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ORIGINAL PAPER

Initial trabeculectomy with 5-fluorouracil with or without subconjunctival bevacizumab in the management of pseudoexfoliation glaucoma

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Abstract

Purpose To investigate the outcomes of trabeculectomy with 5-fluorouracil (5-FU) with or without subconjunctival bevacizumab in the surgical management of pseudoexfoliation glaucoma (PXG).

Methods This retrospective study consisted of 49 cases with PXG who underwent initial trabeculectomy with 5-FU. The cases were divided into two age- and sex-matched groups. In 23 cases, subconjunctival bevacizumab was injected (1.25 mg/0.05 mL) at the end of the surgery and in 26 of them the surgery was performed without bevacizumab. The groups were evaluated for the postoperative differences of the intraocular pressure (IOP) and the number of the anti-glaucomatous medications. Independent *t*, Kolmogorov–Smirnov and Chi square tests were used for statistical analysis.

Results The mean preoperative IOP was 30.91 ± 4.50 mmHg under the mean number of 2.4 ± 0.7 drops in bevacizumab group. The IOP decreased to 10.22 ± 2.63 mmHg (first week), 10.91 ± 1.88 mmHg (first month), 12.35 ± 2.5 mmHg (3rd month), 12.65 ± 2.35 mmHg (sixth month) and 12.7 ± 1.9 mmHg at the final visit. The mean preoperative IOP was 31.27 ± 5.60 mmHg under the mean number of 2.3 ± 0.7 drops in without bevacizumab group. The IOP decreased to 10.08 ± 2.59 mmHg (first week), 11.00 ± 1.87 mmHg (first month), 12.81 ± 2.04 (3rd month), 13.62 ± 2.21 mmHg (sixth month) and 12.9 ± 2.4 mmHg at the final visit. In both groups, IOP reduced significantly postoperatively. There were no significant differences between the preoperative and the postoperative IOP values.

Conclusion The additional benefit of single dose of intraoperative bevacizumab was not observed in trabeculectomy with 5-FU in PXG.

Keywords Trabeculectomy · 5-Fluorouracil · Subconjunctival · Bevacizumab

Introduction

Pseudoexfoliation glaucoma (PXG) is one of the most common types of glaucoma and is more progressive than primary open-angle glaucoma (POAG) [1, 2]. It is frequently associated with higher intraocular pressure (IOP) values and fluctuations than POAG [1, 2]. In case of inadequate profits of medical anti-glaucoma treatment, various types of surgical treatment modalities including trabeculectomy with antimetabolites like mitomycin C (MMC) or fluorouracil (5-FU) can be performed [3].

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Postoperative excessive scarring is known to be one of the most important risk factors for trabeculectomy failure, and antimetabolites are frequently used intra- and postoperatively to reduce tenon fibroblastic activity [4, 5]. MMC has been reported to be more effective in achieving long-term lower IOP control in spite of more side effects like bleb-related infections [4, 5].

Anti-vascular endothelial growth factor (VEGF) agents are increasingly used in ophthalmology for especially age-related macular degeneration (AMD) and other retinal disease those induce neovascularization and macular edema [6, 7]. In these kinds of diseases, their inhibition effects of vasculogenesis and angiogenesis are at the forefront [6, 7]. But these agents also have anti-fibroblastic activity [8–10]. VEGF receptors have been shown to be expressed in tenon fibroblasts [8] and upregulation of VEGF after trabeculectomy can stimulate fibroblastic proliferation [8–10]. These agents have also shown to stimulate TGF-β1 expression and myofibroblast transformation [10]. These have been used in glaucoma filtration surgery because of their anti-fibroblastic activities.

Bevacizumab (Avastin®) is used in the treatment of many types of malign diseases and is a recombinant humanized antibody that binds to all types of VEGF [11]. The aim of this study was to investigate the additional benefit of single dose of subconjunctival bevacizumab on the outcome of trabeculectomy with 5-FU in the surgical management of PXG.

