

# Outcome of needle revisions with subconjunctival 5-fluorouracil in filtration blebs

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**Objective:** To study the outcome of subconjunctival needling with 5-fluorouracil in filtration blebs in the patients who have been treated by trabeculectomy.

**Methods:** Retrospective chart review of glaucoma patients who have been treated by trabeculectomy or combined phaco-trabeculectomy, and needling revision in accordance to indications at Thammasat University Hospital from January 2015 to December 2017 in total of 52 eyes. The treatment result was monitored during a 6 month- period. Success outcome by monitoring IOP and factors affecting failure of procedure are outcome measurement. In needling procedure, 27-gauge needle and 0.1 mL of 50 mg/mL of 5-FU were used.

**Results:** After needle revision, mean IOP decreased from  $20.5 \pm 6.77$  mmHg to  $13.35 \pm 8.11$  mmHg at 6 months ( $p < 0.001$ ), median IOP reduction was 29.70%. Complete success, qualified success and failure were at 63.46%, 19.23%, 17.31%, respectively. Incidence rate of failure was 7.92, using Kaplan-Meier survival analysis. Risk factors for failure of 5-FU needling were pre-needling IOP  $\geq 25$  mmHg (HR 3.81,  $p = 0.047$ ) and secondary glaucoma including NVG (HR=2.6,  $p = 0.154$ ). In addition, serious complication was not detected after monitoring of treatment for 6 full months.

**Conclusion:** Bleb needle revision could reduce IOP in the patients who failed filtering bleb and could restore function of bleb in the patients with increasing trends in IOP from bleb morphology which is at safe and effective procedure.

**Conflicts of interest:** The authors report no conflicts of interest.

**Keywords:** glaucoma, trabeculectomy

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## Introduction

The current treatment of glaucoma consists of topical eye drops, laser and surgery. Trabeculectomy is a surgical treatment of choice in various glaucoma patients. Trabeculectomy is a treatment to reduce

intraocular pressure by shunting aqueous from the anterior chamber to subconjunctival space. The surgical indications include inability to control intraocular pressure and existence of worsening illness despite various combinations of antiglaucoma medications or adherence issues due to complications from eye drops, etc. Success rate of this type of surgery is high. However, findings indicated that success of surgery annually decreased around 10%. Affecting factors contributing to trabeculectomy failure include scarring or fibrosis

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between conjunctiva and episclera layer, resulting in intrableb fibrosis, decrease in aqueous drainage, and inability to control intraocular pressure in the main phase. Various methods that contribute to the effectiveness of a bleb and modulation of wound healing processes to reduce fibrosis includes bleb massage, laser suture lysis, and use of adjunctive antifibrotic agents such as mitomycin C and 5-fluorouracil during surgery or after surgery. Transconjunctival needling revision is used to remove part of fibroses with minimally invasive technique and to restore infiltration. The indications of needle revision consist of bleb encapsulation, inadequate IOP control with an elevated bleb with microcysts, flat bleb with visible sclera flap without microcyst, or any of the aforementioned requiring a topical ocular hypotensive medication, dysesthetic blebs, and leaking blebs. Chart review-based study was conducted to report the outcome of needle revision at 6 months after the procedure. The factors affecting needle revision failure were studied, safety and contingent complications after the procedure were reported. The study was conducted by reviewing charts patients who underwent trabeculectomy and have been treated with needle revision which their intraocular pressures could not be controlled after surgery or other aforesaid indications were existent.

## Methods

Retrospective chart review is conducted on patients at Thammasart University Hospital for a total of 52 eyes. The patients underwent trabeculectomy or a combination of phaco-trabeculectomy or second trabeculectomy. After surgery, needling with 5-FU was performed in accordance with the following indications including inadequate IOP control  $\geq 21$  mmHg with an elevated bleb with microcysts, trend to increase IOP from bleb morphology, leaking bleb, dysesthetic blebs<sup>9</sup> and patients have been excluded in case of

incomplete data of medical records. Treatment results after needling with 5-FU is monitored until 6 months. Data from medical records were collected from January 2015 to December 2017.

