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Original Article

Role of Intrastromal Bevacizumab in Reducing Corneal Neovascularization in Patients Presenting to a Tertiary Care Hospital in Multan

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ABSTRACT

Objective: To assess the effect of a single dose of intrastromal Bevacizumab on anomalous corneal neovessels in patients with corneal neovascularization.
Study Design: Quasi-experimental study.
Place and Duration of Study: Combined Military Hospital Multan, Pakistan from Apr to Sep 2022.
Methodology: After taking informed consent, up to 0.1ml intrastromal injection of Bevacizumab (25mg/ml) was given to 50 eyes with Grade 3 or Grade 4 corneal neovascularization (The primary outcome measure was to assess the efficacy of a single dose of intrastromal Bevacizumab by assessing the decrease in the area of corneal neovascularization at the end of 6 weeks.
Results: At the end of 6 weeks, regression and downgrading of corneal neovascularization were seen. Of the 23 eyes with Grade 4 corneal neovascularization, 21(91.3%) eyes were downgraded to Grade 3, and two eyes (8.69%) were downgraded to Grade 2. Of the 27 eyes with Grade 3 corneal neovascularization, 25 were downgraded to Grade 2(92.6%), and two were downgraded to Grade 1(7.4%). There was a significant decrease in the area of corneal neovascularization from 2.88±0.50 mm before injection and 1.83±0.54 mm after Bevacizumab (p=0.001).
Conclusion: Intrastromal administration of a single dose of Bevacizumab reduced the invasion area of corneal neovascularization at the end of six weeks. The degree of reduction of neovascularization was also dependent on the Grade of corneal neovascularization. Intrastromal Bevacizumab is an effective treatment for corneal neovascularization with minimum local and systemic side effects.

Keywords: Bevacizumab; corneal neovascularization (CNV); intrastromal injection.

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INTRODUCTION

The cornea is the outermost part of the eye, located anterior to the iris. It is a major contributor to the eye's refractive power, focuses light on the retina, and protects the structures inside the eye from germs, dust, and other harmful matter. Avascularity and transparency of the cornea are vital to normal vision.1

Maintaining corneal transparency and avascularity is highly essential to preserve optimal vision. Cornea maintains its avascularity due to the natural balance in its angiogenic and anti-angiogenic factors.2 Angiogenic factors include essential fibroblast growth factor (BFGF), matrix metalloproteinases, vascular endothelial growth factor (VEGF), and anti-angiogenic factors include pigment epithelium-derived factor (PEDF), angiostatin, resting, and endostatin. In the event of an ocular insult, this balance might be disrupted, which can cause an upregulation of angiogenic factors and/or downregulation of anti-angiogenic factors, leading to abnormal new vessels invading the corneal stroma from the limbus.3 This is known as corneal neovascularization (CNV). The new blood vessels formed can cause lipid exudation, leading to inflammation and scarring of the cornea, thus compromising corneal transparency and, therefore, the patient's visual acuity.4

The most common causes of neovascularization are hypoxic insult from contact lens wear, three traumas, four malignancies, infections, five inflammations, corneal ulcers, chemical burns, and loss of limbal stem cells. 5 Different treatment modalities have been explored for corneal neovascularization, such as topical corticosteroids, fine needle diathermy, six anti-VEGF agents, photodynamic therapy, and laser photocoagulation. 6

VEGF is the most potent angiogenic factor in the neovascularization of the cornea. 7,8 Anti-VEGF drugs target this specific factor. One such drug is Bevacizumab , a humanized monoclonal antibody that prevents all VEGF isoforms from binding to endothelial cell receptors, thus inhibiting angiogenesis. It has been used successfully in age-

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related macular degeneration, nine diabetic retinopathy, and central retinal vein occlusion.9 Bevacizumab has been researched in recent years for the treatment of corneal neovascularization with relative success, and our study aims to report the efficacy of a single dose of intrastromal injection of Bevacizumab in the treatment of corneal neovascularization.

METHODOLOGY

The quasi-experimental study was conducted at Combined Military Hospital, Multan, Pakistan from April to September 2022 after approval from the Institutional Review Board of this hospital (ERC No 51/2022). Non-probability convenience sampling was utilized. Raosoft sample size calculator calculated sample size by taking the population of patients taken to be 50, and the response distribution as 50%.10 Patients were chosen according to the severity of the neovessels. The severity was Graded based on the degree of invasion of neovessels in the cornea from the limbus (Table-I).

Table-I: Grades of Corneal Neovascularization (CNV)

Grade 0	<0.5mm
Grade 1	>0.5 to 2mm
Grade 2	>1 to 2mm
Grade 3	>2 to 3mm
Grade 4	>3mm

Inclusion Criteria: Patients of either gender above 15 years of age presenting in the outpatient department with Grade 3 and 4 corneal neovascularization were included.

