

Fibrosis Suppression Therapy in Failed Filtering Blebs After Trabeculectomy: Results of Early Period

Trabekülektomi Sonrası Bleb Yetmezliğinde Fibröz Yanıtı Baskılayıcı Tedavi: Erken Dönem Sonuçları

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ABSTRACT Objective: To evaluate the efficacy of systemic anti-inflammatory fibrosis suppression treatment in patients with early failed filtering blebs after trabeculectomy. **Material and Methods:** Twenty two patients who had systemic anti-inflammatory fibrosis suppression therapy (prednisone 12 mg/day, colchicine 1.5 mg/day and tiaprofenic acid 900 mg/day in 3 doses) because of early bleb failure after trabeculectomy and scored under 6 according to Indiana Bleb Appearance Grading Scale were included in the study. Intraocular pressure (IOP) measurements and bleb scores of them were examined retrospectively before the therapy and weekly for one month after the treatment. **Results:** Medical records of the 8 (36.4%) female and 14 (63.6%) male patients were been evaluated. There was statistically significant difference between IOP values before and at 1-2-3 and 4 weeks after initiation of treatment ($p<0.000$, repeated measure test). We did not determine any statistically significant difference between pretreatment period and 1st week of treatment with regard to bleb scores ($p=0.973$). However; bleb scores of pretreatment period were significantly different from 2nd, 3rd and 4th weeks scores (respectively, $p<0.000$, $p<0.000$, $p<0.000$). IOP decrease and bleb modulation was highly correlated at 2nd, 3rd and 4th weeks (respectively; $r=0.729$, $p<0.000$; $r=0.751$, $p<0.000$; $r=0.864$, $p<0.000$). **Conclusion:** We observed that peroral anti-inflammatory treatment is effective on IOP management and bleb modulation in early postoperative period in our study. We think that it could be an alternative to invasive treatment modalities.

Key Words: Trabeculectomy; glaucoma

ÖZET Amaç: Trabekülektomi sonrası erken dönemde bleb yetmezliği olan hastalarda, sistemik anti-inflamatuar fibröz yanıtı baskılayıcı tedavinin etkisini değerlendirmek. **Gereç ve Yöntemler:** Trabekülektomi sonrası erken dönemde bleb yetmezliği gelişen ve Indiana Bleb Appearance Grading Scale (IBAGS) ölçeğine göre bleb skoru 6'nın altında olan ve sistemik anti-inflamatuar fibröz yanıtı baskılayıcı tedavi (prednison 12 mg/gün, kolşisin 1.5 mg/gün ve tiaprofeniksid 900 mg/günde 3 kez) uygulanan 22 hasta çalışmaya dahil edildi. Göz içi basıncı (GİB) ve bleb skorları, tedavi öncesi, tedavi sonrası 1, 2, 3. ve 4. haftalarda retrospektif olarak değerlendirildi. **Bulgular:** Hastaların 8'i (%36.4) kadın, 14 (%63,6)'ü erkek idi. Tedaviye başlamadan önceki ve tedavi başladıktan sonraki 1, 2, 3. ve 4. haftalardaki GİB değerleri arasında istatistik açıdan anlamlı farklılık vardı ($p<0.000$, repeated measure test). Tedavi öncesi dönem ile tedaviye başladıktan sonraki 1. haftada bleb skorları arasında istatistik açıdan anlamlı farklılık saptanmadı ($p=0,973$). Tedavi öncesindeki bleb skorlarının, tedaviye başladıktan sonraki 2, 3, ve 4. haftadakilerden farklılığı istatistik açıdan anlamlı idi (sırasıyla, $p<0,000$, $p<0,000$, $p<0,000$). GİB azalması ve bleb modülasyonu, 2, 3. ve 4. haftalarda yüksek oranda korele idi (sırasıyla; $r=0,729$, $p<0,000$; $r=0,751$, $p<0,000$; $r=0,864$, $p<0,000$). **Sonuç:** Çalışmamızda erken postoperatif dönemde ağızdan alınan anti-inflamatuar tedavinin GİB kontrolü ve bleb modülasyonunda etkili olduğunu gördük ve invaziv tedavi yöntemlerine alternatif olabileceğini düşünmekteyiz.