Materials and methods

We included 49 eyes of 49 cases of PXG to this retrospective clinical trial. All of the cases had been under control in Glaucoma department of Ulucanlar Eye Research Hospital and had trabeculectomy because of inadequate control of glaucoma between May 2014 and August 2016 in spite of maximal medical anti-glaucoma treatment. Our study was approved by Ethics Committee of Ankara Numune Training Hospital. All of the study procedures were conducted in accordance with the Declaration of Helsinki, and informed consents were taken from all of the participants.

The demographic and clinical characteristics were taken from the medical records of the patients. Best-corrected visual acuities with Snellen charts, anterior and posterior segment examinations, IOP measurements with Goldmann applanation tonometer, central corneal thickness measurements by ultrasonic pachymeter, visual field examinations with Humphrey automated perimeter (Humphrey Field Analyzer; SITA Standard 24-2 strategy, model 750i; Zeiss-Humphrey Instruments, Dublin, CA), gonioscopic examination by Goldmann 3-mirror lens and retinal nerve fiber layer (RNFL) analysis by spectral-domain optical coherence tomography have been done for the decision of surgery. The presence of advanced glaucomatous visual field defects like arcuate, double arcuate, central, paracentral scotomas, central or temporal island with an IOP $\geq$ target pressure in spite of maximum-tolerated medical treatment and optic nerve head changes like cup-to-disk ratio $\geq$ 0.6, generalized neuro-retinal rim defects, peripapillary choroidal atrophy or splitter hemorrhage were the main indications for the surgery. The presence of pseudoexfoliation material on the surface of the lens and/or pupillary margin following pupillary dilation in addition to glaucomatous findings revealed PXG. We excluded the cases who were younger than 40 years of age, who had narrow-angle (< grade 2 according to Shaffer grading system), who had other types of glaucoma other than PXG and who had a history of any ocular trauma, surgery, uveitis or who had early trabeculectomy complications like flat anterior chamber, hyphema, hypotony (< 5 mm Hg) or hypertony (> 21 mm Hg) and inflammation.

According to their medical records, all the eyes had been operated by the same surgeon (Dr. UE) under subtenon anesthesia. After a fornix-based conjunctival flap, a merocell sponge that had been previously soaked in 5-FU (50 mg/ml) was placed underneath the conjunctival flap for 5 min. After one-third-thickness 5 mm × 5 mm scleral flap and a 1.5 mm × 1.5 mm scleral block, the scleral flap had been sutured by two sutures at the two corners of the flap with 10-0 nylon suture and the conjunctiva had been sutured continuously with 8-0 vicryl suture. In 23 cases (group 1), subconjunctival bevacizumab had been injected (1.25 mg/0.05 mL) at the end of the surgery and in 26 of them (group 2) the surgery had been performed without bevacizumab. All of the eyes had received topical prednisolone acetate 1% for 5 times daily for 8 weeks, moxifloxacin 4 times daily for 1 month and cyclopentolate HCl 1% twice daily for 1 month postoperatively. Ocular digital massage had been

provided in all cases between postoperative 2nd week and 2nd month by training the relatives of the patient.

The patients were evaluated for the postoperative differences of IOP values at the 1st week, 1st month, 3rd month and 6th month postoperatively. Also the IOP, the number of anti-glaucomatous medications and the bleb heights according to Indiana bleb grading system at the final visit were evaluated. Independent *t*, Kolmogorov–Smirnov and Chi square tests were used for statistical analysis. We determined IOP $\leq$ 14 mmHg ($\pm$ medical treatment) as success criteria according to The Advanced Glaucoma Intervention Study (AGIS) criteria [12].

Results

The mean age of 13 male (56.5%) and 10 female (43.5%) cases in group 1 was 67.91 $\pm$ 4.92 (58–75 years), and the mean age of 14 male (53.8%) and 12 female (46.2%) cases in group 2 was 67.92 $\pm$ 4.32 (60–76 years). The differences between the age and sex of the groups were not statistically significant ($p = 0.99$, $p = 0.78$, respectively) (Table 1).

