

# The efficacy of bleb needling revision with 5-fluorouracil in encapsulated bleb after unsuccessful trabeculectomy

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DOI: 10.18621/eurj.425740

## ABSTRACT

**Objectives:** To investigate the efficacy of the bleb needling revision (BNR) procedure with the adjunctive use of 5-Fluorouracil (5-FU) in encapsulated bleb after unsuccessful trabeculectomy.

**Methods:** We reviewed 16 eyes of 15 subjects who underwent BNR procedure due to encapsulated bleb after unsuccessful trabeculectomy. Demographic data, type of glaucoma, intraocular pressure (IOP) values of pre-BNR, IOP values of post-BNR at first day, first week and first month, follow up time and complications were recorded from patients' files, retrospectively.

**Results:** The mean follow up time was  $53.1 \pm 26.4$  weeks. The average time between previous unsuccessful trabeculectomy and BNR was  $11.12 \pm 8.79$  weeks. The mean IOP of pre-BNR was  $26.0 \pm 4.4$  mmHg and significantly decreased to  $12.4 \pm 5.0$  mmHg post-BNR at the first day ( $p < 0.001$ ). The mean IOP values of post-BNR at the first week was  $13.3 \pm 4.9$  mmHg and at the first month was  $14.8 \pm 4.8$  mmHg. According to the mean IOP of pre-BNR, the mean IOP values of post-BNR at the first week and at the first month were significantly lower ( $p < 0.001$  and  $p < 0.001$ , respectively). Seven (44%) eyes were achieved success and eight (50%) eyes were achieved qualified success. One (6%) eye was classified as the failure.

**Conclusion:** The bleb needling revision procedure with the adjunctive use of 5-FU in encapsulated bleb after unsuccessful trabeculectomy is a simple, useful and repeatable method to restore the dysfunctional bleb.

**Keywords:** Bleb needling revision, 5-Fluorouracil, encapsulated bleb, trabeculectomy, filtration surgery

*Received: May 21, 2018; Accepted: January 22, 2019; Published Online: June 30, 2019*

Trabeculectomy remains the gold standard surgical procedure in cases that intraocular pressure (IOP) couldn't control with antiglaucomatous medication [1]. Trabeculectomy is a very effective procedure to reduce IOP at the early postoperative period. Nevertheless, its efficiency may decrease over time for some complications such as dysfunctional blebs. Localization of the bleb, episcleral fibrosis, and bleb encapsulation are the bleb-related reasons for the failure of primary filtration surgery [2].

Encapsulated bleb usually seen within 2-8 weeks after filtration surgery and the incidence is reported between 2.5% and 29% in previous studies [3, 4]. Encapsulated bleb was characterized as an elevated, smooth surfaced, tense, thickened, dome-shaped fibrotic membrane. The mechanism of development of encapsulated bleb is not well understood and many factors are responsible for its formation. The encapsulated bleb wall that limiting aqueous outflow is composed of a fibrous, collagenous connective tissue



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which is histopathologically produced as a result of fibroblastic proliferation [5]. Hence, inflammatory reaction and fibroblastic activity may increase the risk of developing encapsulated bleb [6].

The method of Bleb Needling Revision (BNR) which was first described by Ferrer in 1941, is now frequently preferred after unsuccessful filtration surgery [7]. The adjunctive use of antifibrotic agents such as 5-fluorouracil (5-FU) and mitomycin-C (MMC) in BNR is suggested to increase the rate of success of the procedure. 5-FU and MMC inhibit the scarring tissue formation and the proliferation of the fibroblasts which are the primary reasons for dysfunction of the blebs. Thus, BNR with antifibrotic agent is a simple and reliable method that can be an alternative treatment after dysfunctional blebs and reduce the IOP without causing additional healthy conjunctival surface loss and prevents patients from another glaucoma surgery. BNR has very good results but many factors such as age, the number of antiglaucomatous drug used before, history of previous ocular surgery, type of glaucoma, use of antimetabolite in primary filtration surgery and bleb morphology may affect the success of the procedure.

In addition, MMC has higher potency according to 5-FU but more complications have been reported due to use of MMC [1, 6]. Therefore, we prefer to perform the procedure with 5-FU. In this study, we aimed to evaluate the efficiency of the BNR procedure in patients who underwent BNR with adjunctive use of 5-FU after unsuccessful trabeculectomy.