Anahtar Kelimeler: Trabekülektomi; glaukom

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Despite new developing techniques trabeculectomy is still the most preferred surgical treatment in glaucoma. Trabeculectomy (TE) was described firstly in 1968 by Cairns, because of low complication rates and successful intraocular pressure (IOP) controlling features, it is still the gold standard in surgical treatment of glaucoma.^{1,2}

Postoperatively extent and quality of wound modulation determine the success of glaucoma filtration surgery. Although most surgeons want uninhibited wound closure and healing, the glaucoma surgeon strives for a controlled and deliberate disruption of the body's natural tendency to create scar tissue after an incision was made. Most often healing of the scleral flap or scarring of the overlying conjunctiva and Tenon's capsule cause failure of the filtering blebs created to decrease IOP. Once an initial filtering surgery has scarred down, reoperations are more prone to fail because of more potent scarring response.^{3,4} Surgeons tried to handle with this surgical paradox by agents that modulate wound healing, for decades. TE with antifibrotic agents such as 5-fluorouracil (5-FU) and mitomycin-C (MMC) resulted good IOP decrease and fibrosis suppression response.⁵⁻⁷ Despite all these precautions wound healing response is personal and exaggerated wound healing may cause fibrosis of episcleral tissues even in eyes with low risk and surgery may end up with failure.^{8,9}

Clinical trials showed that steroids, even in massive doses, could not be relied on to give adequate control of bleb inflammation and fibrosis in all cases. Molteno offered to use combination of oral prednisone, fluphenamic acid, and colchicine to prevent bleb inflammation and fibrosis in selected cases after drainage by TE or Molteno implant by that way we can overcome ineffective systemic steroids.^{10,11}

Colchicine is a highly poisonous alkaloid, originally extracted from plants of the genus *Colchicum*. The precise mechanism of action has not been completely established, but it's known that colchicine inhibits microtubule polymerization by binding to tubulin. Tubulin is essential to

mitosis, and therefore colchicine effectively functions as a "mitotic poison".

Tiaprofenic acid is a non-steroidal anti-inflammatory drug (NSAID). It blocks the production of prostaglandin which the body produces in response to injury.

Prednisone is the most commonly-prescribed corticosteroid. Prednisone is a glucocorticoid receptor agonist. It is metabolized in the liver to its active form, prednisolone. Prednisolone crosses cell membranes and binds to specific cytoplasmic receptors with high affinity. The result includes inhibition of leukocyte infiltration at the site of inflammation, interference in the function of mediators of inflammatory response, suppression of humoral immune responses, and reduction in edema or scar tissue. The antiinflammatory actions of corticosteroids are thought to involve phospholipase A₂ inhibitory proteins, lipocortins, which control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotriene.

We aimed to evaluate the efficacy of combined systemic anti-inflammatory treatment in cases with early failed filtering blebs because of fibrosis after TE. We evaluated retrospectively the cases that were treated with systemic anti-inflammatory agents because of early failed filtering blebs after mitomycine combined TE in our clinic.

MATERIAL AND METHODS

We reviewed retrospectively the records of patients with glaucoma who underwent MMC combined TE between years 2007-2009 in our clinic. The medications used for suppression of the bleb vascularization were explained to the patients and those who accepted the fibrosis suppression therapy medication were included to the study. All procedures conformed to the Declaration of Helsinki and ethical committee approval was taken. All trabeculectomies were performed by the same surgeon. Blebs were scored by using Indiana Bleb Appearance Grading Scale (IBAGS) by other surgeon (Table 1, Figure 1).^{12,13} Twenty two (32%) patients whose bleb scores were under 6 and

TABLE 1: Indiana bleb appearance grading scale (IBAGS).