## Statistical Analysis

Qualitative variables are reported in percentage and continuous variables are reported in mean $\pm$ SD and median. Cox hazards regression is applied for analyzing each factor to whether it affects failure. Wilcoxon signed-rank test is conducted to compare IOP, number of medications and visual acuity before and after procedure, and Mixed model and pair t-test are conducted to compare IOP of each visit. In addition, Kaplan-Meier survival analysis for failure is applied.

## Bleb needle revision technique

In topical anesthetic, 0.5%Tetracaine Hydrochloride is used at least 4-5 times every 5-10 minutes in combination with vasoconstrictor (Phenylephrine 2.5%). Eye drops are instilled before the procedure. All bleb revisions were performed under slit lamp in a medical examination room.

A 27 guage needle was connected to an syringe insulin. Syringe filled with 5-fluorouracil at a concentration of 50 mg/ml with a volume of 0.2 ml. Eye speculums were used to open the patient's eyes. The needle was inserted into the site of subconjunctiva around 10 mm away temporally or nasally to the site of sclera flap and then straight to main loculation where is over to the site of sclera flap. The needle tip is beveled up and is used to cut and open any episcleral fibrosis. In cases of minimal effect, slides may be performed below the scleral flap to lift the scleral flap or enter the anterior chamber through the filtering ostomy. Restoration of aqueous drainage is considered to be the end point. Vessels, and perforation of any conjunctiva is avoided and no suturing conjunctival is required after the injection of 5-fluorouracil

(50mg/ml) for 0.1 ml into subconjunctiva by injecting over and at the back to the site of blebs.

Leaking point or bleeding after procedure is checked. Eye speculum is removed then topical antibiotic is instilled. The patients are instilled with topical steroid (Prednisolone 1%) every 2 hours and topical antibiotic every 4 hours by day, and they are continuously instilled at home after returning home.

### Data Collection

Data was collected from review chart of outpatients by collecting demographic data such as age, gender, type of glaucoma, type of operation trabeculectomy, second trabeculectomy or combined phaco-trabeculectomy, period after trabeculectomy to first needling, number of antiglaucoma medications, IOP, total number of times of needling, total volumes of 5-FU, and visual acuity. Data at 1 week, 1 month, 3 months and 6 months after needling procedure was collected.

### Outcome measurement

Success outcome of needling with 5-FU at 6 months period and report of factors affecting failure are defined as the following. Complete success was defined as intraocular pressure (IOP) below 21 mmHg without antiglaucoma medication and reduction of intraocular pressure more than 20 % from beginning intraocular pressure without combination of antiglaucoma medication. Qualified success is defined as intraocular pressure below 21 mmHg in combination with antiglaucoma medication and reduction of intraocular pressure more than 20 % from beginning intraocular pressure in combination with antiglaucoma medication.

Failure is defined as intraocular pressure of more than or equaling to 21 mmHg or reduction of intraocular pressure lesser than 20% from beginning intraocular pressure or poor vision equaling to no light percep-

tion or operative requirement for reduction of intraocular pressure such as glaucoma drainage devices, cyclophotocoagulation, cryotherapy, etc.

### Results

According to chart review, we found underwent filtering surgery and needle revision with adjunctive 5-FU for a total of 52 eyes, consisted of 32 men (61.54%) and 20 women (38.46%). Mean age $\pm$ SD was 62.01 $\pm$ 10.18 (range, 37 to 87). Patient demography is shown in Table 1.

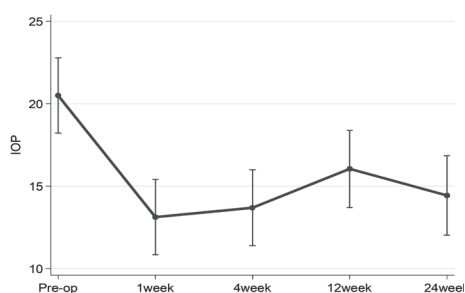
Types of preneedling operations included the patients who were underwent trabeculectomies for 32 eyes (61.54%), trabeculectomies in combination with cataract surgery for 19 eyes (36.54%) and second trabeculectomy for 1 eye (1.92%). All patients in research were administered with 0.4 mg/mL of MMC during their original surgery to be soaked onto cellulose surgical sponge with an application duration ranged between 150 and 180 seconds.