## METHODS

Sixteen eyes of 15 subjects who underwent BNR due to encapsulated bleb after unsuccessful trabeculectomy (IOP  $\geq$  21 mmHg) in Necmettin Erbakan University, Meram School of Medicine, Department of Ophthalmology between March 2015-March 2017 were evaluated retrospectively. The study was approved by the local ethics committee (No:2018/1156) and followed the tenets of the Declaration of Helsinki. Demographic data, type of glaucoma, IOP values of pre-BNR, IOP values of post-BNR at the first day, the first week and the first month which were measured by Goldmann applanation tonometry, follow up time and complications were

recorded from patients files.

The BNR procedure was performed in the operation room using a 27-gauge needle with adjunctive use of 5-FU by two surgeons (MO and EM). After topical anesthetic (Proparacaine Hydrochloride 0.5%), 5% povidone-iodine solutions were instilled into the eye. A 27-gauge needle was inserted into the subconjunctival space to the tight Tenon's capsule around the bleb on the opposite site of the scleral flap, puncture the adherent tissue and lift the scleral flap. The flap was lifted with gentle side-to-side movement, breaking episcleral adhesions until the bleb is reformed. If simple flap dissection failed to form a nonsatisfactory bleb, the needle can be passed under the scleral flap into the anterior chamber. Then, the needle was removed and 5 mg (0.2 ml of 25 mg/ml solution) of 5-FU was subconjunctivally injected superior to the bleb. At the end of the procedure, antibiotic drops (moxifloxacin 0.5%) were instilled into the eye.

History of previous unsuccessful trabeculectomy surgery with or without antifibrotic agents, the presence of dysfunctional blebs due to encapsulated bleb, the presence of patent iridectomy were the inclusion criterion. History of previous multiple trabeculectomies or filtration surgery other than trabeculectomy, the presence of non-patent iridectomy, the presence of corneal epithelial complications, and leaky blebs were the exclusion criterion. The BNR procedure was considered as success IOP < 21 mmHg without antiglaucomatous medication; qualified success defined as IOP < 21 mmHg with antiglaucomatous medication and failure defined as IOP  $\geq$  21 mmHg with antiglaucomatous medication.

## Statistical Analysis

SPSS for Windows (version 17; SPSS Inc, Chicago, Illinois, USA) were used for the analysis. The paired t-test was used to compare IOP. A P value < 0.05 was considered as significant.

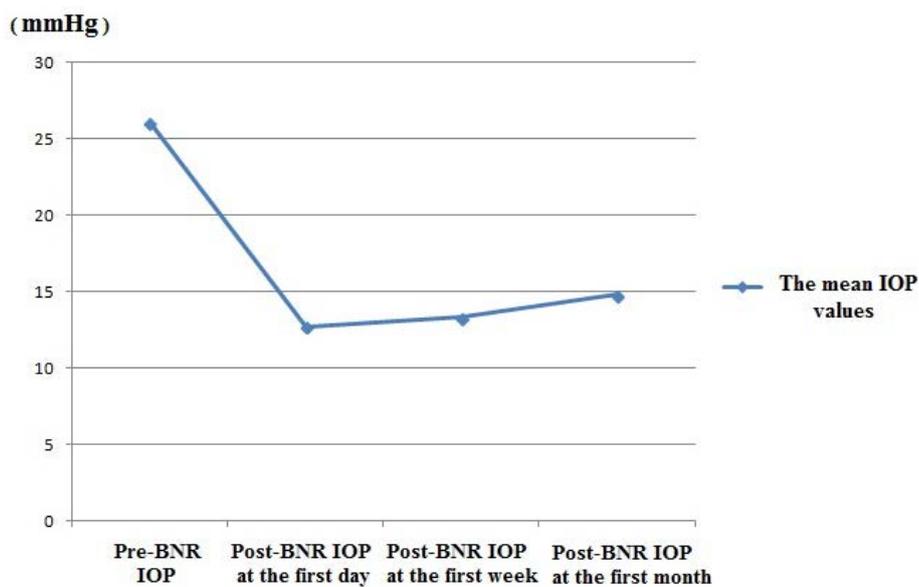
## RESULTS

Sixteen eyes of 15 subjects were included in the study. Three (20%) subjects were female, 12 (80%) subjects were male. The age of subjects ranged

