Original Article

Pterygium Excision with Adjunctive Subconjunctival Bevacizumab

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Purpose: To analyze the efficacy of bevacizumab in primary pterygium excision.

Study Design: Randomized controlled clinical trial.

Place and Duration of Study: Study was done at Shaheed Mohtarma Benazir Bhutto Medical College, Lyari General Hospital, Karachi. Duration of study was six months from 15th October, 2016 to 15th April, 2017.

Material and Methods: 34 eyes of 34 patients (males 22, females 12) with age range from 35 to 60 years (mean age of 45 years SD ± 12.2 years) were included. All patients of primary pterygium were selected and divided into two groups, Group I underwent bevacizumab therapy (0.2 ml which is equal to 5 mg) and Group II placebo (0.2 ml balanced salt solution) given by sub conjunctival injection. After completing all necessary stages of surgery, 0.2 ml (5 mg) bevacizumab was injected in the inferior fornix. All patients were followed for 6 months. Postoperative complications and recurrence were noted. Recurrence was defined as any fibrovascular extension that passed the corneal limbus by more than 1 mm.

Results: The average time for each procedure was 30 ± 10 minutes. During follow up period, the recurrence was noted in 5 patients. 2 eyes out of 17 (11.76%) in group I and 3 eyes out of 17 (17.64%) in group II. Postoperative conjunctival vascularization occurred in 1 patient in group I and 2 patients in group II and subconjunctival hemorrhage occurred in 4 patients in group I and 2 patients in group II while no other ocular complications were observed in any group.

Conclusion: Bevacizumab injection subconjunctivaly showed statistically no significant effect on recurrence of pterygium and having no significant adverse effects.

Key Words: Subconjunctival injection, Bevacizumab, Pterygium Excision.

A pterygium is a triangular fibro vascular sub epithelial ingrowth of degenerative bulbar conjunctival tissue over the limbus onto the cornea". Pterygium typically develops in patients who have been exposed to hot climates, chronic dryness and ultraviolet radiations[1]. The pathogenesis of pterygia is so far not known[2,3]. Various factors such as genetic and many immunological factors play a vital role in the disease progression[4,5].

Jin J et al expressed that pterygium contains increased levels of VEGF and decreased levels of pigment epithelium-derived factor (PEDF) and angiogenic inhibitor. This changed ratio leads to the development of pterygia[6].

The treatment of pterygium is controversial since pterygium is composed of proliferating fibro vascular tissue, its progression requires neovascularization.[7]

Mitomycin-C, 5-fluorouracil, corticosteroids and beta irradiations have been tried along with pterygium excision to prevent recurrence of pterygia[8,9]. In the past, many aseptic techniques were used for removal of pterygium such as horse hair and threads etc[10].

Bevacizumab (Avastin; Roche, USA) is a recombinant humanized monoclonal antibody. It is an inhibitor of VEGF, which interferes with the growth of endothelial cells. This drug has been tried off-label in neovascular ocular diseases with timely good results[11-13].

Bevacizumab pharmacokinetics are quite different i.e. the dose does not cause increase in efficacy but rather it increases its half-life [14]. This was the main reason behind the usage of 5 mg (Bevacizumab 3 times level of normal dose) subconjunctivaly after primary excision of pterygium, as there was altering data regarding its dose, the current study did not observe any local or systemic side effect[15-16].

After extensive literature search, the mechanism of action of bevacizumab in pterygium is not well understood. However, the longest reported duration of action is achieved via intravitreal route[17].

MATERIAL AND METHODS

During the period of 15 October 2016 to 15 April 2017, this randomized placebo controlled clinical trial study was conducted at the Shaheed Mohtarma Benazir Bhutto Medical College Lyari (SMBBMCL) and Sindh Government Lyari General Hospital. Written informed consent was taken from all the patients. 34 eyes of 34 patients were selected and were randomly divided into two groups, Group I (Bevacizumab) and Group II, Balanced Salt Solution (BSS). Pterygium more than 3 mm involving visual axis causing decreased visual acuity or cosmetic disfigurement were included in our study.

