Intraoperative Mitomycin-C versus Bevacizumab on Success Rate of Phacotrabeculectomy

Panahibazaz MR, MD*, 2. Zamani M, MD, 3 Sharifipoor F, MD 4 Khoshnod S, MD, 5 Latifi M, MD

ARTICLE INFO

Article history:
Received 20.01.2014
Accepted 10.03.2015

Keywords:
Bevacizumab, Mitomycin-C, Phacotrabeculectomy

*Corresponding Author
Panahibazaz MR, MD
Jondi Shapoor University of Medical Sciences, Ahvaz, Iran
e-mail: panahibazaz_m@yahoo.com

ABSTRACT

Background and objective: To compare the success rate of mitomycin-C Versus bevacizumab for prevention of bleb failure following phacotrabeculectomy.

Material Methods: In this study 74 eyes of 69 patients with uncontrolled IOP, progressive visual field loss and cataract were randomized in two groups. In the first group, after conjunctival peritomy at the sclera flap site, sponge pats soaked in mitomycin C with concentration of 0.25mg/ml were applied for 3 minutes. In the second group, bevacizumab with concentration of 1.25mg/0.5ml was injected adjacent to the bleb at the end of surgery.

Results: Seventy four eyes of 69 patients including 41 men and 28 women with mean age of 66.92±9.8 years and 64.57±8.8 years in either study group respectively were included. Data, collected from 6 to 12 months after surgery, were analyzed. Mean intraocular pressure in the bevacizumab group was significantly higher than the MMC group (15.91±4.9 mmHg vs 12.76±3.1 mmHg, P=0.001) at 6 months and (15.76±3.26 mmHg vs 13±2.4 mmHg, P=0.003) at the end of 12 months. Bleb characteristics including extension, elevation and vascularity showed no significant difference between two groups. (P values 0.94, 0.93, 0.41 after 6 months, and 0.56, 0.58, 0.89 after 1 year of follow up respectively). One eye in the second group underwent trabeculectomy because of uncontrolled IOP despite using 3 antiglaucoma medications. One eye in each group underwent bleb revision due to failing bleb. No side effects related to the medications were noted in any of the two groups.

Conclusion: Mitomycin C is more effective than bevacizumab for IOP control after phacotrabeculectomy; however, there is no difference between the two agents in terms of bleb characteristics and side effects.

© 2015 FADAK PUBLICATIONS All rights reserved.

Introduction

Glaucoma refers to a group of eye diseases whose main result is optic neuropathy associated with the reduced visual field. IOP is one of the factors causing this disease. Over time, increased intraocular pressure damages neurons and vascular tissue. However, cataract is one of the major causes of blindness and impaired vision in the world and cataract surgery is the only treatment of lens opacity. There are several methods such as Trabeculectomy for creating an aqueous humor outflow to reduce IOP, which was provided by Cairns in late 1960s. The commonest cause of the failure of filtering surgery is the restorative response. After the acute phase of inflammation, angiogenesis and migration of endothelial cells of blood vessels occur in the proliferative phase (days 5 to 14) which are among the factors of bleb failure.

Histological studies have shown that the maximum amplification of subconjunctival Fibroblasts occurs during the days 3-5 following the operation. Many factors including the transforming growth factor, platelet-derived growth factor, fibroblast growth factor and keratinocytes growth factor stimulates the proliferation of Tenon capsule fibroblasts resulting in scarring of the conjunctiva. Factors, such as FU-5 and MMC, that decrease the activity of fibroblasts, help limit scarring. But as these factors increase the adverse effects of chronic Hypotony with Maculopathy, bleb leak, bleb infection and Endophthalmitis, there has been less consideration of replacing them with medications with fewer side effects. Bevacizumab is a blocking factor of vascular endothelial growth and an effective factor in healing and can be considered a counterpart to Mitomycin C with fewer side-
effects in Phicotrabeculectomy surgery. In this study, to prove or disprove this hypothesis, the effects and side effects of Mitomycin C and bevacizumab were compared, the patients were checked for at least one year, and the mean increase in IOP and bleb characteristics were compared according to Indiana Grading Scale.