The median interval between original filtration and first needling procedure was 64.5 days, with a range of 3 days to 6 years. Mean total number of needle revisions was 2.61 $\pm$ 2.48 times and median was 2 times (range, 1 to 13).

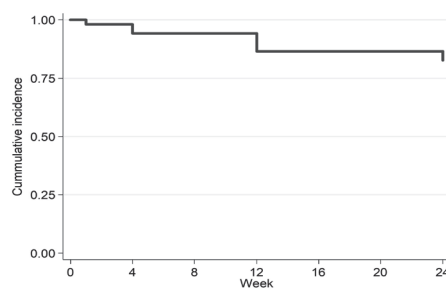
The finding indicated overall mean IOP reduction at 6 months was 27.68 $\pm$ 25.44%, median was 29.70% with range of 0 to 70%. Mean preneedling IOP was 20.5 $\pm$ 6.77 mmHg, mean postneedling IOP at 1 week, 1 month, 3 months and 6 months were 13.11 $\pm$ 8.71, 13.49 $\pm$ 7.56, 15.44 $\pm$ 10.24, and 13.35 $\pm$ 8.11 mmHg, respectively. IOP values statistically significantly decreased in every postneedling visit ( $p<0.001$ ). The change in IOP is illustrated in Figure 1. Complete success for 33 eyes from 52 eyes on criteria basis was 63.46%. Mean $\pm$ SD preneedling IOP was 19.30 $\pm$ 7.13 mmHg, decreasing to be 11.33 $\pm$ 3.14 mmHg at the 6th month ( $p<0.001$ ). Postneedling IOP statistically significantly decreased in

**Table 1:** Patient demography

Demographic Factor	N	Percent
Total number of patients	52(eyes)	100
Gender		
Male	32	61.54
Female	20	38.46
Eye		
Right	33	63.46
Left	19	36.54
Diagnosis		
POAG	19	36.54
PACG	16	30.77
NVG	9	17.31
Secondary Glaucoma	8	15.38
Initial Surgery		
Trabeculectomy	32	61.54
Combined phaco-trabeculectomy	19	36.54
Second Trabeculectomy	1	1.92
Indication of needle revision		
IOP > 21 mmHg	28	53.85
Bleb morphology	22	42.31
Bleb leakage	2	3.85

**Figure 1:** The change in IOP

every visit upon comparison with preneedling. Qualified success for 10 eyes from 52 eyes was 19.23%. Mean preneedling IOP was  $20.90 \pm 5.44$  mmHg, decreasing to be  $14.50 \pm 4.50$  mmHg ( $p=0.032$ ). IOP values also statistically significantly decreased upon comparison with preneedling IOP. Failure of 9 eyes was 17.31%. Mean IOP was  $21.0 \pm 1.41$  mmHg. Post-needling IOP did not decrease. The finding indicated mean at  $41.0 \pm 26.87$  mmHg,

**Figure 2:** Incidence rate of failure at 7.92 using Kaplan-Meier survival analysis

median at 41 mmHg, with range of 22 to 60 mmHg. Incidence rate of failure at 7.92 using Kaplan-Meier survival analysis as shown in Figure 2. According to 9 eyes in the group of failure, 8 eyes of patients were further operated by glaucoma drainage device, and the other 1 eye of patient was treated with cryocyclotherapy. Potential risk factors for failure are shown in Table 2. There was no significant differ-

