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Trabeculectomy with or without Intraoperative Sub-conjunctival Injection of Bevacizumab in Treating Refractory Glaucoma

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Abstract

Purpose: To evaluate the efficacy of intraoperative sub-conjunctival injection of bevacizumab as an adjunct regiem to trabeculectomy for the treatment of refractory glaucoma.

Design: Prospective randomized clinical trial.

Patients and Methods: Fifty-five consecutive eyes scheduled for trabeculectomy were randomly included. In the study group (n= 30), bevacizumab (0.05 ml, 1.25 mg) was injected in the sub-conjunctiva adjacent to the bleb using a 30-gauge needle and tuberculin syringe immediately after the surgery. In the control group (n= 25) surgery was completed without bevacizumab injection. Surgical success was defined as a complete success if the intraocular pressure (IOP) was 21 mm Hg or less with an IOP reduction of greater than or equal to 20% without anti-glaucoma medications. Success rates in both groups were compared using Kaplan-Meier survival curves and the log-rank test. The morphologic characteristics of the filtering blebs were evaluated using the Indiana Bleb Appearance Grading Scale.

Results: Fifty-five eyes completed the study, with a follow-up of 12 months. Complete success rates were 73.3% for the study group and 70.0% for the control group (P=0.67) at 12 months. Reduction in vascularity of the filtering blebs was statistically significant in the study group (P=0.001). IOP measurements and postoperative complications in both groups were not significant at all visits (P>0.05).

Conclusions: Trabeculectomy with intraoperative sub-conjunctival injection of bevacizumab may offer a useful option for improving the outcome of filtering bleb in refractory glaucoma.

Keywords: Bevacizumab; Trabeculectomy; Refractory glaucoma

Introduction

Unlike most surgical procedures, success of glaucoma filtering surgery is achieved through the inhibition of wound healing [1]. The process of wound healing is composed of 2 processes: replacement and regeneration by collagen lay-down from fibroblasts. The initial steps in wound healing are inflammation and coagulation, leading to a cascade of biological events including cellular, hormonal, and growth factor release. These events finally lead to scar tissue formation. To reduce wound healing, mitomycin C is widely used to inhibit fibroblast proliferation in trabeculectomy and it results in relatively avascular filtration blebs with less fibro vascular scarring and an increased success rate [2].However, because of their non-specific mechanisms of action, these agents can cause widespread cell death and apoptosis, resulting in potentially sight-threatening complications such as severe postoperative hypo tony, bleb leaks, and endophthalmitis. Thus alternative antifibrotic agents are needed.

Recent advances in understanding the mechanism of angiogenesis have facilitated the development of new treatment options for neovascular ocular diseases. Neovascularization (NV) occurs as a result of angiogenic stimuli, including the vascular endothelial growth factor (VEGF) [3]. Bevacizumab (Avastin®; Genentech, South San Francisco, CA, USA) is a recombinant humanized monoclonal immunoglobulin G1 antibody that inhibits the biological activity of all VEGF-A isoforms [4]. In the field of ophthalmology, encouraging data from clinical studies involving intravitreal bevacizumab injection to treat age-related macular degeneration, severe proliferative diabetic retinopathy, and iris neovascularization have led to trials involving different routes of bevacizumab administration to treat various eye disorders [5]. Topical or subconjunctival application of bevacizumab was found to be effective for inhibiting corneal neovascularization in both an experimental rat model and in humans [6].

Modulating the wound healing process to lessen scar formation around the scleral flap plays a crucial role in the success of glaucoma filtering surgery. The use of antimetabolites, such as mitomycin C (MMC) or 5-fluorouracil (5-FU), has been widely advocated for trabeculectomy to modulate fibroblast proliferation. A recent pathological study demonstrated that neutralization of VEGF reduced vascularity and decreased scar formation during wound healing, showing that VEGF strongly influenced scar tissue formation [7]. Jonas et al. [8] also showed the efficacy of intravitreal bevacizumab injection as a supplementary procedure in standard trabeculectomy for eyes showing neovascularization or persistent macular edema.. Recently, Grewal et al. [9] showed that 11 of 12 eyes (92%) that underwent trabeculectomy exhibited successful intraocular pressure (IOP) control with sub conjunctival bevacizumab injection.