Methodology

This study was carried out as a clinical trial on 74 eyes of 69 patients suffering from open and close-angled glaucoma. Despite receiving less than 3 anti-glaucoma medications, the intraocular pressure had not been controlled and there were progressive changes in the Glaucomatosis of optic nerve or progressive visual field loss (VF loss). In these patients, the cataract was at the level of nuclear Sclerosis (+3) (NS +3) or (cortical 3+) or opacity of posterior sub-capsule (+2) (PSC 2+) which had caused vision loss and it was predicted that they needed cataract surgery soon after Trabeculectomy operation. Patients suffering congenital glaucoma and youth glaucoma, those who had the history of previous surgery except for YAG laser PI, pregnant and lactating women, eyes with uveitis and other complications of diabetes, and patients with known sensitivity to bevacizumab were excluded from the study. Consent forms were signed by all patients to participate in the study and surgery. The patients were randomly divided into two groups. Mitomycin C (Kyowa; Kyowa Hakko Kogyo co, LTd) was used in the first group after peritomy in the scleral flap graft, and bevacizumab (Avastin; F.Hoffmann-La Roche LTd Basel, Switeland) was used in the second group in the form of sub-conjunctival injection. One site operation was performed under topical anesthesia obtained through local or general anesthesia. A 4-5mm cut was made on conjunctiva and Tenon in the upper quadrant. After making homeostasis in patients of Mitomycin C group, a sponge soaked in Mitomycin C with a concentration of 0.25 mg/ml was placed for 3 minutes in the subconjunctival and Tenon. After removing the sponge and irrigating with 30 cc Balanced Salt Solution (BSS), 3 × 4 mm of the scleral flap was removed. Making an incision in the clear cornea, anterior Capsulorhexis, hydroseduction, and Hydrolination were performed and the lens nucleus was suspended and the cortex contents were removed by aspiration. After placing the hydrophilic acrylic intraocular lens in the capsule bag, 1×2mm of the Trabeculum block was removed and after peripheral Iridectomy, the scleral flap and conjunctiva were stitched with 3 0-10 nylon stitches and nylon thread, respectively. In Group B, all the surgery procedures were the same as those in the patients in Group A without Mitomycin C and in the end, by use of insulin syringe and a needle No 30, bevacizumab with a 1.25 mg/0.05ml concentration was injected next to the bleb. For the prevention of endophthalmitis in both groups, 50 mgs of cefazolin and 2 mgs of dexamethasone were injected in subconjunctival 180° distant from the bleb. Upon examining the day after surgery, ciprofloxacin and betamethasone 0.01 drops began to be used every 6 hours and 2 hours, respectively. Topical antibiotics were stopped after 5 days. Topical steroids gradually decreased to twice a day and were stopped after two months. After the operation, the patients underwent ophthalmologic examination in days 1, 3, 7, 14, 30, 90, 180 and once after every three months in the period under study. In each visual examination, the intraocular pressure was evaluated using a tonometer and considering bleb characteristics including extension and elevation as well as the vessels and was classified on the basis of Indiana Grading Scale. The number and side-effects of IOP-lowering drugs used, the need for post-operative suture removal, or secondary operation were recorded. In the follow-up period, the photographs were taken from the eyes. Results for each of the eyes were statistically analyzed at the end of 6 and 12 months using SPSS version 15. Independent t test was carried out for comparison of means, Chi-square tests for comparison of proportions and Mann-Whitney test for evaluation of bleb characteristics. Signification level of the tests was 0.05%. Using the Chi-square, statistical analysis in the subgroups was done based on the type of glaucoma and its impact on the success rate. The eyes with close and open angle glaucoma were 19 and 18, respectively in Group A and 18 and 19, respectively in Group B. Intraocular pressure less than or equal to 16 mm Hg or a 30% reduction in the initial pressure without medication for at least 3 months after surgery was considered as a treatment success, and the intraocular pressure using topical glaucoma medications for at least 3 months after surgery was considered as a partial success. Intraocular pressure greater than 16 mmHg or no 30% reduction in the initial pressure with or without medication and the need to redo a Trabeculectomy was defined as a treatment failure. Findings

The age mean was 66.92 ± 9.81 in group A (Mitomycin C) (43 to 81 years) and 64.57± 8.81 in group B (bevacizumab) (45 to 79 years)

The mean pre-operative IOP was 20.74 ± 5/53 mm Hg in group A (Mitomycin c) and 23.11± 5/41 mmHg (P = 0.06) in group B (bevacizumab), and the average number of drugs used before surgery in groups A and B was 2.37±0.88 (from 1 to 5 medications) and 2.89±0.84 (from 1 to 5 medications), respectively (P = 0/005). The ratio of cup to disc on the optic nerve head was recorded at 0.83± 0.18 in group A and 0.75±0/21 in group B (P = 0/07). Six months after surgery, the mean intraocular pressure was recorded at 12.76 ± 3.07 mmHg in group A and 15.91 ± 3.07 in group B (P = 0.001); Twelve months after surgery, the mean intraocular pressure was recorded at 13.65 ± 2.48 mmHg in group A and 15.76 ± 3.26 in group B (P = 0.003) (diagram 1). The mean number of medications used in six months in the two groups was 0.24 ± 0.43 and 0.78 ± 1.08 (P = 0/01), respectively. The mean number of medications used in twelve months in the two groups was 0.51 ± 0.69 and 0.92 ± 0.98 (P = 0/04), respectively.