The mean preoperative IOP was 30.91 $\pm$ 4.50 mmHg (24–42 mmHg) under the mean number of 2.4 $\pm$ 0.7 drops in group 1 and 31.27 $\pm$ 5.60 mmHg (23–43 mmHg) under the mean number of 2.3 $\pm$ 0.7 drops in without group 2. There were no statistically significant differences between the preoperative IOP and the number of anti-glaucoma medications between the groups ($p = 0.81$, $p = 0.79$, respectively) (Table 2).

The postoperative IOP values are summarized in Table 2. In both groups, IOP statistically significantly decreased postoperatively at the 1st week, 1st month, 3rd month and 6th month without any anti-glaucoma medications ($p < 0.001$ for all). In group 1, the postoperative IOP values were 10.22 $\pm$ 2.63 mmHg (6–16 mmHg) at the first week, 10.91 $\pm$ 1.88 mmHg (8–15 mmHg) at the first month, 12.35 $\pm$ 2.50 mmHg (8–18 mmHg) at the 3rd month and 12.65 $\pm$ 2.35 mmHg (8–16 mmHg) the sixth month. In group 2, the postoperative IOP values were 10.08 $\pm$ 2.59 mmHg (6–14 mmHg) at the first week, 11.00 $\pm$ 1.87 mmHg (8–14 mmHg) at the first month, 12.81 $\pm$ 2.04 mmHg (9–16 mmHg) at the 3rd month and 13.62 $\pm$ 2.21 mmHg (9–19 mmHg) at the sixth month. There were no significant differences between the preoperative and the postoperative IOP values of the groups within the 6 months (Table 2). In 1 eye in group 1 and 2 eyes in group 2, just one needling procedure had been performed at about 3rd postoperative week. Also 5-FU (5 mg/0.1 ml) was injected subconjunctivally just after the needling procedures. In all of these 3 eyes, IOP was under control after these procedures. There were no statistically significant differences between the rates of bleb failure and the number of needling procedures between the groups ($p = 0.72$).

The mean follow-up period of group 1 was 19.5 $\pm$ 9.1 months (7–37 months), and it was 18.6 $\pm$ 7.1 months (9–38 months) in group 2 ($p = 0.71$). The mean IOP at the final visit was 12.7 $\pm$ 1.9 mmHg (9–16 mmHg) under the mean 0.8 $\pm$ 0.7 drops (0–2 drops) in group 1 and the mean IOP at the final visit was 12.9 $\pm$ 2.4 mmHg (8–17 mmHg) under the mean 1.0 $\pm$ 0.7 drops (0–2 drops) in without group 2. There were no significant differences between the mean IOP and the number of medications between the groups at the final visit ($p = 0.81$, $p = 0.29$, respectively) (Table 2). Also there was no significant difference between the grading scores of the bleb heights at the final visit ($p = 0.66$) (Table 2). Postoperative success according to our criteria was achieved in 20 eyes (87%) in group 1 and in 20 eyes (77%) in group 2 at the final visit (Table 2, Figs. 1, 2). There was no significant difference between the rates of success criteria of the groups ($p = 0365$) (Table 2).

Table 1 The demographic characteristics of the cases

	Bevacizumab group	Without bevacizumab group	*p* value
Sex: (*n*/%)	13 male (56.5%)	14 male (53.8%)	0.78
	10 female (43.5%)	12 female (46.2%)	
Mean age (range)	67.91 $\pm$ 4.92 (58–75 years)	67.92 $\pm$ 4.32 (60–76 years)	0.99

Table 2 The preoperative and postoperative intraocular pressure and the number of anti-glaucoma medications of the groups

