COMPARISON OF EFFICACY OF BEVACIZUMAB VS MITOMYCIN-C IN AUGMENTED TRABECULECTOMY

Ophthalmology

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ABSTRACT

Background: Bevacizumab is inhibitor of vascular endothelial growth factor (VEGF), which plays a major role in physiological vasculogenesis and angiogenesis. Currently pegaptanib, ranibizumab and bevacizumab are the monoclonal antibodies used against VEGF.

Aims: To compare the efficacy of subconjunctival bevacizumab to that of subtenonmitomycin-C (MMC) on the wound healing process in trabeculectomy.

Materials and methods: Department of Ophthalmology, Command Hospital (Eastern Command), Kolkata. Patients of Primary Open Angle Glaucoma (POAG). January 2016 – June 2017. Two groups: 30 in each group. (Calculated after assuming α error 0.05, power 80%). Randomization was done using website; www.graphpad.com/quickcalcs/index. Patients were divided in two groups- Group A, who underwent trabeculectomy with mitomycin-C and group B, who underwent trabeculectomy with bevacizumab.

Result & Analysis: In both groups intraocular pressure (IOP) was taken in preoperative, 01 month, 06 month, 12 month and 18 month post operative period. Percentage decrease in IOP from pre-op is studied at 01, 06, 12 and 18 months.

Conclusion: Glaucoma is a leading cause of irreversible blindness throughout the world. It has become the second most common cause of bilateral blindness. Lowering of the IOP is the first priority in POAG with anti glaucoma medications, however if patient's IOP is uncontrolled with maximally tolerated antiglaucoma medications or there is noncompliance to anti glaucoma medications then patients can be planned for surgery to achieve target IOP. Trabeculectomy is the mainstay of surgical management of glaucoma.

KEYWORDS

Bevacizumab, Mitomycin-c, Augmented trabeculectomy.

INTRODUCTION

Glaucoma is defined as a disturbance of the structural or functional integrity of the optic nerve that can usually be arrested or diminished by adequate lowering of intraocular pressure (IOP).¹ The glaucomas have been divided into primary and secondary types. This division is arbitrary and artificial, in that all glaucomas are secondary to some abnormality, whether inherited or environmental. The historical basis for this division was the assumption that the initial events leading to outflow obstruction and IOP elevation in those glaucomas called primary (e.g., open-angle, angle-closure, and congenital) are confined to the anterior chamber angle or conventional outflow pathway, with no apparent contribution from other ocular or systemic disorders.² These conditions typically are bilateral and probably have a genetic basis.

Corticosteroids:

Considerable attention has been given to measures—primarily medication use—that may prevent bleb failure by modulating the wound healing process. The first of these to be used clinically were the corticosteroids. Tissue culture studies of human Tenon capsule fibroblasts have shown that both corticosteroids and nonsteroidal anti-inflammatory drugs inhibit cell attachment and proliferation.³ Clinical investigations have confirmed the efficacy of topical corticosteroids, although no additional benefit was achieved with systemic steroids.

To compare the efficacy of subconjunctival bevacizumab to that of subtenonmitomycin-C (MMC) on the wound healing process in trabeculectomy.

MATERIALS AND METHODS

1. Study area: Department of Ophthalmology, Command Hospital (Eastern Command), Kolkata.

2. Study population: Patients of Primary Open Angle Glaucoma (POAG).

3. Study period: January 2016 – June 2017.

4. Sample size: Two groups: 30 in each group. (Calculated after assuming α error 0.05, power 80%). Randomization was done using

website; www.graphpad.com/quickcalcs/index. Patients were divided in two groups- Group A, who underwent trabeculectomy with mitomycin-C and group B, who underwent trabeculectomy with bevacizumab.

5. INCLUSION CRITERIA

1. Age between 40-80 yr old.
2. Diagnosis of POAG on maximally tolerated medical treatment with uncontrolled IOP or the target IOP not reached.
3. Diagnosis of POAG with intolerance for antiglaucoma medications, noncompliance to anti glaucoma medications.