Parameters	Range	Represent	Notes
Height (H)	0-4	Flat (0) to high (4)	
Extent (E)	0-3	<1 h to >4	
Vascularity (V)	0-4	Avascular to extensive	V1=avascular and cystic
Siedel (S)	0-2	S0=no leak, S1=pinpoint leaks, S2=streaming	

treated with anti-inflammatory fibrosis suppressors apart from IOP in early postoperative days (1-7 days) enrolled to our study. Forty seven (68%) patients without failure filtering bleb were excluded from our study. Fibrosis suppression treatment did not been administrated in case or probability of pregnancy.

Age, gender, ocular and systemic diseases (diabetes, vascular disease, hypertension, renal function, respiratory disease, alcoholism, malignant disease, and major illness), best corrected visual acuity (BCVA) measurement, slit lamp biomicroscopy findings, fundus examination with +90 diopter lens, IOP measurements with Goldmann appplanation tonometer and Humphrey visual field analyses of the study patients were evaluated. Anterior segment and filtering bleb were photographed and bleb scores were noted on postoperative 1st day, 3rd day and 1st week. Patients whose bleb scores were under 6 were administrated with systemic anti-inflammatory fibrosis suppression therapy and seen and photographed again at 1st, 2nd, 3rd and 4th weeks. Later period were excluded because the lack of data.

Date of TE, type of anesthesia, surgical technique, intraoperative and postoperative complications and initiation time and duration of systemic anti-inflammatory fibrosis suppression treatment were noted also.

SURGICAL TECHNIQUE

Entry was optimized by a corneal traction suture, and a fornix-based conjunctival flap was created. A large sub-Tenon’s pocket was fashioned with full dissection of normal and anomalous ligamentous attachments. After cauterization of exposed conjunctival vessels 0.4 mg/ml mitomycine was applied for 45 seconds (30-60 sec). The edge of conjuncti-

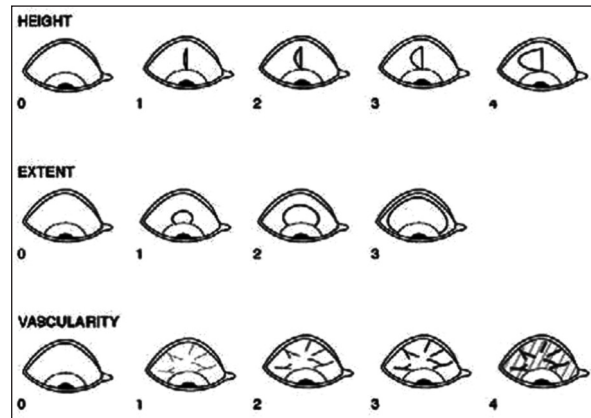


FIGURE 1: Indiana Bleb Appearance Grading Scale (IBAGS).

val wound was protected from contact of antifibrotic throughout the application. Then the area was irrigated thoroughly with 20 to 50 ml of balanced salt solution. A 50% thickness lamellar scleral flap in size of approximately 4x3 mm was created. A paracentesis was performed, and an anterior ostium was formed with a Descemet’s membrane punch, followed by peripheral iridectomy. The edges of the scleral flap were closed with interrupted 10-0 nylon sutures. The conjunctiva and Tenon’s capsule were closed with 10-0 nylon purse-string sutures at either end of the peritomy augmented with central mattress sutures as needed to ensure watertight closure. Subconjunctival antibiotics and steroids were given at the end of the procedure.

All glaucoma medications were discontinued postoperatively and prednisone acetate 1% and ciprofloxacin hydrochloride 0.3% were prescribed 4 times a day for 4-6 weeks. The routine protocol for postoperative follow-up in patients with TE was used. Adjuvant therapies; such as digital massage, argon suturolysis for the tight suture were applied in case of IOP increase.