We conducted this prospective randomized study with the intention to determine whether intraoperative sub-conjunctival injection of bevacizumb during trabeculectomy is an adjuvant procedure for the treatment of refractory glaucoma.

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Patients and Methods

All patients with consecutive uncontrolled refractory glaucoma scheduled for trabeculectomy surgery without phacoemulsification. Patients were randomly allocated into two groups: trabeculectomy with intraoperative sub-conjunctival injection of bevacizumab (study group= 30 eyes) and trabeculectomy without intraoperative sub-conjunctival injection of bevacizumab (control group= 25 eyes). The eyes were randomized after enrollment using computer-generated randomized numbers when they were admitted. Bilateral patients were enrolled in this study separately when they were admitted. No patients were operated bilaterally during one admission.

Patients aged 40 years or older of either gender with uncontrolled IOP, receiving maximum tolerated medical therapy, and requiring trabeculectomy were included.

Exclusion criteria included age less than 40 years; patients were known to be allergic to bevacizumb, patients with medical conditions that could increase the risk of complications, pregnant or breast feeding women, and mental illness or dementia. Signed informed consent was obtained from all patients. The study was conducted in accordance with the tenets of the Declaration of Helsinki (1989) of the world medical association.

Trabeculectomy was performed after the administration of the peribulbar anaesthesia with lidocaine. A fornix-based conjunctival flap was used. Tenon's capsule was gently dissected between the capsule and episclera. Careful hemostasis was performed with bipolar cautery. A half-thickness 4.0 × 4.0-mm rectangular scleral flap was fashioned in the superior area up to the clear cornea. A 4 × 4-mm sponge soaked in a 0.4 mg/ml (0.04%) solution of mitomycin C was applied for 5 minutes beneath the conjunctival and scleral flap, and the area was irrigated thoroughly with 50 ml physiological saline [10,11]. A 3.0 × 4.0-mm-deep sclerectomy was done. The trabeculectomy was followed by a peripheral iridectomy. The scleral flap was sutured with 10-0 nylon mattress sutures (MANI, Tochigi, Japan). Just before closure the conjunctival incision, a 0.05 ml reconstituted bevacizumab (1.25mg) was injected sub conjunctivally adjacent to the bleb using a single-use 30-gauge needle and a tuberculin syringe to the study group. The conjunctiva and Tenon's capsule were closed in a single continuous layer with 8-0 vicryl sutures (Ethicon Inc., Mumbai, India).

The postoperative regimen for all participants included topical 0.5% moxifloxacin hydrochloride (Alcon Ophthalmic Solutions; Inc., Texas, USA) 3 times per day for 1 month, a steroid (1% predinosolone acetate, Predforte; Allergan, Irvine, CA, USA) 4 times per day for 1 month and 2 times per day for 2 months and once daily for 3 months, and cycloplegic eye drops (1% atropine sulphate, Isoptoatropine, Alcon Ophthalmic Solutions; Inc., Texas, USA) 3 times per day for 1 month. Suture lysis was performed after surgery to titrate IOP to the desired level. Anti-glaucoma therapy was added for IOP control when bleb function was inadequate to achieve the target IOP.

Preoperative data obtained for each patient included age, gender, type of glaucoma, number of anti-glaucoma medications, IOP using Goldmann applanation tonometry, and best-corrected visual acuity (BCVA). The primary outcome measures were defined as: 1) complete success, defined as having an IOP of 21 mm Hg or less and an IOP reduction of greater than or equal to 20% without anti-glaucoma medication, and 2) qualified success, defined as having an IOP of 21 mm Hg or less and an IOP reduction of greater than or equal to 20% with anti-glaucoma medication [12,13]. Patients considered to have failed treatment were those requiring additional surgery, including needling, or those with an IOP of more than 22 mm Hg (after the 3-month visit) despite medication.