6. EXCLUSION CRITERIA

1. Angle-closure glaucoma
2. Secondary glaucoma
3. Coexistence of visually disabling cataract and glaucoma requiring combined phacotrabeculectomy
4. History of previous conjunctival surgery
5. History of any previous anti-VEGFs therapy
6. History of any other previous intraocular surgery
7. Any ocular condition that would prevent accurate IOP measurement
8. Active ocular infection or inflammation
9. Patient with uncontrolled systemic hypertension, congestive heart disease, and renal failure or history of systemic thromboembolic disease
10. Known allergy to bevacizumab or mitomycin-C
11. Women of childbearing potential without contraception or actively breast feeding

RESULTS & ANALYSIS

It was found that diagnosed cases of POAG planned for surgery (Trabeculectomy) were enrolled in the study after applying exclusion criteria. The cases were diagnosed clinically based on IOP, visual fields, gonioscopy and optic nerve head analysis by OCT. Thereafter eligible cases were taken up for trabeculectomy. Patients were then divided into 2 groups: group A in which a trabeculectomy with

Mitomycin-C and group B in which trabeculectomy with Bevacizumab was performed. These 60 patients were followed up for 18 months in the post operative period. Each group had 30 patients. In both groups intraocular pressure (IOP) was taken in preoperative, 01 month, 06 month, 12 month and 18 month post operative period. Percentage decrease in IOP from pre-op is studied at 01, 06, 12 and 18 months. In both groups visual field analysis (24-2) done and mean deviation (MD) was taken in preoperative, 01 month, 06 month, 12 month and 18 month post operative period. Percentage decrease in MD from pre-op is studied at 01, 06, 12 and 18 months. In both groups optic nerve head analysis done and retinal nerve fibre layer (RNFL) was taken in preoperative, 01 month, 06 month, 12 month and 18 month post operative period. Percentage decrease in RNFL from pre-op is studied at 01, 06, 12 and 18 months.

Our study found that in both groups bleb morphology was compared as bleb height, bleb extent, bleb vascularity and bleb Seidal's test at preoperative, 01 month, 06 month, 12 month and 18 month post operative period. Percentage change in bleb height from pre-op is studied at 01, 06, 12 and 18 months. In both groups bleb morphology analysis done and bleb extent was measured at preoperative, 01 month, 06 month, 12 month and 18 month post operative period. Percentage change in bleb extent from pre-op is studied at 01, 06, 12 and 18 months. In both groups bleb morphology analysis done and bleb vascularity was measured at preoperative, 01 month, 06 month, 12 month and 18 month post operative period. Percentage change in bleb vascularity from pre-op is studied at 01, 06, 12 and 18 months. Seidal's test was negative pre-operative and post-operative till 18 months in both the groups.

DISCUSSION

Trabeculectomy, with its many modifications, is the most commonly used guarded filtration procedure. Cairns introduced the modern-day trabeculectomy in the 1960s.⁴ It was initially believed that aqueous escaped through the cut ends of Schlemm's canal, but it subsequently became obvious that the major effect of the surgery occurred via filtration of aqueous into the subconjunctival space. The reduced incidence of hypotony and flat anterior chambers made trabeculectomy attractive to glaucoma surgeons.

Fujishiro Tet al⁵ in their prospective interventional study on 27 patients with advanced open-angle glaucoma (OAG) examined them prospectively for 12 months after trabeculectomy. IOP, BCVA and visual fields were the parameter assessed at the end of 12 months after trabeculectomy with mitomycin C. At the end of 12 months mean BCVA (log MAR) showed no significant change during the 12-month follow-up, IOP decreased from 19.7 ± 5.8 to 9.7 ± 2.6 mm Hg ($P < 0.001$) over postoperative 1 year. The slopes of all VF parameters did not significantly differ from zero ($P > 0.33$), and none of the presumed factors significantly correlated with the slopes of those parameters ($P > 0.14$). There were two eyes (7%) and one eye (4%) with ≥ 2 lines of deterioration in BCVA (decimal fraction) at 1 and 12 months, respectively, after surgery with no apparent causes. In our study the mean preoperative IOP in the bevacizumab group improved from 26.4 ± 2.59 mm Hg to 16.40 ± 1.99 mm Hg at one and half year ($P < 0.001$). The mean preoperative IOP in the MMC group improved from 25.33 ± 2.94 mm Hg to 15.8 ± 2.12 mm Hg at one and half year ($P < 0.001$). IOP was comparable between two groups at one year and half year ($P = 0.109$). At the end of 18 months mean BCVA (log MAR) showed no significant change.