SYSTEMIC ANTI-INFLAMMATORY FIBROSIS SUPPRESSION

Prednisone 4 mg three times a day (total daily dose 12 mg), Colchicine 0.5 mg three times a day (total daily dose 1.5 mg) and a non-steroidal anti-inflammatory agent called tiaprofenic acid 300 mg twice a day had been prescribed for all cases. An oral proton pump inhibitor (lansoprazole) was prescribed for all patients to protect them from the gastrointestinal side effects of treatment. Treatment protocol was applied for 4 weeks.

STATISTICAL ANALYSIS

Statistical analysis was performed using the statistical package SSPS v.15.0. Pre-treatment and post-treatment measurements were compared statistically by using paired samples t-test. The p values were corrected using the Bonferroni method. Repeated measure test was used for grouped data at different time points. The correlation between IOP and bleb score were statistically analyzed by using Pearson's correlation test. P value >0.05 was considered as statistically significant.

RESULTS

Eight (36.4%) female and 14 (63.6%) male patients with filtering bleb failure after MMC TE enrolled to the study. Mean age was 33±10.3 (28-74) years. Twelve (54.6%) of the study eyes were right, 10 (45.4%) were left eyes. Table 2 demonstrates the distribution of patients according to the glaucoma type. Mean preoperative IOP was 27.2±3.0 (24-32) mmHg. Fourteen (63.6%) of 22 patients had TE

TABLE 2: Types of glaucoma.

Type of Glaucoma	Patients n (%)
Pseudoexfoliative glaucoma	7 (31.8%)
Primary open angle glaucoma	6 (27.2%)
Secondary glaucoma	5 (22.8%)
Primary closed angle glaucoma	4 (18.2%)
Total n (%)	22 (100%)

with antimetabolite. We did not meet any side effect which requires discontinuation of fibrosis suppression treatment.

We observed that failure of filtering bleb occurs in mean 3.9 (3-7) postoperative day after TE with MMC, mean IOP at this time was 25.8±4.5 (19-36) mmHg and the mean bleb score was 3.6±1.1 (2-5) according to IBAGS.

Mean IOP was 21.4±3.3 (16-28) mmHg and mean bleb score was 4±1.4 (1-8) at 1st week under fibrosis suppression treatment. Mean IOP was 17.5±3.9 (10-28) mmHg and mean bleb score was 7.6±2.2 (4-12) at 2nd week under fibrosis suppression treatment. Mean IOP was 17.2±3.9 (12-26) mmHg and mean bleb score was 8.4±2.3 (4-12) at 3rd week under fibrosis suppression treatment. Mean IOP was 17.5±4.7 (12-28) mmHg and mean bleb score was 8.4±2.5 (4-12) at 4th week under fibrosis suppression treatment. Table 3 demonstrates the mean IOP and bleb scores before and after fibrosis suppression treatment. Figure 2 shows appearance of the bleb before and 1 month after fibrosis suppression therapy.

TABLE 3: Mean IOP and bleb scores before and after treatment.

Time with regard to treatment	Mean intraocular pressure (mmHg)±SD	Mean Bleb score±SD
Pretreatment	25.8±4.5	3.6±1.1
1. week	21.4±3.3	4.0±1.4
2. week	17.5±3.9	7.6±2.2
3. week	17.2±3.9	8.4±2.3
4. week	17.5±4.7	8.4±2.5
6. month	15.6±2.3	8.5±2.3
p value*	p<0.001	p<0.001

*Repeated measure test.

Statistically significant p values were written in bold.