At each postoperative visit, the examination included measurement of BCVA, IOP, slit-lamp biomicroscopy, Seidel testing, number of anti-glaucoma medications, number of laser suture lysis, presence of complications, and morphologic characteristics of the filtering bleb using the Indiana Bleb Appearance Grading Scale (IBAGS), which is a reproducible system for classifying bleb from a standard photographs (Topcon SL-D7, Tokyo, Japan) with the eye looking inferiorly to display the largest available area of the superior conjunctiva. IBAGS has been described previous [14].

IBAGS Briefly, a set of reference photographs for each parameter on the grading scale is provided to the examiner. Four parameters are scored : height (H) of the bleb, with a scale of HO (flat) to H4 (high); extent (E) of the bleb, with a scale ranging from E0 (less than one clock hour) to E3 (more than four clock hours); vascularity (V) of the bleb, with a scale of VO (avascular) to V4 (extensive vascularity); and leakage assessed by Siedel test, with a scale graded from S0 (no leak), S1 (pinpoint leaks), and S2 (streaming). Postoperative data, collected 1 week, 1 month, 3 months, 6 months, 9 months, and 12 months after surgery.

Statistical analysis

All data were analyzed were performed using SPSS software version 15.0 (SPSS Inc, Chicago, Illinois, USA). Continuous variables were analyzed using the unpaired Student *t* test or paired *t* test as appropriate. The number of preoperative and postoperative anti-glaucoma medications and the number of laser suture lysis were analyzed by Mann–Whitney *U* test between study and control groups. The number of anti-glaucoma medications between before and after trabeculectomy was analyzed by Wilcoxon signed-rank test. The χ^2 or Fisher exact tests were used to evaluate categorical data as appropriate. Kaplan-Meier survival analysis and the log-rank test were used to determine success rates in both groups. P values of less than 0.05 were considered statistically significant.

Results

Fifty-five eyes of 48 patients were enrolled in the study, of which 30 were assigned to receive trabeculectomy with intraoperative sub-conjunctival injection of bevacizumb (study group) and 25 were assigned to trabeculectomy without intraoperative sub-conjunctival injection of bevacizumb (control group). All patients completed the study at the 12-month follow-up visit.

The average age was 62.8±13.5 years in the study group and 60.1±12.8 years in the control group. There were 22 males and 8 females in the study group and 20 males and 5 females in the control group. Preoperative clinical characteristics are presented for both groups in Table 1. There were no significant differences between the both groups in terms of type of glaucoma, number of prescribed anti-glaucoma medications, preoperative IOP, and preoperative BCVA in the log MAR value. The preoperative best corrected decimal visual acuities ranged from 0.05 to 0.16 in the study group and from 0.06 t0 0.18 in the control group.

Mean IOPs for both groups with complete success at all visits are listed in Table 2. Postoperative IOP levels were significantly lower than preoperative levels for the 2 groups at all intervals (P<0.001). IOP measurements did not differ significantly between the groups at any interval.

Parameters	Study Group (n = 30)	Control Group(n = 25)	*P**
Type of glaucoma			
Neovascular	18 (60.0%)	15 (60.0%)	0.53
Post-PKP	2 (6.7%)	1 (4.0%)	
Uveitic	6 (20.0%)	4 (16.0%)	
Post- vitrectomy	4 (13.3%)	5 (20.0%)	
Preoperative visual acuity (logMAR)	0.87 ± 0.53	0.76 ± 0.68	0.36
Preoperative intraocular pressure (mm Hg)	31.36 ±5.48	32.20 ± 8.64	0.35
Number of anti-glaucoma medications	3.2 ± 0.42	3.4 ± 0.63	0.32

LogMAR = logarithm of the minimum angle of resolution,
PKP = penetrating keratoplasty, y = year.
*Significant at P <0.05

Table1: Clinical characteristics of the study and control groups.

Parameters	Study Group (n = 22)	Control Group (n = 14)	*P**
Postoperative visit			
1-month visit	11.5 ± 3.5	10.3 ± 5.3	0.64
6-month visit	11.3 ± 3.5	11.4 ± 3.5	0.64
12-month visit	11.9 ± 5.7	11.2 ± 4.3	0.64

*Significant at P <0.05

Table 2: Mean intraocular pressure (mm Hg) at follow-up postoperative visits of complete success for the study and control groups.