Kaushik J et al⁶ studied the efficacy of Bevacizumab compared to mitomycin C modulated trabeculectomy in 27 patients with primary open-angle glaucoma (POAG) prospectively for 12 months after trabeculectomy. BCVA, IOP, Mean no. of medication, bleb morphology and complications were the parameters assessed after trabeculectomy with mitomycin C and bevacizumab. At the end of 12 months mean BCVA (log MAR) showed no significant change. The mean preoperative IOP in the bevacizumab group improved from 22.41 ± 1.08 mm Hg with 3.2 ± 0.9 glaucoma medications to 13.68 ± 0.79 mm Hg with 0.11 ± 0.32 glaucoma medications at one year ($P < 0.001$). The mean preoperative IOP in the MMC group improved from 22.64 ± 0.90 mm Hg with 3.1 ± 0.8 glaucoma medications to 13.84 ± 0.73 mm Hg with 0.17 ± 0.38 glaucoma medications at one year ($P < 0.001$). There were no significant differences found in bleb morphological features according to MBGS in regard to central bleb area, peripheral bleb area, height and central vascularity between the two groups at six months and one year. No significant intraoperative

complications were reported. In our study IOP was comparable between two groups at one year and half year ($P = 0.109$). At the end of 18 months mean BCVA (log MAR) showed no significant change. No significant differences were found in bleb morphological features based on IABGS regarding bleb height, bleb extent, and bleb Seidal's test between the two groups at one month, six month, one year and at one and half year. However, there was a statistically significant difference in bleb vascularity with bevacizumab group exhibiting a low degree of vascularity at one month ($P < 0.001$).

Justyna K R et al⁷ in their study Blebs were evaluated for vascularity by slit-lamp examination with concomitant photographic documentation and intraocular pressure measurement. In their study they found that elevated functional bleb with significantly reduced vascularity was present in 16 eyes, and bleb was flat and nonfunctional in five eyes. Intraocular pressure in all eyes decreased from a mean of 26.6 ± 9.6 mmHg before surgery to 14.6 ± 7.7 mmHg and 15.8 ± 8.3 mmHg at 2 and 6 months after surgery, respectively. Filtration bleb leak was noted in three eyes while on treatment with bevacizumab. The study concluded Topical application of bevacizumab might favor functional bleb formation after trabeculectomy in eyes with a high risk of failure.

Another study by Sengupta et al⁸ which compared the safety and efficacy of 3 subconjunctival bevacizumab injections (1.25 mg/0.05 ml) versus MMC (0.03%) versus bevacizumab soaked sponges (1.25 mg/0.05 ml) in a single-site phacotrabeculectomy on 38 patients of POAG or chronic angle closure glaucoma (CAGC) and found that the subconjunctival bevacizumab was equally effective for short-term control of IOP but has better safety profile than MMC as MMC was associated with more complications than bevacizumab at the follow-up of six months. The success rate for IOP control in subconjunctival bevacizumab group was significantly higher (90%) than MMC group and sponge soaked with bevacizumab group (60% each; $P = 0.04$) in their study.⁷ In our study reduction rate of IOP in subconjunctival bevacizumab group (37.35%) was higher than MMC group (36.84%) at the end of 18 months.

Niloforushan et al⁹ compared the outcome of trabeculectomy with subconjunctival bevacizumab with that of trabeculectomy with MMC in 36 eyes of 34 patients with uncontrolled glaucoma for the period of six months in a randomized controlled trial. They reported that the adjunctive subconjunctival bevacizumab (77.7%) is effective in controlling IOP profile but less effective than that of MMC (88.8%). In our study group reduction rate of IOP in subconjunctival bevacizumab group (37.35%) was higher than MMC group (36.84%) at the end of 18 months and both groups are comparable ($p = 0.109$).