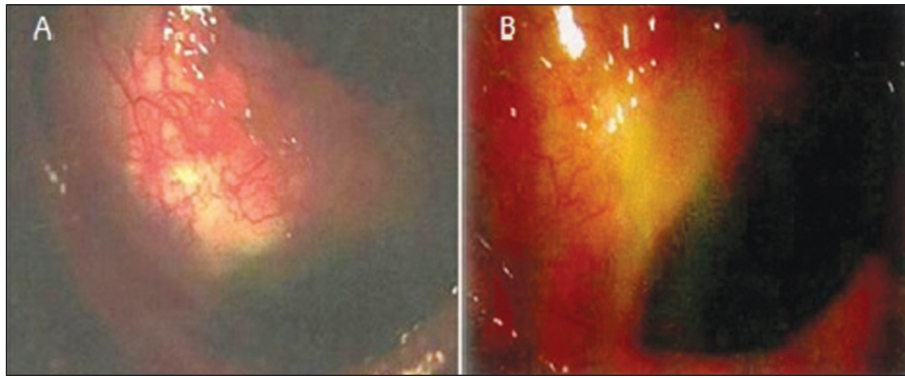


FIGURE 2: Appearance of the bleb before (A) and at 1 month after fibrosis suppression therapy (B).

(See color Figure at <http://www.turkiyeklinikleri.com/journal/oftalmoloji-dergisi/1300-0365/tr-index.html>)

IOP and bleb scores with regard to treatment period were analyzed statistically. There was statistically significant difference between 1st, 2nd, 3rd, 4th weeks and pretreatment IOP values ($p < 0.000$, repeated measure test). Differences between 1st week and 2nd, 3rd and 4th weeks of IOP values were statistically significant (respectively, $p = 0.025$, $p = 0.011$, $p = 0.025$). IOP values of 2nd week did not show any significant difference from 3rd and 4th weeks (respectively, $p = 1.000$, $p = 1.000$) There was no significant difference of IOP values between 3rd week and 4th week ($p = 1.000$). This findings show that decrease of IOP begins with the beginning of the treatment and it slows down on 3rd week.

We did not determine any statistically significant difference between pretreatment period and 1st week of treatment with regard to bleb scores ($p = 0.973$). Bleb scores of pretreatment period were significantly different from 2nd, 3rd and 4th weeks scores (respectively, $p < 0.000$, $p < 0.000$, $p < 0.000$). Also when compared with bleb scores of 1st week, scores of 2nd, 3rd and 4th weeks scores were significantly different (respectively, $p < 0.000$, $p < 0.000$, $p < 0.000$). There was no significant difference between bleb scores of 2nd week and 3rd and 4th weeks (respectively $p = 0.737$, $p = 0.737$). Similarly bleb scores of 3rd week were not significantly different from 4th week scores ($p = 1.000$). It means that bleb modulation at 1st week was not prominent though it is notable at 2nd week and slowed down at 3rd week. Table 4 and Table 5 demonstrate statistical analysis of the mean IOP and bleb scores with regard to treatment period.

TABLE 4: Statistical analyze of intraocular pressure values with regard to treatment period (Paired samples t test; p values were corrected using the Bonferroni method).

	1. week	2. week	3. week	4. week	6. month
Pretreatment	p=0.005	p<0.001	p<0.001	p<0.001	p<0.001
1. week	*	p=0.025	p=0.011	p=0.025	p<0.001
2. week	*	*	p=1.000	p=1.000	p=0.016
3. week	*	*	*	p=1.000	p=0.043
4. week	*	*	*	*	p=0.023

Statistically significant p values were written in bold.

TABLE 5: Statistical analyze of bleb scores with regard to treatment period (Paired samples t test; p values were corrected using the Bonferroni method).

	1. week	2. week	3. week	4. week	6. month
Pretreatment	p=0.973	p<0.001	p<0.001	p<0.001	p<0.001
1. week	*	p<0.001	p<0.001	p<0.001	p<0.001
2. week	*	*	p=0.737	p=0.737	p=0.064
3. week	*	*	*	p=1.000	p=0.518
4. week	*	*	*	*	p=0.257

Statistically significant p values were written in bold.

IOP decrease and bleb modulation was not correlated at 1st week ($r = 0.322$, $p = 0.143$, Pearson's correlation analyze). IOP decrease and bleb modulation was highly correlated at 2nd, 3rd and 4th weeks (respectively; $r = 0.729$, $p < 0.000$; $r = 0.751$, $p < 0.000$; $r = 0.864$, $p < 0.000$).

We observed statistically significant IOP decrease at 2nd week and bleb modulation between 2nd

and 3rd weeks in patients whom treated with fibrosis suppression treatment due to failure of filtering bleb.