	Bevacizumab group	Without bevacizumab group	*p* value
Mean range of preop IOP (mmHg)	30.91 ± 4.5 (24–42)	31.27 ± 5.60 (23–43)	0.81
Mean number of preop medications:	2.4 ± 0.7 drops	2.3 ± 0.7 drops	0.89
Mean range of postop IOP 1st week (mmHg)	10.22 ± 2.63 (6–16)	10.08 ± 2.59 (6–14)	0.852
Mean range of postop IOP 1st month (mmHg)	10.91 ± 1.88 (8–15)	11.00 ± 1.87 (8–14)	0.872
Mean range of postop IOP 3rd month (mmHg)	12.35 ± 2. 5 (8–18)	12.81 ± 2.04 (9–16)	0.482
Mean range of postop IOP 6st month (mmHg)	12.65 ± 2.35 (8–16)	13.62 ± 2.21 (9–19)	0.146
Mean range of postop IOP final visit (mmHg)	12.7 ± 1.9 (9–16)	12.9 ± 2.4 (8–17)	0.81
Bleb height final visit	High: 3	High: 6	0.66
	Low: 6	Low: 6	
	Medium: 14	Medium: 14	
Rate of success criteria at the final visit	20 of 23 eyes (87%)	20 of 26 eyes (77%)	0.365

Preop preoperative, *postop* postoperative

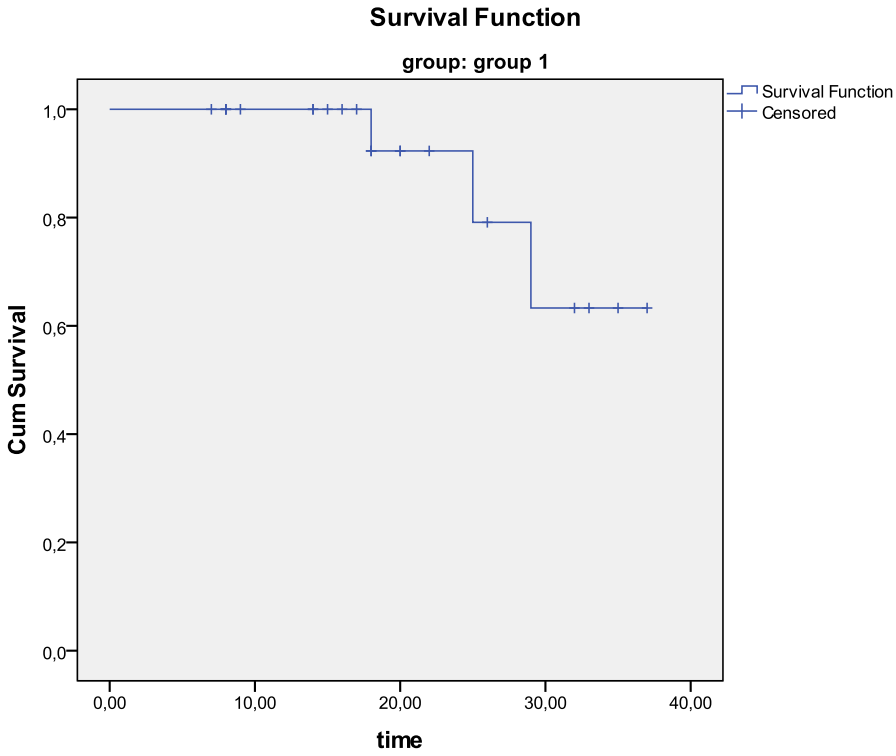

Fig. 1 Survival function of group 1 (with bevacizumab)

Discussion

Tenon fibroblasts are known to be main cells in the regulation of wound healing under the scleral flap after trabeculectomy [4, 5]. Excessive conjunctival and episcleral fibrotic scar formation leads to failure of trabeculectomy and the other bleb-related glaucoma surgeries [4, 5]. MMC and 5-FU are commonly used in order to prevent this fibrosis as pharmacologic enhancement of the surgery, but their side effects including thin avascular bleb and bleb-related infections limit their use [4, 5]. Topical corticosteroid use

