of the local Institutional Review Board of waiver of consent and adhered to the tenets of the Declaration of Helsinki. The study was performed in patients with failed trabeculectomy seen in a glaucoma clinic between November 2017 and April 2019 were treated with bleb needling revision augmented with 5-FU injection by one glaucoma specialist and using the same technique.

Chronic filtering bleb failure was defined as inadequately lowered intraocular pressure (IOP) less than 21 mmHg with anti-glaucoma medication or more than 21 mmHg with or without anti-glaucoma medication over 6 months post trabeculectomy as well as presence of a bleb that was encysted, fibrosed, increased vascularity or flattened blebs.

The 5-FU augmented bleb needling was performed at the slit lamp 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. A lid speculum was inserted. A 27-gauge needle was used to enter subconjunctival space at approximately 8-10 mm distal to the site of failed filtration bleb and incise any Tenon cyst, and on occasion, to slide below the scleral flap and enter the anterior chamber through the filtering ostomy. Once aqueous flow into the bleb is seen, the needle was directed posteriorly and 0.1 ml of 50 mg/ml

of 5-FU was then injected subconjunctivally superior to the re-formed bleb in all cases. Copious irrigation with sterile water and removed the lid speculum. After procedure, the intraocular pressure (IOP) and anterior chamber were checked on the slit lamp. All the patients were instructed to discontinue any anti-glaucoma medication. Topical prednisolone acetate 1% was prescribed every 2 hours while awake for the first week and then 4 times daily. The dose was tapered thereafter according to the clinical appearance of the bleb. Topical moxifloxacin was prescribed for one week in all cases.

Patients were followed up and re-needled as required if the IOP did not reach its goal for each patient based on the severity as well as the history of progression of glaucomatous optic nerve damage or the filtration bleb showed signs of failure such as flattening, encapsulated, cystoid or increase vascularity.

Demographic information obtained included primary trabeculectomy or repeated trabeculectomy with adjunctive MMC in all cases, age, gender, co-morbidities, glaucoma diagnoses, visual acuity, number of needlings and intraocular pressure (IOP) at various time points (month 1, month 3, month 6, month 9 and month 12 post first needling revision with 5 FU injection), any repeat needlings, number of anti-glaucoma medications and any further surgical intervention were recorded. Exclusive criteria consisted of age < 20 years old, 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 intraocular pressure (IOP) was measured using the same Goldmann applanation tonometry and slit lamp for every patient on every visit. Success was defined as maintenance of IOP $\geq$ 6 mm Hg and $\leq$ 21 mmHg in absence of further surgery or without anti-glaucoma medication at 12 months after first bleb needling revision with 5-FU injection. The use of any anti-glaucoma medications, repeat trabeculectomy or glaucoma drainage device, adjunctive laser treatment with Selective Laser Trabeculoplasty (SLT) would constitute as a needle revision failure at 12 months after first needling revision. Hypotony was defined as an IOP of less than 6 mmHg.

Statistical analyses were performed using IBM SPSS statistic version 19.0 (IBMcorp, 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 chi-square test or Fisher's exact test for categorical variables. 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 values were compared at a significance level of 0.05.

Result

Fifty-two eyes of 52 patients were enrolled in the study. One eye was excluded as they relocated. Population consisted of 23 males (45%) and 28 females (55%) in Thai patients. Needling revision with 5-FU injection was attempted on 51 eyes of 51 consecutive patients. Glaucoma diagnosed included primary open angle glaucoma (POAG) in 30 eyes (59%) primary angle closure glaucoma (PACG) in 18 eyes (35%) and secondary glaucoma of 3 eyes (6% included 2 traumatic glaucoma, 1 uveitic glaucoma).

Twenty-seven (53%) of 51 eyes were phakic and 24 eyes (47%) were pseudophakic. Primary trabeculectomy had been performed in 33 eyes (64.7%) and 18 eyes (35.3 %) had undergone repeat trabeculectomy. The mean age of the 51 patients was 62.7 ± 21.4 years (Range

32-80). The demographics of the study population were listed in Table 1.