Parameters	Study Group (n = 22)	Control Group (n = 14)	*P**
Height	0.9 ± 0.8	1.6 ± 0.6	0.64
Horizontal extent	1.2 ± 0.6	1.9 ± 0.8	0.73
Vascularity	0.7 ± 0.6	2.1 ± 0.8	0.01
Leakage	0	0	

*Significant at P <0.05

Table 3: Bleb morphologic characteristics (according to the Indiana Bleb Appearance Grading Scale) of complete success for the study and control groups.

Parameters	Study Group (n = 30)	Control Group (n = 25)	*P**
Postoperative complications			
Hypo tony	4 (23.1%)	3 (14.8%)	0.46
Choroidal detachment	2 (7.7%)	1 (3.7%)	0.37
Leakage from suture	2 (7.7%)	3 (18.5%)	0.39

*Significant at P <0.05

Table 4: Postoperative complications for the study and control groups.

Postoperative BCVA at 12 months did not differ significantly between the groups (study group: 0.72 ± 0.63; control group: 0.91 ± 0.60 in the log MAR value, P = 0.62).

The mean number of prescribed anti-glaucoma medications used in the study group dropped from a preoperative mean of 3.2 ± 0.6 to a 12-month postoperative mean of 0.8 ± 1.3 (P <0 .001), and in the control group from 3.2 ± 0.7 to 1.1 ± 1.2 (P <0 .001).

The mean number of argon laser suture lysis was 1.4 ± 1.8 in the control group and 0.4 ± 0.8 in the study group and there was a statistically significant difference between the 2 groups (P = 0.03).

The morphologic characteristics of the filtering blebs of complete success for both groups, defined in terms of the Indiana Bleb Appearance Grading Scale, are shown in Table 3. There was no statistically significant difference between the 2 groups regarding bleb height, extent, and leakage (P >0.5). Vascularity was restricted to the periphery of the blebs and reduced statistically in the study group (P=0.01).

The complications encountered at the postoperative period are listed in Table 4. The most frequent complications were hypo tony (IOP< 6 mmHg) (17 eyes; 12.7%) and micro leakage at the conjunctival suture site (5 eyes; 9.0%). No statistically significant difference was found between the study and control groups about postoperative complications. Hypo tony maculopathy, late bleb leak, bleb-associated infection, and corneal decompensation were not found in any of our patients.

Discussion

Glaucoma implant may fail to achieve the target IOP in refractory glaucoma is most often attributable to excessive fibrosis around the reservoir. However, in many cases with inadequate IOP control following primary glaucoma drainage device implantation, surgical options may be limited to cyclophotocoagulation or placement of a second aqueous shunt. Cyclodestructive procedures destroy the ciliary body because of the risks of uveitis, vision loss, hypo tony, and phthisis [15].

Conventional trabeculectomy is reported to be less successful in eyes that have undergone failed glaucoma surgery or have a disease with poor prognosis such as neovascular or uveitic glaucomas, probably due to the aggressive wound healing process associated with excessive inflammation, adhesion, or angiogenesis [16]. The low success rates of filtering surgery in these eyes have led to investigation of the adjunct trabeculectomy regimen. The use of anti-metabolites (MMC or 5-flurouracil), amniotic membrane, or even photodynamic therapy has been advocated to enhance the surgical outcomes [17].

Angiogenesis, the process of new blood vessel formation, is an integral part in the proliferative phase of wound healing, supplying oxygen and nutrients to support the rapid growth of cell-mediated repair. Wilgus, et al. [18] reported that VEGF promoted angiogenesis and scar formation in early fetal skin and that a VEGF blockade influenced the organization of scar tissue. VEGF neutralization not only reduced the amount of scar tissue formed, but also improved the quality of the scar tissue. Bleb failure was defined as the appearance of a flat, vascularized, and scarred bleb. Bleb failure occurs because of increased vascularization of the conjunctiva with associated migration of fibroblast secondary to cytokines toward the wound healing causing scarring and closure of the fistula tract leading to flap fibrosis. Modifying the wound healing process of the scleral flap upon trabeculectomy could enhance the surgical outcome. The topical and systemic applications of bevacizumab significantly inhibit both inflammation-induced angiogenesis and lymph angiogenesis in the cornea [19]. Reducing the amount of cytokines (e.g., fibroblast growth factor, VEGF) released from the vessels to the site of injury by blocking angiogenesis with bevacizumab may indirectly render the scleral flap less adherent to its original site during the immediate postoperative period, allowing more fluid to drain through the flap. Another possible explanation could be that bevacizumab itself acts on the scleral flap's scar formation directly through fibroblast modulation [18].