Vandewalle E et al¹⁰ studied the efficacy and safety of a single intracameral bevacizumab injection to improve the outcome of trabeculectomy and 138 patients completed a 12-month follow-up, 69 of whom were in the bevacizumab treated group. IOP at 1 year postoperatively was significantly lower than baseline (placebo: 25.6 ± 9.9 mm Hg vs 11.5 ± 3.9 mm Hg, $p < 0.01$; bevacizumab: 24.8 ± 8.1 mm Hg vs 11.9 ± 3.8 mm Hg, $p < 0.01$), with no difference between treatment groups ($p = 0.69$). Furthermore, per-operative administration of intracameral bevacizumab was reported to be associated with significantly less additional intervention (needling) during the one-year follow-up period in trabeculectomy in a randomized trial of 138 patients with POAG.

Bevacizumab (BEV) was compared with MMC as adjunctive in the needling revision of failed trabeculectomy blebs in a prospective study of 29 patients of failed trabeculectomy by Franco et al.¹¹ Twenty-nine eyes of 29 patients were included: 15 eyes with MMC and 14 eyes with BEV. There was no statistical difference in the IOP reduction between the groups (MMC $32.6 \pm 16.1\%$ vs BEV $30.1 \pm 12.0\%$, $p = 0.6$). The BEV group showed similar reduction in the number of antiglaucoma drugs compared to the MMC group ($p = 0.6$). Absolute success was found in 28.5% of the BEV group and in 6.6% of patients with MMC. Qualified success was found in 64.3% and 73.4%, respectively, both limited to 180 days.

A similar control of IOP and reduction of number of anti-glaucoma medications was noticed in Kidde et al study.¹² In contrast to our study, no benefit of subconjunctival bevacizumab in patients with POAG undergoing trabeculectomy with MMC in a prospective randomized placebo-controlled trial at one-year follow up was noticed.

CONCLUSION

Glaucoma is a leading cause of irreversible blindness throughout the world. It has become the second most common cause of bilateral blindness. Lowering of the IOP is the first priority in POAG with anti glaucoma medications, however if patient's IOP is uncontrolled with maximally tolerated antiglaucoma medications or there is noncompliance to anti glaucoma medications then patients can be planned for surgery to achieve target IOP. Trabeculectomy is the mainstay of surgical management of glaucoma. We have done trabeculectomy in our study cases which was modulated with two different medications. The results were comparable for both study groups.

In conclusion, bevacizumab appears as an effective and comparable to MMC following trabeculectomy at one and half year follow-up in POAG patients. The reduced bleb conjunctival vascularity post bevacizumab augmented trabeculectomy might improve the bleb survival rate at one and half year. However, further study with larger cohort and longer follow-up is needed before shift to bevacizumab from MMC in trabeculectomy.

The small sample size, absence of controls, and short follow-up (one and half year) were the major limiting factors in their study.

Table 4. Change in Intraocular pressure (IOP) and Change in Bleb Extent (in terms of the radial clock face)

	Group A (in mmHg)	Group B (in mmHg)	p-value
Pre operative (baseline) IOP	25.33 ± 2.94	26.40 ± 2.59	0.094
Change in IOP at 01 month from baseline (in %)	-48.01 ± 8.28	-47.26 ± 12.58	0.976
Change in IOP at 06 month from baseline (in %)	-41.06 ± 10.13	-40.41 ± 8.23	0.900
Change in IOP at 12 month from baseline (in %)	-39.94 ± 11.43	-40.76 ± 13.1	0.588
Change in IOP at 18 month from baseline (in %)	-36.84 ± 10.73	-37.35 ± 9.5	0.716
Pre operative	0.00	0.00	1.00
Change in Bleb extent at 01 month from baseline (in %)	+190 ± 30.51	+173.33 ± 44.98	0.098
Change in Bleb extent at 01 month from baseline (in %)	+220 ± 40.68	+230 ± 46.61	0.375
Change in Bleb extent at 01 month from baseline (in %)	+223.33 ± 43.02	+230 ± 46.61	0.563
Change in Bleb extent at 01 month from baseline (in %)	+223.33 ± 43.02	+230 ± 46.61	0.563

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