The mean number of needle revision was 1.88 (Range 1-10). The mean time since the trabeculectomy to first needling revision was 68 ± 32 months (Range 6- 120 months). The time interval between the trabeculectomy and first needling revision had no predictive effect on outcome of the needling between the success group and failure group. (Table2)

Needling had been successful in 41 (80.4 %) eyes and had failed in 10 eyes (19.6 %). The mean pre-needling IOP was 24.8 ± 12.6 mmHg and 13.5 ± 7.4 mmHg at 12 months post first needling. The IOP was significantly reduced from first month throughout 12 months post first needle revision with 5-FU injection ($P < 0.001$). The IOP was steady and maintained at 12 months (Figure1). The average number of topical medications taken before needle revision was 2.60 ± 1.4. At 6 months and 12 months, the average number of topical glaucoma medications used was 0.3 ± 0.5 both time period. There was a statistically significant decrease in number of glaucoma drugs at 1 month to 12 months ($P < 0.001$, Figure 2). However, there was no difference between the number of medications used at baseline between the success group and failure group ($P > 0.05$, Table 2).

Characteristics of patients with success and failure following needling revision with 5-FU injection were prescribed in Table 2. The two groups were similar in age, gender, type of glaucoma, mean number of pre-needling glaucoma medication, lens status and pre-needling bleb morphology. However, significant differences were found in three variables between the two groups when a multivariate analysis using Cox proportional hazard regression analysis was performed. Prognostic factors for failure of needling revision with 5-FU injection were listed in Table 3 included pre- needling IOP > 25 mmHg (HR =3.1, P= 0.0003), ≥ 3 previous needling revisions (HR = 2.6, P = 0.0012) and history of repeated filtration surgery before performed this procedure (HR = 1.8, P = 0.011).

The morphology of failed blebs that required revision needling consisted of 13 encapsulated (25.5%), 12 flattened (23.5 %), 12 cystoid (23.5) and 14 increased vascularity (27.5 %). Bleb morphology was not a prognostic factor for failure of needling revision. Thirty-one eyes had previous ocular surgery other than trabeculectomy including phacoemulsification in 24 eyes and pterygium excision with conjunctival auto-graft in 7 eyes.

Ten eyes (19.6 %) that did not respond to at least 3 episodes of needling and required additional glaucoma treatment consisted of 6 eyes of POAG, 3 eyes of PACG and 1 eye of secondary glaucoma. Four eyes required revised trabeculectomy, 2 eyes required glaucoma drainage device implantation and 4 eyes required anti-glaucoma medication. Complications following revision needling with 5-FU injection was found in 6 (11.8%) of 51 eyes. Minimal gross hyphema was observed in 2 eyes and non-sustained hypotony was found in 1 eye. There were no other procedures required in these three eyes. Three eyes of 27 phakic eyes (11%) had lost greater than 2 lines of visual acuity in the Snellen chart compared with the pre-needling group at 6 months due to dense posterior subcapsular cataract. All three of these eyes subsequently underwent cataract surgery with good recovery of vision 20/40 to 20/30 at 12 month and success IOP control without any anti-glaucoma medications. There were no serious sight threatening complications or ocular surface problems found such as bleb leakage, flat anterior chamber, choroidal effusion, suprachoroidal hemorrhage, aqueous misdirection, endothelial decompensation, endophthalmitis, and filamental/punctate keratitis.

Table 1: Patient demographics

Demographics	Number	Percent
Age (years old)	62.7 ± 12.4 (Range 32-80)	-
Gender (person)		
- Male	23	45
- Female	28	55
Type of glaucoma (eye)		
- POAG	30	59
- PACG	18	35
- Secondary glaucoma	3	6
Underlying disease (person)		
- None	24	67
- Diabetic mellitus	3	8
- Hypertension	5	14
- Dyslipidemia	4	11
Lens status		
- Phakic	27	53
- Pseudophakic	24	47
Pre-needle revision bleb morphology		
- Encapsulated Flattened	13	25.5
- Cystoid	12	23.5
- Increase vascularity	14	27.5
Filtration surgery		
- Primary trabeculectomy	33	64.7
- Repeat trabeculectomy	18	35.3

Table 2: Characteristics of patients with success and failure following needling revision with 5-FU injection