The best corrected visual acuity (BCVA) based on LogMAR unit before operation was 1.36± 0.61 in group A and 1.39 ± 0.58 (P = 0.78) in the group B, and at the end of the study, it was 0.87 ± 0.63 and 0.91 ± 0.43 in group A and B, respectively.

Complete success rate after 6 months was 64.86% in group A and 64.86% in group B; the relative success was 24.32% in group A and 18.91% in group; the failure was 10.81% in group A and 16.21% in group B. At the end of the study, with the minimum follow-up of one year for each of the eyes, the complete success rate after 6 months was 10.81% in group A and 16.21% in group B.
was 56.8% in group A and 43.2% in group B; the relative success was 30.1% in group A and 22% in group; in the same period, the failure was 13.2% in group A and 34.8% in group B.

Diagram 1. Comparison of mean IOP between Group A (Mitomycin C) and group B (bevacizumab) in the period of study

The bleb characteristics regarding the height and size of vessels were compared in the two groups based on Indiana Grading Scale (six months after the operation, the P value was 0.41, 0.93, 0.94 respectively, and at the end of the study, it was 0.89, 0.85, and 0.56 respectively) (diagrams a and b)

Diagram 2. a) Comparison of bleb characteristics such as width, height and vessels between Group A (Mitomycin C) and group B (bevacizumab) after 6 months

Diagram 2. b) Comparison of bleb characteristics such as width, height and vessels between Group A (Mitomycin C) and group B (bevacizumab) after 12 months

Analysis of intraocular pressure in the sub-groups at the end of the study following at least one year based on the type of glaucoma showed that in Mitomycin group, the complete and partial success rate was 89% in eyes with close angle glaucoma (17 eyes from 19) and treatment failure was 10.5% (2 cases); the values in bevacizumab group are 50% (9 from 18) and 50%, respectively (P = 0.01).

The same study showed that in eyes with open angle glaucoma in Mitomycin group, the complete and partial success rate was 83.3% in eyes with close angle glaucoma (15 eyes from 18) and 3 eyes had treatment failure; in bevacizumab group, from 19 eyes, 15 eyes had complete and partial success rate and 4 eyes had treatment failure (78.9% to 21.1%) (P = 0.73).

No side effects associated with drugs (Mitomycin, and bevacizumab) were reported in any of the groups, and none of the patients had postoperative endophthalmitis. One patient in group B (bevacizumab) underwent a new Trabeculectomy surgery as intraocular pressure was not controlled with the maximum medication in day 90 after the initial treatment. Due to the non-formation of the proper bleb after opening the stitches, one eye in group B and one eye in group A underwent bleb restoring surgery in days 21 and 26 after the operation. In 5 patients (3 patients in group A and 2 patients in group B), hypotony and shallow anterior chamber was observed and in 2 of them (one in each group), there was Choroidal effusion which had gradual and spontaneous recovery without surgical intervention. During Phaco-emulsification, 5 patients suffered an outflow of vitreous humor for which anterior vitrectomy was performed (3 eyes in group A and 2 eyes in group B). In 2 patients with Phaco-Trabeculectomy in both eyes, one of the eyes was randomly in group A and the other was in group B. The first patient was a 54-year-old woman whose right eye was in group A and the left eye was in and group B. Before operation, the IOP with 3 medications was 18 mmHg in the right eye and 19 mmHg in the left eye. After the operation, intraocular pressure without medication decreased to 13 mm Hg in both eyes on the day 180 (Figure 1). The second patient was a 53 year-old-woman whose right eye was in group B and the left eye was in and group A. Before operation, the IOP with 5 medications was 48 mmHg in in both eyes. On the day 180 after the operation, the intraocular pressure with 2 medications decreased to 14 mm Hg in the right eye, and without mediation decreased to 12 mm Hg in the left eye.

Discussion

Angiogenesis is a process that plays an important role in wound healing, because achieving many of the factors involved in wound healing is possible through the formation of new vessels. In Trabeculectomy, too, the response of wound healing that is important in the control of intraocular pressure is the aim of many studies. Bleb failure is due to the increase of conjunctival vessels followed by Fibroblasts migration in response to released cytokines through the course of epithelial-scleral wound healing and deep fibrous-scleral layers of Tenon capsule and formation of formation of fibrosis. Scarring in bleb is due to increased fibroblast proliferation and increase of conversion factor B, and collagen production by them. Therefore, control of neo-vascularization as an unfavorable trend after filtering operation has been the aim of many studies. In neo-vascularization, VEGF, preliminary fibroblast growth factor, insulin growth factor, and ocular epithelial growth factor, are the most important factors among which VEGF plays an important role in the proliferative phase of wound healing.

