ORIGINAL ARTICLE

Efficacy of sub-conjunctival and topical bevacizumab in high-risk corneal transplant survival

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Abstract

Objective: To evaluate the effectiveness of subconjunctival bevacizumab and topical bevacizumab in preventing neovascularisation on high-risk corneal grafts.

Methods: The randomised, controlled, parallel group study was carried out from February 2008 to April 2012 at Isra Postgraduate Institute of Ophthalmology and Yasin Eye Hospital, Karachi. Eyes with high-risk corneal transplantation with corneal neovascularisation were included in the trial. Patients were randomly allocated to 3 groups: A, B and C. After penetrating keratoplasty, Group A patients received subconjunctival bevacizumab (2.5 mg/ 0.1 ml), Group B, patients received sham injection, while Group C patients received topical bevacizumab (2.5%, 25 mg/ml). It was self-administered 4 times a day for 24 weeks. Group B was the control group. Corneal neovascular invasion area was measured using mathematical software programme Mat Lab. Data analyses were done using SPSS version 19.

Results: Of the total 122 patients, there were 41 (33.88%) each in Group A and B, while Group C had 40 (32.78%) patients. Among the 3 groups, mean corneal neovascular invasion area was minimum in Group A (n=3; 6.23%), while in Group B it was 12.3% (n=5). Group C had the maximum corneal neovascular invasion area after 24 weks (n=11; 26.7%). Maximum number of patients (n=36; 87.80%) attained visual acuity of 6/36 or better in Group A followed by Group C (n=26; 65%) and Group B (n=17; 41.46%).

Conclusion: Subconjunctival bevacizumab reduces the recurrence of neovascularisation and, thus, helps increasing the frequency of graft survival in cases of high-risk corneal transplants. When used topically, it is less effective.

Keywords: Subconjunctival, Topical, Corneal neovascularisation. (JPMA 63: 1256; 2013)

Introduction

Corneal graft failure is one of the most common causes of performing keratoplasty again.[1] When vessels are present on the cornea, the chances of graft rejection are very high, and it is considered a high-risk corneal graft surgery.[2] This high rate of corneal graft failure in cases of vascularised corneas is because after corneal graft these patients can still develop severe immune reaction against the graft and even immunosuppressive therapy cannot help much in such cases.[3]

Several investigations have been carried out to modulate this immune reaction in order to improve keratoplasty results; prevention of further angiogenesis is also one of the areas worked on for this purpose.[4,5] Many molecular factors have been identified in different studies that can be important elements in angiogenesis.[6] One of the factors identified to be among the factors related to neovascularisation is vascular endothelial growth factor (VEGF).[7] Many VEGF inhibitors have been identified and are used for many retinal disorders.[8] One of them is bevacizumab.

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Considering the effectiveness of bevacizumab as an anti-VEGF, it has been investigated as a possible treatment option for neovascularisation on cornea.[9-14] One study carried out on animals showed that when bevacizumab was injected systemically in animals having vascularised corneas before doing keratoplasty, the result was improved survival of corneal graft.[4] It can be assumed that bevacizumab, when used either topically or subconjunctivally, might result in increasing the survival of the corneal graft after keratoplasty by inhibiting the vascularisation on the grafted cornea. Considering these facts, we wanted through this study to assess the effectiveness of bevacizubam in reducing neovascularisation, thus resulting in better prognosis in high-risk cases.