Characteristics	Success (n= 41 eyes, 80.4%)	Failure (n = 10 eyes, 19.6 %)	*P*
Age (mean ± SD)	62.5 ± 10.4	62.9 ± 5.8	0.924
Gender Male Female	 18 23	 5 5	 0.462
Time interval to first needling (months)	67 ± 36 (Range 6-114)	69 ± 42 (Range 36 -120)	0.944
Mean number of needling revision	1.8	3.2	0.0012
Type of glaucoma (eye) POAG PACG Secondary glaucoma	 24 (58.5 %) 15 (36.6 %) 2 (4.9 %)	 6 (70.0 %) 3 (30.0 %) 1 (10.0 %)	 0.554
Mean pre-needling IOP (mmHg)	22.4	32.2	0.0003
Mean pre-needling glaucoma medication	2.3 ± 1.7	2.6 ± 1.4	0.956
Lens status Phakic Pseudophakic	 22 (53.7%) 19 (46.3%)	 5 (50%) 5 (50%)	 0.536
Pre-needling bleb morphology Encapsulated Flattened Cystoid Increase vascularity	 11 (26.8 %) 9 (22.0 %) 10 (24.4%) 11 (26.8 %)	 2 (20.0 %) 3 (30.0 %) 2 (20.0 %) 3 (30.0 %)	 0.403
Filtration surgery Primary trabeculectomy Repeat trabeculectomy	 31 (75.6 %) 10 (24.4 %)	 2 (20.0 %) 8 (80.0 %)	 0.011

Chi-square and Fisher's exact test for categorical groups and independent t test for continuous variables

Table 3: Risk factors for failure of needling revision with 5-FU injection: Coefficients and risk estimated per Cox Proportion Hazard Regression Model

Prognostic factor	Coefficient ± Standard error	*P*	Hazard Ratio	95% CI on Risk Ratio	
				Lower	Upper
Pre- needling IOP > 25 mmHg	1.25 ± 0.33	0.0003	3.1	1.5	6.6
Needling revision ≥ 3 times	1.05 ± 0.31	0.0012	2.6	1.3	5.4
Repeated filtration surgery	0.79 ± 0.29	0.011	1.8	1.1	4.1

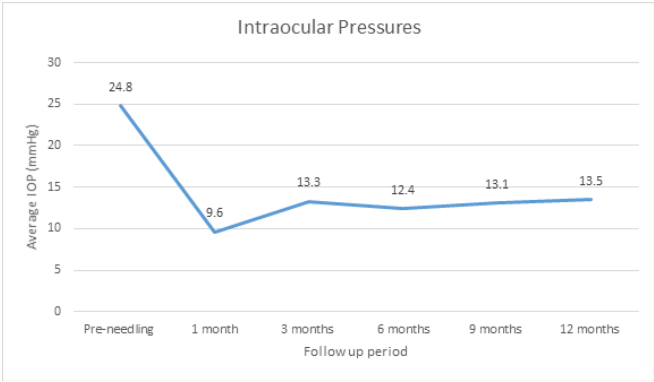

Figure 1: Mean intraocular pressure (mmHg) pre- and post-needling with 5-FU injection at all time intervals after first procedure

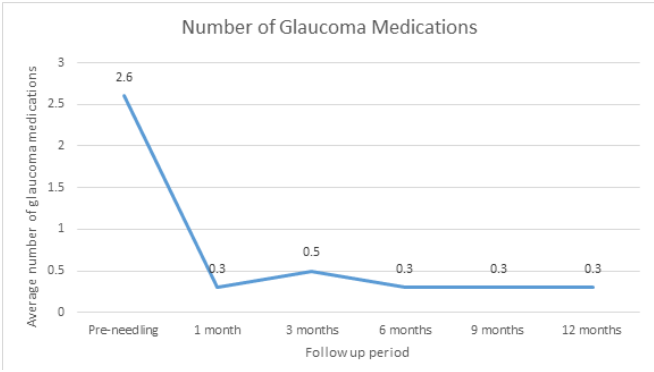

Figure 2: Mean number of topical glaucoma medications pre- and post-needling with 5-FU injection at all time intervals after first procedure

Discussion

The most common cause of trabeculectomy failure is scarring. Treatment of elevated intraocular pressure after surgery include digital massage, release of sutures early, reuse of topical anti-glaucoma medication, laser procedure (SLT, ALT), needle revision or repeated trabeculectomy if the bleb continues to fail after a period of time.[7]