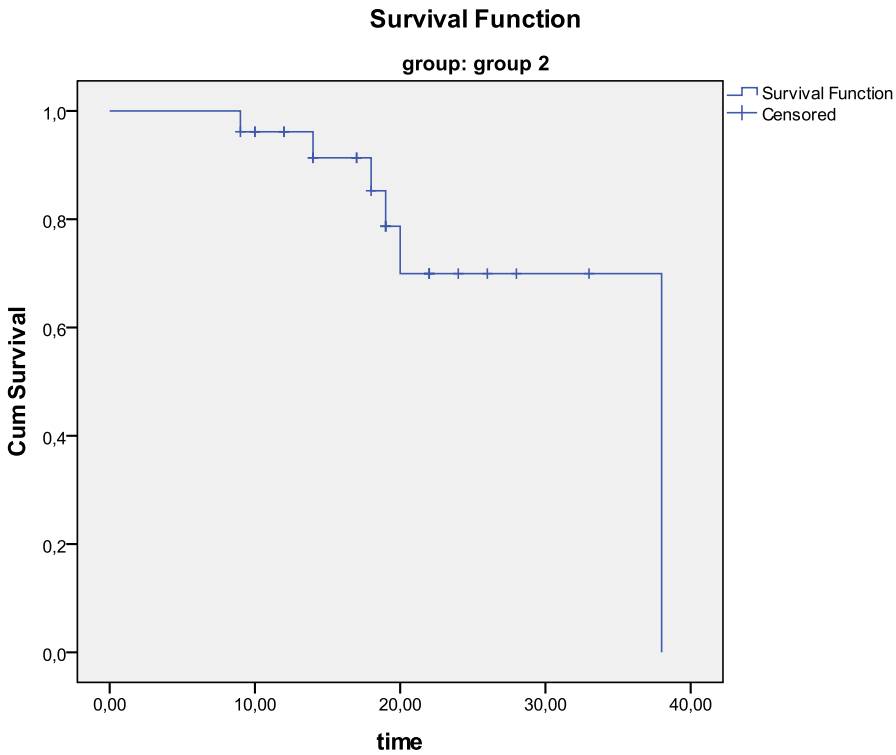

Fig. 2 Survival function of group 1 (without bevacizumab)

also prevents bleb fibrosis and helps bleb survival by inhibiting wound healing [13]. Corticosteroid agents do this action through inhibition of macrophage functions and suppression of phagocytosis and enzymes like collagenase, plasminogen activator and growth factors [13]. Like antimetabolites, side effects of long-term corticosteroid use also limit their use. This fact causes searches for safer procedures and safer modulators of wound healing. Here in this study, we investigated the effect subconjunctival injection of bevacizumab, an anti-VEGF agent, at the end of the surgery on the success of trabeculectomy with 5-FU in PXG cases. We excluded the cases with intraoperative and/or early postoperative complications in order to minimize any other possible factors those might affect the outcomes of the surgery. We thought even a minor complication might adversely affect the outcomes and make difficulties to evaluate the effect of subconjunctival injection of bevacizumab on surgical success.

In addition to their well-known inhibition effects of vasculogenesis and angiogenesis [5, 6], anti-VEGF agents are also known to be having anti-fibroblastic affect in wound healing via stimulating TGF-β1 expression and myofibroblast transformation [8–10]. There are some experimental studies about the association of VEGF and wound healing in trabeculectomy [8, 14, 15]. Li et al. [8] investigated VEGF levels of humor aqueous (HA) after filtering surgery. They found upregulated levels of VEGF of HA in both glaucoma patients and in the rabbit model and observed that bevacizumab had reduced the proliferation of fibroblasts in vitro and improved surgical outcome. Esson et al. [14] found elevated VEGF gene expression the postoperative blebs in a rat glaucoma filtering surgery model. Ozgonul et al. [15] investigated the effect of bevacizumab on wound healing in an experimental trabeculectomy model with the eyes of New Zealand rabbits. They divided the eyes into 4 groups as balanced salt solution subconjunctival injection into the bleb area, bevacizumab subconjunctival injection into the bleb area, bevacizumab injection into the vitreous and subconjunctival injection of 5-FU into the non-bleb area after the surgery. They concluded that subconjunctival injection of bevacizumab into the bleb area was more effective than the other methods in increasing the success of trabeculectomy.