**Table 2:** Hazard ratio failure of bleb needling

Study Factors	Category	Hazard Ratio	95%Confidence Interval	P-Value
Gender	Male	1.26	(0.31,5.04)	0.743
	Female	1		
Eye	Right	1	(0.61,8.59)	0.213
	Left	2.3		
Diagnosis	Primary Glaucoma	1	(0.69,9.68)	0.154
	Secondary Glaucoma	2.60		
Preneedling IOP	High ( $\geq 25$ mmHg )	3.81	(1.02,14.23)	0.047
	Low ( $< 25$ mmHg )	1		

ence with respect to gender or laterality. Upon comparison between primary glaucoma including POAG and PACG, and secondary glaucoma including NVG, the finding revealed that secondary glaucoma including NVG was rather the risk factor of the group of failure at hazard ratio of 2.60 ( $p=0.154$ ). There was indifference with respect to time to needling in the group of success upon comparison with the group of failure ( $p=0.72$ ) using Wilcoxon rank-sum test method. The finding revealed that preneedling IOP particularly when  $IOP \geq 25$  mmHg affected failure rather than in the group where IOP was lesser than hazard ratio at 3.81 ( $p=0.047$ ). Mean number of preneedling antiglaucoma medications was  $0.32 \pm 0.73$  and median was 0 (range 0-3); and mean number of postneedling antiglaucoma medications was  $0.56 \pm 1.09$  and median was 0 (range 0-4). The finding indicated that there was indifference of number of drugs before and after operation whereas  $p$  value was 0.11, no serious complication, no visual loss up to no light perception in studying group and no decrease in visual acuity by 2 or more snellen line. Preneedling mean $\pm$ SD logMAR VA was  $0.76 \pm 0.86$  and median was 0.54, with a range of logMAR 0 to logMAR 3. Postneedling mean $\pm$ SD logMAR VA was  $0.85 \pm 1.02$  and median was 0.50, with a range of logMAR 0 to logMAR 3. There was statistical significant indiffer-

ence whereas  $p$  value was 0.88. Postneedling leakage was detected for 1 case from total number of cases and conservative treatment was performed.

### Discussion

The significant cause of trabeculectomy bleb failure was scarring and fibrosis at episclera. Various treatment methods included from antiglaucoma medication to re-surgery. Needle revision is the simple and effective operation in rescuing bleb. Revision of failed filtration bleb through a small conjunctival incision was first described in 1941. After that, many authors have proposed various methods from use of needle gauges in different no. to small needle knife but under the same principle of disrupting subconjunctival scar tissue and restoring bleb function.<sup>1,2</sup> Several studies have used either 5-fluorouracil (5-FU) or mitomycin-C (MMC) in needling. 5-FU has been more preferred for use by most of around over 60%. Wei Liu et al.<sup>6</sup> studied comparative case series in comparison between subconjunctival MMC (0.1 mL of 0.2 mg/mL) and 5-FU (0.1mL of 50 mg/mL) in needling. The finding indicated that MMC was more effective than 5-FU for early dysfunction bleb. Meanwhile, Palejwala et al.<sup>8</sup> found that there was no apparent difference between the use of 5-FU and use of MMC. In our research, adjunctive subconjunctival 5-FU was used

in combination with needling for all cases in concentration of 0.1 mL of 50 mg/mL. After monitoring treatment until completing 6 months, serious complication from injection of subconjunctival 5-FU was not detected.

Regarding to outcome, several studies reported success rate of needling ranging from 39% to 91%, depending on criteria in each study and studying duration.<sup>3</sup> In our research, complete success, qualified success and failure are defined in similarity to several researches. David C. Broadway et al.<sup>3</sup> reported the outcome of needle revision in combination with subconjunctival injection using 5-fluorouracil in the patients who were used to be performed for surgery in shunting aqueous from eyeball to subconjunctival space and intraocular pressure was uncontrollable after surgery. The monitoring was performed at least 9 months after surgery for 101 eyes. The definition of success outcome is 1 reduction of intraocular pressure lesser than 22 mmHg, or 2. reduction of intraocular pressure more than 30% from the beginning intraocular pressure. The finding indicated success rate at 75% in 1 year, 52% in 3 years, and 56% in 1 year, 40% in 3 years in accordance with definition 1 and 2, respectively. Mustafa S. Kapasi et al.<sup>5</sup> studied the efficiency of subconjunctival needling revision using 5-FU when administered to patients who had non filtering, flat, or encapsulated blebs over 1 year after the original surgery, under 2 years period of treatment outcome monitoring. The finding of the studying result revealed that mean intraocular pressure decreased from 23.5 mmHg to be 13 mmHg (10.5 mmHg at 44.8%). It was concluded that late 5-FU needling was an effective method to control IOP. Yung-Sung Lee et al.<sup>7</sup> studied risk factor of failure of needle revision in combination with subconjunctival injection using 5-fluorouracil in the patients who failed from surgery in shunting aqueous