Patients and Methods

The randomised, controlled, parallel group study was carried out from February 2008 to April 2012 at Isra Postgraduate Institute of Ophthalmology and Yasin Eye Hospital, Karachi. Patients were recruited according to the inclusion criteria from February 2008 to September 2011; all the patients were followed up for 6 months after the procedure. Eyes with high-risk corneal transplantation with corneal neovascularisation were included using probability purposive sampling. The sample size was not

calculated but was dependent on the incident of patients presenting with inclusion and exclusion criteria. Ethical approval was taken from the ethical committee of Isra Postgraduate Institute of Ophthalmology. Informed written consent was taken from all participants. Indications for Penetrating Keratoplasty (PKP) were: vascularised leucomas after herpetic keratitis, traumatic keratitis or chemical burn, advanced pseudophakic bullous keratopathy with superficial and deep corneal vascularisation, severe infection in hereditary corneal dystrophy, and failed corneal grafts. Patients were randomly allocated to 3 groups: A, B and C. Group B was the control group as these patients did not receive the drug. Neither the subjects nor the investigators were masked, but those who tested visual acuity, optometrists and statistical analysers were masked regarding the group assignment. Before initiation of the procedure, baseline data was recorded in a proforma. After penetrating keratoplasty, Group A patients were given subconjunctival bevacizumab of dose of 2.5mg/0.1ml which was injected at all the quadrants in each patient at the end of surgery and at followup visits. One or two injections were applied. In Group B, patients were given sham injection at all the quadrants at the end of surgery and at followup visits. One or two injections were applied. In Group C, topical bevacizumab (2.5%, 25mg/ml) was self-administered 4 times a day for 24 weeks. Followup period was 2 to 8 months. In order to reduce effect modifiers during the period, all patients were exposed to similar topical and systemic medications such as systemic steroids and topical steroids according to weight adjustments. Patients were asked to come for followup every 4 weeks from the first post-operative day. On every followup, digital corneal photograph was taken along with the visual acuity. Patients not keeping up with followups were excluded from the study in order to rule out possible confounding variables.

The primary outcome variable was corneal neovascular invasion area, while the secondary variable was change in visual acuity. In order to do the assessment of neovessels on the grafted cornea, a quantitave method was used. Photograph of the corneas after keratoplasty were first taken and then these photographs were processed using different softwares such as Photoshop and MatLab. By using these softwares neovessels on the grafted corneas were identified and the area covered by the neovessels on the grafted cornea was measured. This neovascularised area was calculated as a percentage of grafted cornea covered by the neovessels. Data analysis was done using SPSS version 19. Frequencies of age, gender and groups were calculated. Primary variable, neovascular invasion area, was compared among the 3 groups using Friedman test. The secondary variable, change in visual acuity, was also compared using Friedman test. P value of less than 0.05 was considered significant.

Results

Of the 122 patients in the study, 41 (33.88%) each were in Group A and Group B, Group C had 40 (32.78%). Besides, 87 (71.3%) were males and 35 (28.7%) were females. The