The use of 5-FU in needling revisions exhibited an effective outcome in many studies if performed early in the postoperative period.[7,8,12] Repeating injections and needling are often necessary to achieve successful outcomes.[13] Variable success rates have been reported in the literature. It is difficult to make comparisons across the studies due to different study lengths, sample size, definition of success and antimetabolite used. Ewing and Stamper first reported 91.7% overall success in a small sample of 12 cases using 5-FU augmented bleb needling in 1990.[8] Success in their study was defined as target IOP achieved with or without use of topical medications. The mean follow up was 9 months. In some studies, the success rates range from 54% to 84% at 1 year, depending on different definition of success and case selection.[13,14,15,16,17]

In the present study, we reported efficacy of this procedure in chronic filtering bleb failure over 6 months after trabeculectomy in Thai eyes with 80.4 % success rate without serious visual threatening complications. We also reported on factors associated with procedural failure. This report is the first and largest prospective cohort study of 5-FU augmented bleb needling performed in Thai patients.

Makornwattana *et al* reported a success rate of 100 % of multiple needle revisions and 5-FU injection in over 14- month old dysfunctional blebs to achieve IOP less than 21 mmHg without anti-glaucoma medication for at least 3 months post-interventional in case series of 8 Thai patients.[11] Our prospective study included 51 eyes all of which had undergone a needle revision with 5-FU injection. Success was defined as the same criteria to the aforementioned study with the difference that our study has a 12 month follow up period after initial needling. Our success rate was 80.4%, which supported the efficacy and safety of needle revision augmented with 5-FU injection in chronic dysfunctional blebs in Thai patients. Moreover, we also identified the 3 risk factors for the failure of a needling procedure included pre- needling IOP > 25 mmHg, needling revision ≥ 3 times and history of repeated filtration surgery before performed this procedure.

Prutthipongsit *et al* reported an overall success rate of 82.69 % in both acute and late failure of filtration blebs at 6 months follow up in a retrospective study in Thai patients.[12] However, this study defined outcomes as complete success (target IOP < 21 mmHg without topical glaucoma medication and no addition of other surgical procedures), qualified success (IOP < 21 mmHg with topical glaucoma medications) and failure (IOP> 21 mmHg together with the execution of other surgical procedure). Pre-needling IOP > 25 mmHg and secondary glaucoma were the risks factors of failure of 5-FU needling in this study, supported our prospective study results in a 12 month follow up period.

Our finding showed 80.4% of patients benefited from the late bleb needling revision as a surgical adjunct. The length of the interval between the surgery and needling revision had no predictive effect on outcome of the needling. The role of previous repeated filtration surgery is interesting. The patients who experience a repeated filtration surgery had a risk factor of failure of needle revision. This suggests bleb revision by needling is an effective procedure to prevent subconjunctival fibrosis from filtration surgery with potentially improved success rate of

repeated filtration surgery in the future. On the other hand, when performing bleb needling revision, one should be aware of failure in repeated trabeculectomy.

Shin *et al* identified risk factors for failure of 5-FU needling revision for failed conjunctival filtration blebs included pre-needling IOP > 30 mmHg, lack of MMC use during the previous filtration surgery and IOP > 10 mmHg immediately following needling revision.[19] This study reported a cumulative success rate of 45% at 1 year, 33% at 2 years and 28% at 4 years. Our study exhibited more success rate at 1 year than this study maybe due to the use of adjunctive MMC in all cases, both primary trabeculectomy and repeated trabeculectomy in our study. The lower rate of success than our study is propositionally due to the study population being African American ethnicity, who have been shown to have a greater tendency for poor pressure control following surgery.[14] Other issues may be due to a different definition of success in each study, the longer duration follow up time in our study, in which failure of the trabeculectomy bleb can occur due to fibrotic proliferation as a part of the wound healing response.[3,4] However, a higher pre-needling IOP is associated with failure, which is in agreement with our study and Tsai AS et al. [21] that supported the use of MMC during the original glaucoma filtration surgery seems to be a beneficial factor in the future success of 5-FU needling revision due to long lasting on local fibroblasts. [19,20]

Tsai AS *et al* reported complete a success rate of 62% in POAG and PACG at 12 months. In addition to a success rate of 57.9% for POAG and 63.0% in PACG at 24 months with the same criteria of success as our study which defined as IOP ≤ 21 mmHg in absence of further surgery or use of anti-glaucoma medications.[21] This study recruited 175 eyes with mean needling attempts 1.9 ± 1.4 and 2 ± 1.6 for POAG and PACG respectively. Most of the population were Chinese ethnicity (72% in POAG, 81.4% in PACG). The mean interval between filtration surgery and bleb needling was 299.9 ± 616.4 days for POAG and 167.1 ± 272.2 days in PACG. The success rate between POAG and PACG were not significantly different and a higher pre-needling IOP were associated with failure, which supported the results in Thai patients in our study. Asian eyes have a greater propensity for scarring.[3,4] However, the results in Singapore and Thailand revealed that bleb needling revision with 5-FU injection which performed in chronic bleb failure can rescue and restore bleb function in Asian eyes.