Patients with a history of myocardial infarction and vascular thrombosis in the last six months and allergic to bevacizumab were excluded. Patients with diabetes, pregnancy, lactation, glaucoma, regurgitation from lacrimal puncta indicating nasolacrimal duct block, any ocular disease or inflammation, autoimmune disorders and previous eye surgery were not included. Following criteria for bevacizumab allergy assessment was applied.

1. All patients were kept in ward for six hours after procedure for observing blood pressure, hypersensitivity reactions such as localized flushes, urticaria, dyspnoea and angioedema.
2. Hypertension was managed with anti hypertensive e.g. calcium channel blockers after consultation with physician.
3. Emergency trolley containing Inj: Solucortef, Inj: Chlorpheniramine maleate, Inj: Adrenaline, Airway Tube, Ambo bag, I/V Cannula /Normal Saline Drip, Disposable Syringes and Hand Gloves were ready to deal with any emergency.

We recorded all patients' demographic data, best-corrected visual acuity, manifest refraction, keratometry reading, and intra ocular pressure by Goldmann Applanation tonometer, detailed slit lamp examination including horizontal length and grading of pterygium in mm and Fundus examination. All patients were examined before and after surgery on each visit on day 1, 7, 30, 90 and 180. Post injection complications such as sub conjunctival hemorrhage, corneal abrasion infection etc were analyzed if observed.

In both groups, excision of pterygium was done via conjunctival flap method. Group I was injected with 5 mg / 0.2 ml (2.5 mg / 0.1 ml) of bevacizumab and Group II was injected with 0.2 ml of BSS at the end of surgery.

Proparacaine HCl was used as a local anesthetic. Sub conjunctival 2% lidocaine with 1:100000 adrenaline was used in area of pterygium. After completing all necessary stages of surgery, 0.2 ml, (5 mg) bevacizumab was injected in the inferior fornix. Dexamethasone 1 mg and Moxifloxacin 5 mg was given topically QID (Quarter in die) with Hydroxypropyl methyl cellulose QID for 4 weeks.

RESULTS

The Study group comprised 34 eyes of 34 patients (males 22, females 12) with primary pterygium (there were 11 males and 6 females in each group). There was no statistically significant difference regarding the age or gender between the groups ($P > 0.05$). Visual acuity of all the patients in the study after procedure was improved or maintained without further deterioration of vision even in a single patient (Table 2).

The difference between the groups relating to pre operative visual acuity, daily sun exposure, pterygium size and type, keratometric readings or intra ocular pressure was not significant ($P > 0.05$). During follow up period recurrence was noted in five patients, 2 eyes out of 17 (11.76%) in group 1 and 3 eyes out of 17 (17.64%) in group 2 (Table 3).

Postoperative conjunctival vascularization occurred in three patients (8.82%) out of 34 patients (1 in group I and 2 in groups II), which was observed in the recurrent cases. Apart from sub conjunctival hemorrhage which was seen in four patients in group I and two patients in group II, which resolved within two weeks.

Table 1: Demographic data of (34 patients).

		Gender		Eye	
Age	**No. & (%) of Patients**	**Male**	**Female**	**Right**	**Left**
< 45 years	19 (55.8%)	22 (64.7%)	12 (35.3%)	12 (35.3%)	22 (64.7%)
> 45 years	15 (44.4%)				

Table 2: Comparison of the pre-operative and the post-operative visual acuity of 34 eyes studied.

Visual acuity	Pre-operative patients	Post-operative patients
6/6	10	19
6/9	11	09
6/12	08	04
6/18	03	02
6/60	02	00

Table 3: Recurrence of pterygium between two groups.