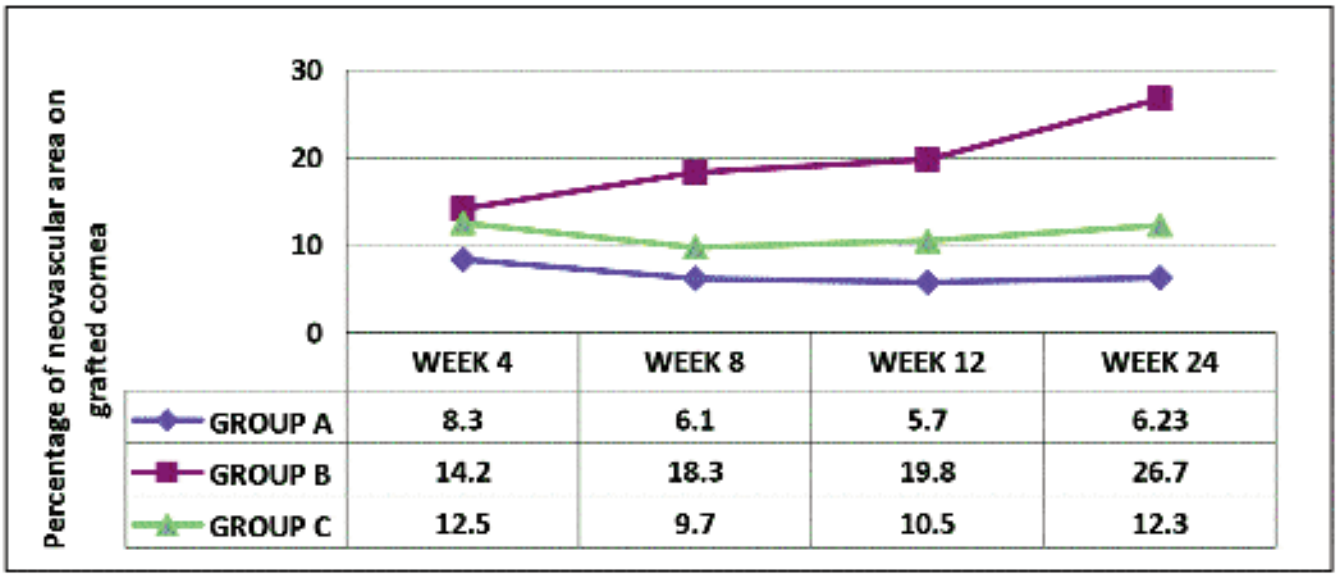

Figure-1: Corneal neovascular invasion area among the three groups.