**Table 1.** Demographic data and IOP values

Eye No.	Gender	Age	Type of Glaucoma	Pre-BNR IOP (mmHg)	Post-BNR IOP at first day (mmHg)	Post-BNR IOP at first week (mmHg)	Post-BNR IOP at first month (mmHg)
1	M	22	Traumatic	21.2	7	10	14
2	M	33	POAG	23.4	8	16	14,2
3	F	57	POAG	27	6	6	12
4	F	73	POAG	25.8	17	16.8	15.6
5	M	25	POAG	25,5	12	12.5	11.5
6	M	25	POAG	30.3	15.1	10.1	13.1
7	M	65	POAG	26.1	15.1	11.1	11.1
8	M	69	Pseudoexfoliation	23.7	17.7	10.7	14.7
9	M	54	Uveitic	25	5	7	8
10	M	45	Pseudoexfoliation	25.8	12.8	10.1	10.4
11	F	59	POAG	22.6	16.6	16.6	15.6
12	M	37	POAG	21.2	16.2	16.2	17.2
13	M	57	POAG	22.2	13.4	17.6	15.8
14	M	35	Traumatic	25.1	12.3	9.4	16.4
15	M	18	Traumatic	36.9	9.9	19.3	17.3
16	M	62	Neovascular	34.4	19.7	23.7	29.7

BNR = bleb needling revision, IOP = intraocular pressure, POAG = primary open-angle glaucoma, M = male, F = female



**Figure 1.** The mean IOP values of patients. BNR = bleb needling revision, IOP = intraocular pressur

**Table 2.** Pre-BNR and Post-BNR characteristics

Eye No.	Time between trabeculectomy and BNR (week)	Antimetabolite agent use in previous trabeculectomy	Follow up time (week)	The number of antiglaucomatous medication	Success	Complication
1	8	5-FU	26	None	Yes	None
2	4	5-FU	80	One	Qualified	None
3	4	None	124	None	Yes	None
4	10	None	44	One	Qualified	None
5	10	5-FU	48	None	Yes	None
6	7	5-FU	36	Two	Qualified	Late Leakage
7	9	None	25	None	Yes	None
8	16	None	76	One	Qualified	None
9	5	None	34	None	Yes	None
10	29	None	61	None	Yes	None
11	28	None	64	Three	Qualified	Bullous Keratopathy
12	8	None	76	Two	Qualified	Late Leakage
13	26	5-FU	53	One	Qualified	None
14	4	5-FU	34	None	Yes	None
15	6	None	40	One	Qualified	None
16	4	None	28	Three	Failure	None

BNR = bleb needling revision, IOP = intraocular pressure, 5-FU = 5-Fluorouracil

between 18-73 years old and the mean age of subjects was  $46.0 \pm 18.2$  years (Table 1). All eyes were underwent conventional trabeculectomy previously and six of them were with adjunctive use of 5-FU (Table 2).

There were nine (56%) eyes with primary open-angle glaucoma (POAG) and seven (44%) eyes with secondary glaucoma such as one eye had neovascular glaucoma, one eye had chronic uveitis, two eyes had pseudoexfoliation glaucoma, three eyes had glaucoma following serious trauma to the globe (Table 1). The average time between previous unsuccessful trabeculectomy and BNR ranged between 4-29 weeks and the mean time was  $11.12 \pm 8.79$  weeks. The mean IOP of pre-BNR was  $26.0 \pm 4.4$  mmHg and significantly decreased to  $12.7 \pm 4.4$  mmHg post-BNR at the first day ( $p < 0.001$ ). The mean IOP values of post-BNR at the first week were  $13.3 \pm 4.9$  mmHg and at the first month was  $14.8 \pm 4.8$  mmHg (Figure 1). The mean follow up time was  $53.1 \pm 26.4$  weeks (range 25 to 124 weeks). According to the mean IOP of pre-BNR, the mean IOP values of post-BNR at the first week and at the first month were significantly

lower ( $p < 0.001$  and  $p < 0.001$ , respectively). Seven (44%) eyes were achieved success and eight (50%) eyes were achieved qualified success. One (6%) eye was classified as failure. Complications such as late-onset bleb leakage in two eyes and bullous keratopathy in one eye observed in three (19%) eyes as shown in Table 2.