The effect of the glaucoma type on bleb success had not been evaluated statistically because of small sample size.

DISCUSSION

Conjunctival and episcleral fibrosis has remarkable effect on the prolonged success of TE procedures.^{8,14} Needling revision of blebs with antifibrotic agents has been suggested to be ineffective method for reestablishing the filtration pathways and improving the function of failed or failing blebs.¹⁵⁻¹⁷ Subconjunctival injection of 5-FU is administered traditionally as an adjunct after the needling procedure and successful revisions of blebs have been reported.^{15,17-19} However, repeated injections and needling are often necessary to achieve a successful outcome.²⁰ Repeated interventions have significant problems such as frequent hospital visits and potential risk of serious ocular complications, like corneal epithelial toxicity to 5FU, endophthalmitis and ocular pain.²¹

Many studies claim that variations of conjunctival wound placement and flap size and shape do not substantially affect the final outcome of TE.²² With MMC, early bleb leaks are more critical with fornix-based flaps, whereas late bleb leaks and infection are more common with limbus-based flaps.²³ Before the introduction of antimetabolites, the conjunctival flap used to be fornix-based before the introduction of antimetabolites, then it was more commonly limbus-based to reduce the risk of leaks, and recently it tends to be fornix-based again to enhance posterior aqueous diffusion. MMC, is very common and increases the tonometric success of TE but also the rate of postoperative complications, unless it did not used with accurate technique.

New wound-healing modulators under clinical investigation for TE are anti-vascular endothelial growth factor (VEGF) agents and collagen matrix implants (OloGen), but the latter did not show significant advantages in a pilot study.²⁴

Ozgonul et al. showed that post-operative subconjunctival injection of bevacizumab is more effective than intravitreal bevacizumab or subconjunctival 5-FU injections for bleb survival in an experimental TE model.²⁵ Arslan et al. found that topically administration of Tacrolimus and Octreotide effectively reduced the subconjunctival scarring response 2 weeks after experimental glaucoma filtration surgery.²⁶ In a comparative study with Interceed and Surgicel, Akyol and Akpolat²⁷ observed that both these agents seem to suppress vascularization but they have no significant effect on fibroblast proliferation. In our study, we studied the effect of oral steroid, nonsteroid antiinflammatory drug (NSAID) and Colchicine on bleb vascularization. We observed that this treatment is effective on bleb modulation in early postoperative period.

When IOP elevated after failed TE, digital ocular massage and laser suture lysis may be performed.²⁵⁻²⁷ The next intervention is a minimally invasive reparative surgery of the filtering bleb by transconjunctival needle revision in case of ineffectivity.^{23,24,26} Finally, if filtration is still inadequate, an invasive reparative surgery of the filtering bleb or another filtering procedure at a new location may be required.^{25,28,29}

Bleb appearance is related with intraocular pressure control, but overall success of glaucoma surgery depends on more than just the final intraocular pressure.^{20,30} Other factors such as bleb-related complications are also important and this recognition has generated increasing interest in quantifying and recording bleb characteristics. The grading scales described by Picht and Grehn, the Indiana Bleb Appearance Grading Scale (IBAGS), the Moorfields Bleb Grading System (MBGS) and Wuerzburg bleb classification score enable recording and encoding bleb appearance.^{12,31-33} The MBGS and the IBAGS are the most recent. We used IBAGS for scoring blebs and prescribed fibrosis suppression treatment for bleb scores under six.

The deficiencies of our study are not to involve a control group and the shortness of follow-up pe-

riod because of the missed data of long term follow-up.

We observed that peroral anti-inflammatory treatment is effective on IOP management and bleb modulation in early postoperative period. We think that it could be an alternative to invasive treatment

modalities. However, we think that this treatment may be effective on long term period, because it's well known that postoperative wound healing slows down after 1 month and this study shows that wound healing modulation with fibrosis suppression treatment in first postoperative month is considerable.

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