Inhibition of neo-vascularization messages by anti-VEGF factors decreases fibroblast proliferation through affecting cytokines such as and reducing the combined effect of VEGF-A and FGF-2. Accordingly, it inhibits step 2 of wound healing, namely, vascularization and proliferation of fibroblasts. The inhibitory effect of vascularization inhibitors has been confirmed in controlling the proliferation and migration of fibroblasts of Tenon capsules. In previous studies, intravitreal injection of Bevacizumab has been found effective in neo-vascular glaucoma and restoring the failed bleb. Vascularized blebs have poorer prognosis than avascular blebs, which may explain the role of angiogenesis inhibitors in improving diagnosis. According to the literature, the available Anti-Fibrinolytic agents such as Mitomycin C which are now widely used have 70-80% success rates. Scleral cystic blebs are regions without central cell which are surrounded by a ring of cells that have stopped growing. These cells can potentially stimulate fibrosis and predispose the bleb to scarring. According to previous studies, bevacizumab causes an increase of bleb angiogenesis three months after injection and can prevent scleral cystic blebs, which is to be taken into account as benefits of bevacizumab compared to anti-fibrinolytic agents. According to the study done by Grewal et al on 12 eyes, bevacizumab subconjunctival injection near the bleb at the end of Trabeculectomy had success in controlling intraocular pressure in 92% of the cases. The average loss of pressure in this study was 52%.

In a separate study by the same authors, in 5 patients with bilateral Trabeculectomy, subconjunctival bevacizumab was used in one eye at the end of the operation and Mitomycin C was used during the operation. In weeks 1 and 4 after the operation, there were statistically fewer vessels and less bleb width in the eyes for which

DOI: 43
subconjunctival bevacizumab had been injected compared to the eyes treated with Mitomycin C, and the mean intraocular pressure was 14 mmHg in bevacizumab group and 12 mmHg Mitomycin C group. In both of the articles, the authors had concluded that bevacizumab can be substituted for Mitomycin C in the prevention of bleb failure after Trabeculectomy. Although the two recent studies concern Trabeculectomy surgery, regarding the success rate of surgery, it is comparable with our results in the first 6 months after the operation.

In our study, 74 eyes with glaucoma and cataracts were compared in two groups. After 6 months, the mean intraocular pressure in group A (Mitomycin C) was less than that in group B (bevacizumab) and the number of glaucoma medications required to control IOP was significantly more in the bevacizumab group than in Mitomycin C. However, the complete success rate of operation, defined as IOP≤16 mmHg or a reduction greater than 30% without medication, was 64.86% in both groups.

With a longer follow-up as one year for each eye, the success rate decreased to 56.8% in group A and 43.2% in group B with a certain change which was mainly related to changes of increased intraocular pressure in patients with close angle glaucoma, particularly in the bevacizumab group.

In the same group, treatment failure increased from 16.2 to 34.8%. none of the eyes required surgery but the average number of anti-glaucoma medication changed from 0.24±0.43 and 0.78±1.08 respectively in groups A and B following 6 months after the operation to 0.51±0.69 and 0.92±0.98 respectively in the two groups following at least one year of follow-up after the operation for each eye. Statistical comparison of bleb characteristics such as width, height, and angiogenesis does not show a significant difference at the end of a year and the follow-up for each of the eyes in the two groups.

As previously mentioned, a decrease in the size and height was observed in group B and decreased vessel was observed in group A. The decrease in success rate and the change in bleb characteristics through the increase of follow-up have been emphasized in studies of other authors too. Comparison of Mitomycin C and bevacizumab as a medication for preventing or delaying the formation of scar in bleb showed that through a longer follow-up, the stability of the effect of bevacizumab is less than that of Mitomycin C and the potential loss of filtration increases.

This indicates that the medicinal effect of bevacizumab in inhibition of scarring requires further studies on human conjunctival and the dosage of the medication may need to be increased or repeated. In this study, a dosage of 1.25 mg was used. This dosage of the medication in the vitreous causes no side effects and fully blocks VEGF in the vitreous. But it seems that the use of this dosage of medication in PhacoTrabeculectomy requires further investigation. By varying the dosage of bevacizumab, using multiple doses instead of a single dose, and using long-acting forms of the drug, in case of production, there will be the possibility of more comparisons between bevacizumab and Mitomycin C and Trabeculectomy surgery.

References

DOI: 44