## DISCUSSION

One of the most important factors that determining the success of trabeculectomy and bleb function is the degree of healing process in the filtration zone [8, 9]. A variety of risk factors such as excessive surgical trauma and increased inflammatory process after an early period of filtration surgery which is related to the development of encapsulated bleb have been reported in the literature [5, 6]. This suggests that these risk factors are not a definite etiology for the presence of encapsulated bleb formation [6]. Even so, surgical trauma and increased postoperative inflammation may probably lead to increase the risk of encapsulated bleb

development [10]. Although there is currently no definitive treatment to prevent bleb failure and encapsulated bleb. Indeed, many drugs and different treatment methods are still being studied.

One of the drugs used to inhibit fibroblastic proliferation and enhance the success of the filtration surgery by allowing the bleb to remain functional is 5-FU. The use of 5-FU adjunctive with filtration surgery or BNR procedure and also injections after filtration surgery can be done. Many researchers have reported the efficacy of the BNR with 5-FU in unsuccessful bleb after filtration surgery [11, 12]. Notably, IOP decreased by an average of 10.5 mmHg (44.8%) immediately after the BNR procedure in the study of Kapasi and Birt [11]. Broadway *et al.* [13] showed 47% success rate in encapsulated bleb after BNR with adjunctive 5-FU and it was reported that the mean IOP being reduced from 26.5 mmHg to 15 mmHg after a median of 1 BNR procedure. Also, the mean IOP was lower in the BNR with 5-FU group ( $12.1 \pm 2.8$  mmHg) compared to the medical treatment group ( $15.1 \pm 2.1$  mmHg) in the study of Suzuki and Susanna [14]. In our study, it was found that the mean IOP values decreased by 51% (reduced from  $26.0 \pm 4.4$  mmHg to  $12.7 \pm 4.4$  mmHg) at the postoperative 1st month compared to the mean preoperative IOP values.

MMC is another antifibrotic agent in filtration surgery and in BNR procedure but more complications have been reported due to use of MMC [15, 16]. In a retrospective study comparing MMC and 5-FU, there was no difference in success between using MMC and 5-FU, and early postoperative IOP was reported to be the only predictor of success [17]. Complications such as hemorrhage, infection, late-onset bleb leakage, hypotonia, choroidal detachment and suprachoroidal hemorrhage can occur with rarely due to BNR procedure. Anand *et al.* [18] have reported that MMC is a more patent antifibrotic agent but also they reported that in the MMC group, blebitis and late bleb leakage were reported more frequently than in the 5-FU group. In this study, we observed late-onset bleb leakage in two eyes and bullous keratopathy in one eye.

Previous studies have reported that the short time between previous unsuccessful trabeculectomy and the BNR procedure has an adverse effect on bleb function [19, 20]. Shetty *et al.* [21] suggested that

immediate BNR after trabeculectomy could be unsuccessful due to the ongoing episcleral inflammation caused by the previous surgery. On the other hand, Gutierrez-Ortiz *et al.* [20] proposed that the success of the BNR procedure was highly correlated with glaucoma filtration surgery performed less than 4 months previously. In this study, the time elapsed between previous trabeculectomy and BNR procedure was ranged 4 to 29 weeks and additionally in twelve eyes the time was  $\leq 10$  weeks. Indeed, we achieved success in seven of sixteen eyes and in eight eyes antiglaucomatous medication is needed after the BNR procedure (qualified success). The overall success rate of the BNR procedure in the study was 94%.

Moreover, there may be an eventual decrease in efficiency in the BNR procedure over time. IOP  $> 30$  mmHg before the procedure, high IOP after the procedure, lack of use antimetabolite in previous filtration surgery, type of glaucoma are the risk factors that affect the efficiency of the BNR procedure [22]. Generally, repeated BNR with adjunctive 5-FU provide revive of filtration in dysfunctional bleb and prevent other surgery [23]. Indeed, additional surgery may be needed in some cases. Patients with neovascular glaucoma or secondary glaucoma (uveitic glaucoma, traumatic glaucoma, pseudoexfoliation glaucoma, etc.) constitute a high-risk group. In our study, in one risky eye which had neovascular glaucoma IOP couldn't control with antiglaucomatous medication after the BNR procedure and Ahmed glaucoma valve implantation had to be performed.

## CONCLUSION

In conclusion, despite limitations of this study such as small sample size, retrospective design, and the absence of the control group, the BNR procedure with adjunctive use of 5-FU effectively reduces IOP or decreases the number of antiglaucomatous drugs in patients with encapsulated bleb and it is a simple, effective and repeatable method for the failure of bleb filtration after trabeculectomy.

### Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

### Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

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