from eyeball to subconjunctival space for 41 eyes. The definition of success is intraocular pressure lesser than 21 mmHg or reduction of beginning intraocular pressure at least 20% without drug combinations. The finding revealed that survival of blebs at 6, 12 and 24 months were 42%, 39% and 23%, respectively. In our research, the finding indicated decrease in mean IOP from  $20.5 \pm 6.77$  mmHg to be  $13.35 \pm 8.11$  mmHg, mean percentage of IOP reduction was 27.69%, and success rate consisting of complete and qualified success was 82.69%. Upon analysis on statistical data, the finding revealed statistical significant decrease in IOP upon comparison with beginning IOP in every visit at week 1, month 1, month 3 and month 6 both in the groups of complete success and qualified success. However, due to 22 eyes from 52 eyes (42.31%) that were treated with needling in accordance with bleb morphology indication, there was a tendency of failure, whereas beginning IOP was not higher than 21 mmHg, this indication maybe over indicated. As a result this study found no statistical difference of number of medications before and after procedure that was dissimilar to several previous paper. Several researches reported that bleb morphology affected postneedling bleb survival.<sup>7</sup> The finding revealed that small central bleb extension and flat bleb were higher related to the opportunity of failure.<sup>2</sup> In this research, this variable was not studied since it is retrospective study. Grading system data result was differently recorded by each surgeon and bleb morphology data was incomplete. Therefore, the said data was not taken for analysis. However, the finding indicated that bleb morphology in the group of failure was often in flat bleb and thick tenon.

In this research, the finding revealed failure due to IOP > 21 mmHg and surgical requirement for other operations for 9 eyes from total of 52 eyes or 17.31% and



incidence rate of failure around 8%. Several researches studied factors affecting preneedling bleb survival and the finding indicated that there were similar risk factors such as preneedling IOP > 30 mmHg, no use of mitomycin C during trabeculectomy, immediate IOP after needle revision > 10 mmHg, time to first needling < 4 months, high IOP after needle revision within 1 week, and bleb morphology as aforementioned. The author's finding of this research revealed that the statistical significant affecting factor included preneedling IOP  $\geq$  25 mmHg (HR 3.81,  $p=0.047$ ). Other factor that might have clinical effect but had no statistical significance included type of glaucoma particularly in the group of secondary glaucoma such as NVG and uveitic glaucoma that risk of failure was detected at bleb rather than the group of primary glaucoma (HR 2.60,  $p=0.154$ ). There was statistical significant indifference on gender, laterality, and time to first needling. Due to recording of incomplete data in medical records, postneedling immediate IOP was not taken for statistical analysis.

Regarding to safety after monitoring until completing 6 months, serious complication such as loss of vision up to no light perception was not detected. The finding indicated that log MAR VA value was indifferent before and after procedure. Just one case was detected for leakage after needling and recovered by conservative treatment. The report of infection or hypotony was not detected at all.

Limitation of this research included retrospective chart review, resulting incompleteness and inadequacy of some data taken for analysis such as immediate IOP reduction, bleb morphology, etc. Even though needle revision was operated using the same technique but there might be variables from surgeons due to the operations by various surgeons. In addition, 6 months treatment monitoring period might be too

short, resulting in insufficient examination of long-term perspective. Possible future directions will include prospective study for eliminating variables that may affect research, recording and collecting data necessary for research, and scheduling longer monitoring period.

Conclusively, needle revision was useful for patients who were unable to control IOP after trabeculectomy in term of restoration of IOP control to be within the criteria throughout 6 months monitoring period, ability to restore function of bleb, easy and safe procedure. The risk factors affecting failure included secondary glaucoma especially NVG and preneedling IOP which was more than 25 mmHg.

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