Groups	Total Patients	Recurrence
Group I (Bevacizumab group)	17	2 eyes (11.76%)
Group II (BSS group)	17	3 eyes (17.64%)

No corneal abrasion, infection, persistent epithelial defect and uveitis were noted after surgery (Table 4).

Table 4: Ocular Complications.

Complications	Group I	Group II	Total
Sub conjunctival Hemorrhage	04	02	06
Conjunctival Vascularization	01	02	03
Ocular Surface Toxicity	00	00	00
Corneal Abrasion	00	00	00
Persistent Epithelial Defect	00	00	00
Infection	00	00	00
Uveitis	00	00	00

DISCUSSION

Fibrovascular proliferation and inflammation play a pivotal role in the pathogenesis of pterygium, which is a degenerative process. The extent and grade of pterygium seem to predict recurrences after surgery quite reliably[18]. Many immunological and genetic factors have been found in the progression of the disease[4,5]. The development of pterygium depends upon the imbalance of angiogenic and anti-angiogenic factors[6]. The findings of abundant levels of VEGF in pterygium may lead to the use of anti VEGF therapy like bevacizumab, in regressing local blood vessels and size of pterygium at a statistically significant level. The therapeutic effects of bevacizumab are not well understood to date mainly due to decrease in sample size and lack of randomized control trials. The present aim of our study is to use anti VEGF therapy in the treatment of primary pterygium in Pakistani population.

However the current study have shown statistically, no beneficial effect of sub conjunctival bevacizumab (2.5 mg / 0.1 ml) on preventing the

recurrence of pterygium in given sample size over six months duration like study done by Razeghinejad MR et al[19]. In this study they used a total of 7.5 mg subconjunctival bevacizumab. 5 mg / 0.2 ml on the day of surgery and 2.5 mg / 0.1 ml on the fourth day after surgery. This is comparable to our study in which we used a total of 2.5 mg / 0.1 ml of bevacizumab for only one time.

Although studies by Rashid Omar et al and Alhammami et al showed that sub-conjunctival bevacizumab reduces size and recurrence rate of pterygium[20, 21]. Like our study, the researchers in their studies did not found statistically significant ocular complications and allergies. Another researcher Oguz et al in his study found decreased recurrence rate of pterygium[22]. Mohammad-Reza et al, in their study found clinically significant effect of sub conjunctival bevacizumab injection on pterygium recurrence but not statistically [23].

The current study as seen in Table 04 did not observe any local ocular complications and allergies statistically like ocular surface toxicity, corneal abrasion, persistent epithelial defect and infection. This was really an astonishing finding in contrast to finding of Kim et al [24], who found spontaneous loss of epithelial integrity in excess percentage. In their study, they used high concentration (1.25%) of bevacizumab topically twice daily for two months. The findings are impactful as it is one time use and less in complications. This clearly indicates that the safety of topical bevacizumab is inversely proportional to the duration of the treatment.

So, from our study it is seen that single per operative subconjunctival injection of bevacizumab can be safely used without significant ocular complications and allergies. It decreases recurrence rate of primary pterygium, but this decrease was not statistically significant.

More over bevacizumab has been observed in six human trials to be safe during subconjunctival administration; it helps in halting fibrovascular proliferative process by stopping G_1 and G_0 phase and initiating apoptosis. Our current study showed effect of bevacizumab on pterygium proliferation and recurrence is not significant statistically.

A recent study demonstrated no recurrence of pterygium in the duration of six years of the subconjunctival bevacizumab injection while in the current we have not observed such finding maybe due to the lesser duration of study. In a study done by Hirst LW et al, he defined the time interval required to follow the patients after pterygium excision to recurrence of the disease should be acceptably one year[25]. In the current study, follow up period was six months.

It is suggested that in future for promising and clarification of results longer follow up and increased sample size is needed.

CONCLUSION

Bevacizumab injection given sub conjunctival, showed statistically no significant effect on recurrence of pterygium and no significant adverse effects.

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