Several risk factors for failure of 5-FU needle revision were identified, including lack of mitomycin C (MMC) use during the initial filtration surgery,[19] fornix based trabeculectomies,[22] pre-needling IOP >30 mmHg,[7,18] IOP >10 mmHg immediately following needling revision,[7,14,19] and elevated bleb with highly vascularized or microcysts.[16] In our study, we found that needling revision more than 3 times was a great risk factor associated with needling revision failure. This is similar to previous studies by Tsai AS *et al*[21] and Wong *et al*[23] which also studied in Asian eyes. Bleb needling can in itself induce inflammation and fibrotic proliferation, an increase in the number of needling procedures suggest that eyes undergoing this procedure have a greater propensity to scar.

Lee *et al* reported a flat central bleb and flat bleb height were risks factor of needle revision failure in Taiwanese eyes with 23 months follow up period.[24] Rotchford and King also identified a flat bleb was a risk factor of failure with 41 months follow up period in United Kingdom.[16] In our present study, there was no significant difference of pre-needling bleb morphology between the success and failure group.

Bleb needling is a relatively safe

procedure.[7,21] Complications are mostly minor and consist of conjunctival wound leak, small hyphema, corneal epithelial toxicity and transient shallow of anterior chamber. Visual threatening complications include significant hypotony, suprachoroidal hemorrhage, malignant glaucoma, endophthalmitis related to blebitis can occur but are rare. Zeng L *et al* performed needling revision in operating theater in all cases to easy to resolve complication during procedure such as bleb leak, flatten anterior chamber.[17] Mercieca K *et al* performed a cross-sectional online survey distributed to glaucoma specialists in United Kingdom, they reported bleb needling was performed in the operating room by 56 % of responders.[25] In our study, although we performed this procedure at the slit lamp in all cases, there were no major visual threatening complications found. Needling revision is a safe and simple method which can rescue failing blebs.[8] In our study, there were no serious corneal toxicity from 5-FU injections which may be prevented by a copious irrigation with sterile water in all cases and only an average 1.8 injection of 5-FU. Copious irrigation with a sterile water is recommended in all cases.[11]

Three of 27 phakic eyes (11%) lost visual acuity greater than 2 lines on Snellen chart compared with the pre-needling level at 6 months due to dense posterior subcapsular cataract. Zenq *et al* reported 24% had cataract surgery after needle revision surgery.[17] The development of cataract post-trabeculectomy and needle revision is another significant issue. All three patients in this study subsequently underwent cataract surgery with good recovery of vision 20/40 to 20/30 and success IOP control without any anti-glaucoma medications at 12 months. However, after cataract surgery, the risk of bleb failure increases 8-fold with expected survival time reduced from 190 weeks to 34 weeks in previous study.

Although we performed a prospective study, our study has some limitations pertaining to the non-randomized methodology and the lack of a control group. Moreover, the repeated needling revisions depended on the clinician's judgement during 12 months follow up period. In addition, no objective bleb grading system has been used to describe the morphologic features. Three eyes with secondary glaucoma may interfere the results of primary glaucoma and the goal of success is the IOP of less than 21 mmHg may not be safe for advanced glaucoma patients. Future randomized control trials are required to reduce bias. Extension of follow up over 12 months post initial needling and clarification of objective bleb grading system and inclusion of only primary glaucoma patients and defined the definition of success depending on the severity of glaucoma are recommended in future studies.

Conclusion

Late bleb needling revision with 5-FU injection is still an effective and lasting treatment for the majority of failed trabeculectomies and avoid further surgery in Thai patients. Risk factors for failure of the initial 5-FU needling revision included pre- needling IOP > 25 mmHg, needling revision ≥ 3 times and history of repeated filtration surgery before performed this procedure. More than one needling is frequently necessary to achieve treatment goals. The procedure is relatively safe, with a short operating time and is minimally invasive with infrequent complications.

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