Wu et al. [20] recently demonstrated VEGF's ability to induce keloid fibroblast proliferation and suggested the presence of functional VEGF receptors on fibroblasts. A recent study showed that postoperative subconjunctival injection of bevacizumab was associated with improved trabeculectomy bleb survival in the rabbit model, suggesting bevacizumab may be a useful agent for improving the success rate and limiting scar tissue formation after trabeculectomy [21].

Subconjunctival fibrosis, a major cause of inadequate IOP lowering after trabeculectomy, is heralded by increased bleb vascularity. Reduction in bleb vascularity may limit the amount of scar formation. This study illustrates long tem reduction in bleb vascularity following intraoperative sub-conjunctival injection of bevacizumb during trabeculectomy for the treatment of refractory glaucoma

The present study revealed no significant differences between the success rates of trabeculectomy with intraoperative sub-conjunctival injection of bevacizumb or without intraoperative injection within the 12-month follow-up period or postoperative IOP. Additionally, there was no significant difference in the number of complications. However, the number of argon laser suture lysis after trabeculectomy was significantly reduced in the study group versus the control group. It has been reported that eyes that undergo laser suture lysis are more likely to have poorer IOP controls than eyes not requiring laser suture lysis. Bevacizumb may suppress wound healing around the scleral flap and reduce the number of argon laser suture lysis postoperatively.

In the present study, we observed that the bleb height, and extent decreased over a follow-up of 12 months in both groups. Clinically, regression of smaller blood vessels was noted in the study group. After 3 weeks of bevacizumab injection, there was regression of the bleb vascularity. The bleb vascularity started to maintain 4 months after surgery. This might have prevented the development of cystic avascular bleb, that more prone to scarring after glaucoma filtration surgery, despite treatment with anti-metabolites, because they have a central cellular area that may be surrounded by a ring of growth–arrested cells stimulating fibrosis [22]. In addition, reducing doses of prednisolone cover was continued up to 2 months after surgery in the study group.

The success rate of trabeculectomy with mitomycin C for the treatment of neovascular glaucoma at 1 year is reported in about 29% to 67% of cases [23,24]. Our complete success rate for neovascular glaucoma with intraoperative sub-conjunctival injection of bevacizumb was 72.2% (13 eyes) and without intraoperative sub-conjunctival injection of bevacizumb was 66.0% (9 eyes). Our success rate of trabeculectomy with intraoperative sub-conjunctival injection of bevacizumb for the treatment of neovascular glaucoma is better than previously reported, but no statistically significant difference between the success rates of the study and control groups was shown in this study ($P= 0.67$). This result may imply the anti-angiogenic effect of bevacizumb. Sub-conjunctival injection of bevacizumb has the possibility to increase the success rate of trabeculectomy for neovascular glaucoma with its anti-angiogenic effect.

Bevacizumb is an anti-inflammatory drug, so the effect of bevacizumb for filtration surgery seems to be more effective for inflammatory glaucoma such as neovascular glaucoma, uveitic glaucoma, and glaucoma postpenetrating keratoplasty. Bevacizumb may be a useful agent for improving success and limiting scar tissue formation after trbeculectomy.

In conclusion, intraoperative sub-conjunctival injection of bevacizumb for the treatment of refractory glaucoma neither increased the success rate nor decreased postoperative complications of trabeculectomy. This alternative method of bevacizumb application seems to improve the function of the filtering bleb in cases with refractory glaucoma, because it brings rapid resolution of bleb vascularity and control of IOP. Thus blockage of angiogenesis and fibroblast modulation with anti-VEGF agent may provide some benefits for glaucoma filtering surgery.

Declaration of Interest

None of the authors has a financial or proprietary in any material or method mentioned. The authors alone are responsible for the content of the paper.

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