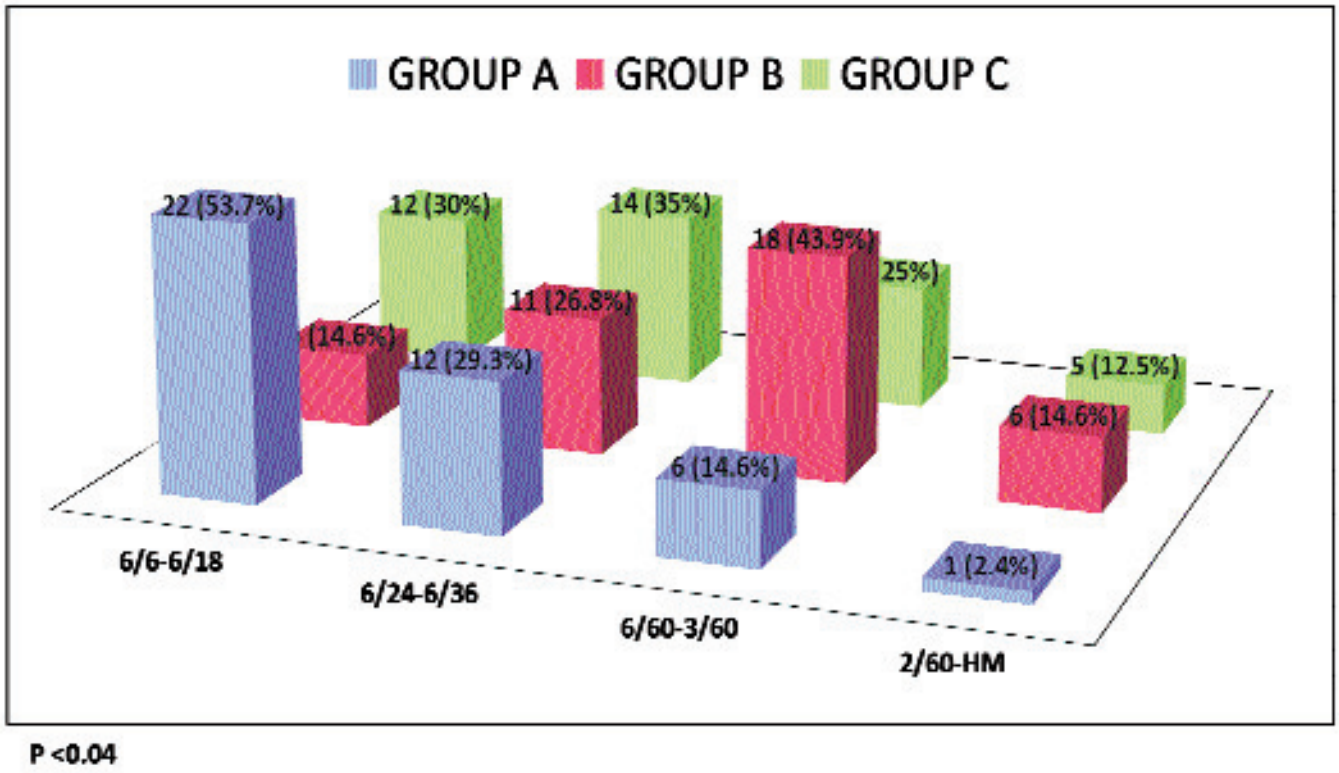

Figure-2: Visual acuity among the groups (N=122).

mean age of the patients was 52.07±5.54 years and ranged between 39 and 67 years.

Among the 3 groups, the mean corneal neovascular invasion area was the minimum in Group A (p <0.03) (Figure-1). Also, 36 (87.8%) patients in Group A attained visual acuity of 6/36 or better, while there were 17 (41.5%) in Group B and 26 (65%) in Group C (p <0.04) (Figure-2).

Discussion

The results of the study showed that bevacizumab, when used either subconjunctivally or topically, resulted in reduction on neovascularisation on the grafted cornea and thus improved the survival of corneal graft after keratoplasty. But on the other hand, it was also noted that reduction of neovascularisation by bevacizumab given subconjunctivally was much better than the bevacizumab given topically. Similarly, bevacizumab given subconjunctivally also resulted in much better corneal graft survival after keratoplasty compared to bevacizumab given topically. One possible explanation to this difference in effectiveness between the two forms of dosing is that the topical route might not be able to gain good penetration when compared to the subconjunctival route. Histology shows the presence of tight junction within the corneal epithelium, which might result in decreased penetration,[15] specially bevacizumab as it is a large molecule (mol. Wt. of 149 kDa).

Several studies have also been performed on bevacizumab when given subconjunctivally for the treatment of corneal neovascularisation not related to keratoplasty, and they have shown extremely promising results in reducing the neovessels on the treated corneas.[11,13,16,17] Although subconjunctival bevacizumab resulted in reduction of neovascularization on grafted corneas after keratoplasty, but it failed to regress it completely, and one possible reason for it is the under-dosing of bevacizumab which needs to be looked for in further studies.[12] Another possibility of failure in complete regression of neovessels is that the vessels that are present before on the recipient bed of the cornea are extremely stable and may be not affected by the anti-VEGF therapy.[18] The presence of other angiogenic factors apart from VEGF might be another reason behind the failure to completely regress the neovessels on the grafted cornea.[6]

Whenever neovessels are present on the cornea, this will result in poor success rate after keratoplasty due to failed corneal graft.[19] The success rate after keratoplasty

improves from 13.3% to 3.5% when keratoplasty is performed in corneas with mild vascular growths on its bed to no vessels on its bed. And it can go further to 28% and 65% when the corneal bed has moderate and severe neovascularisation respectively.[20] In our study, a marked reduction was observed in the corneal grafts after keratoplasty in patients treated with bevacizumab, either topical or subconjunctival, thus resulting in improved survival of corneal grafts after keratoplasty. This effect was more pronounced when bevacizumab was used subconjunctivally rather than topically.

The main limitations of the study were that it was conducted in only 2 centres, thus not much of the variability was available in terms of patients. Both the centres were located in an urban setting, dealing mostly with population of similar ethnic backgrounds.

The main objective of the study was to analyse the effectiveness of bevacizumab in preventing neovessels formation on the grafted cornea in cases of high risks as has been shown in many different studies before in different parts of the world,[10-13] but no such study had been carried out in our community. The results of the current study are very much comparable with those done earlier.[10-13]

Conclusion

Bevacizumab, when given subconjunctivally, can help in increasing the frequency of graft survival in cases of high-risk corneal transplants. When used topically as well, it increases the probability of graft survival, but is not as effective as the subconjunctival route. More studies are needed to further strengthen these conclusions.

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