There are also some clinical studies reported before about the anti-fibroblastic effect of anti-VEGF agents in glaucoma surgery like ours. Kiddee et al. [16]

investigated the efficacy of single injection of subconjunctival bevacizumab at the end of the surgery in their primary open-angle glaucoma (POAG) cases who had undergone primary trabeculectomy with MMC. In a 1-year follow-up period, they observed no additional benefit of bevacizumab injection on the outcome of trabeculectomy with MMC. Like Kiddee et al.'s study, we also investigated the efficacy of single injection of subconjunctival bevacizumab at the end of primary trabeculectomy and found no additional benefit of single dose of bevacizumab on the outcome of the surgery. But unlike their study, our cases had PXG and we used 5-FU. Additionally, we evaluated the bleb heights of the groups and found no significant differences. Another important difference was that our mean follow-up period was 19.5 ± 9.1 months in bevacizumab group and 18.6 ± 7.1 months in without bevacizumab group. Suh and Kee [17] investigated the efficacy of bevacizumab on the outcomes of trabeculectomy with 5-FU like in our study. Different from us, they injected 5-FU subconjunctivally at the end of the surgery in all cases and additionally injected bevacizumab both subconjunctivally and intracamerally in some of them. They compared the results of 5-FU injection group and 5-FU + intracameral-subconjunctival bevacizumab group. They observed no significant differences between IOP values like in our study, but they had longer follow-up period as 2 years. There are some studies that have shown the additional benefit of subconjunctival anti-VEGF injection in trabeculectomy with antimetabolites. Freiberg et al. [18] had performed trabeculectomy with MMC in their cases with different kinds of glaucoma including open-angle glaucoma types, primary closed-angle glaucoma and ocular hypertension. They did multiple subconjunctival injections of 5-FU in one group and additionally single dose of subconjunctival bevacizumab in the other group. They stated that injection of bevacizumab reduced the number of subconjunctival 5-FU injections significantly. When compared with topical MMC in IOP control, intraoperative subconjunctival bevacizumab was found to be a safe and effective method but not superior than MMC according to Akkan and Cilsim study [19].

Subconjunctival bevacizumab can also be used after needling procedures postoperatively. Tai et al. [20] compared the results of needle revision with bevacizumab + MMC and MMC alone in failed blebs of trabeculectomy and ExPress implant within the 6 postoperative month. They found greater success rates in bevacizumab + MMC group. They included all types of glaucoma cases in their study. In our previous study, we compared the efficacy and complications of bevacizumab versus 5-FU-augmented bleb needling in failed trabeculectomy and found 5-FU to be more effective [21]. We performed 5-FU-augmented bleb needling at about 3rd postoperative week in 1 eye in bevacizumab and 2 eyes in without bevacizumab groups, and there was no significant difference between the rates of bleb failure. All these 3 procedures were successful to control IOP, and there was no need for additional needling. But we did not use bevacizumab in needling procedures because our aim was to investigate the effect of only single dose of intraoperative subconjunctival injection.

The major reason for similar results of with and without bevacizumab groups in our study was thought to be single injection of the agent. If we had injected bevacizumab several times within the first 2 weeks, we should have significantly different results in bevacizumab group most probably. In an experimental rabbit glaucoma model, a subconjunctival bevacizumab-loaded polyurethane implant was well-tolerated and found to be effective in reducing the number of fibroblasts [22].

As conclusion, trabeculectomy with 5-FU was found to be an effective and safe surgery in cases with PXG in about mean 18-months follow-up period. Though bevacizumab has anti-fibrotic activity according to the previous reports, we observed similar reduction of IOP after 5-FU-augmented trabeculectomy with or without single intraoperative subconjunctival injection of bevacizumab in PXG. However, studies with longer follow-up period and with different types of glaucoma are required in order to demonstrate the long-term results of the anti-fibrotic effects of subconjunctival bevacizumab.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest related to this manuscript.

Ethical approval Our presentation was approved by Ethics Committee of Numune Training and Research Hospital. All of the study procedures were conducted in accordance with the Declaration of Helsinki, and informed consents were taken from all of the participants. This manuscript was presented in

European Society of Cataract and Refractive Surgery Congress, Lisbon, 2017 as a presented poster.

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