Exclusion Criteria: Patients with any active ocular disease, recent ocular surgery, extreme corneal thinning, ischemic heart disease, uncontrolled hypertension, pregnant or lactating women, and history of stroke were excluded.

The history and a thorough ocular examination, including best corrected visual acuity (BCVA), intra-ocular pressure (IOP) measurement, slit-lamp, and fundus examination of the patient, were carried out by the same ophthalmologist and the area of corneal neovascularization was measured on a slit lamp. Written informed consent was taken from all patients before the procedure. Corneal photographs were taken for each case to document the pre-procedure and post-procedure findings objectively.

Using an aseptic technique and under topical anaesthesia, the patients' eyes were given a single dose of intrastromal Bevacizumab by the same ophthalmologist under a surgical microscope. Bevacizumab (25mg/ml) was prepared in an insulin syringe with a 30G needle, and up to 0.1ml (2.5mg) intrastromal Bevacizumab injection was given under topical anesthesia (proparacaine hydrochloride 0.5%) at the site where maximum concentration of neovascularization was present to achieve adequate stromal hydration around the neovessels. The patients were prescribed moxifloxacin eye drops four times daily for one week post-operatively.

Patients were reviewed on day 1 and day 7 to observe for any possible adverse effects, but the final assessment and grading were done at the end of 6 weeks. At each follow-up, the same ophthalmologist gave patients a complete ocular examination, including BCVA, IOP measurement, slit-lamp, and fundus examination. A close eye was kept on any systemic side effects by inquiring the patients about their health and recording their blood pressure. The mean corneal neovascularization area before and after Bevacizumab administration was noted.

Data was analyzed using the Statistical Package for the Social Sciences. Mean and standard deviation were calculated for quantitative variables and frequency and percentages were calculated for qualitative variables. Differences in the mean area of corneal neovascularization before the administration of Bevacizumab and after six weeks were compared using paired t-test. The p-value less than or equal to 0.05 was considered significant.

RESULTS

A total of 50 eyes of 50 patients with Grade 3 and 4 corneal neovascularization were enrolled in our study. Out of the 50 patients, 36 (72%) of the patients were males and 14(28%) of the patients were females. The mean age of the patients was 44.38 ± 10.12 years, with a range of 16 to 64 years. Out of 50 eyes, 23(46%) eyes had Grade 4 CNV and 27(54%) eyes had Grade 3 CNV.

The efficacy of a single dose of intrastromal Bevacizumab treatment was evaluated at the end of 6 weeks by assessing the Grade of corneal neovascularization. Regression and downgrading of corneal neovessels were observed. Out of the 23 eyes with Grade 4 CNV, 21 eyes down Graded to Grade 3 CNV (91.3%) and two eyes down Graded to Grade 2 CNV (8.69%) (Figure-I); out of the 27 eyes with Grade 3 CNV, 25 eyes downGraded to Grade 2 CNV (92.6%) and two eyes down Graded to Grade 1 CNV (7.4%) (Figure-II).

The area of CNV significantly decreased from 2.88±0.50mm before injection to 1.83 ± 0.54 mm after Bevacizumab (p=0.001) (Table-II).

Table-II: Comparison of Mean Area of Corneal Neovascularization Before and After Administration of Intrastromal Bevacizumab (n=50)

	Before Administration of Intratromal Bevacizumab (Mean±SD)	After Administration of Intratromal Bevacizumab (Mean±SD)	*p*-value
Mean Area of Corneal Neovascularization	2.88±0.50mm	1.83±0.54 mm	0.001

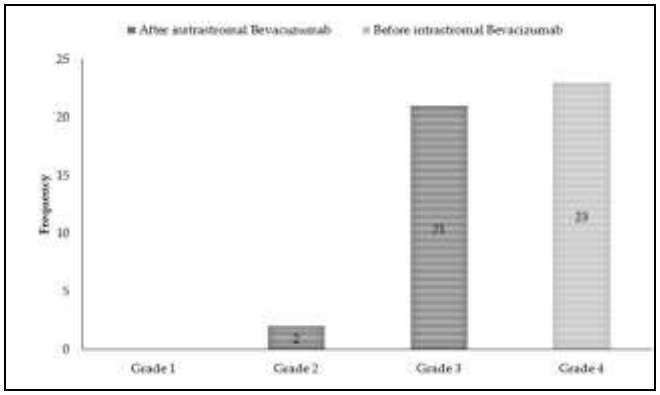

Figure-I : Reduction of Grade Severity in Patients with Grade 4 Corneal Neovascularization

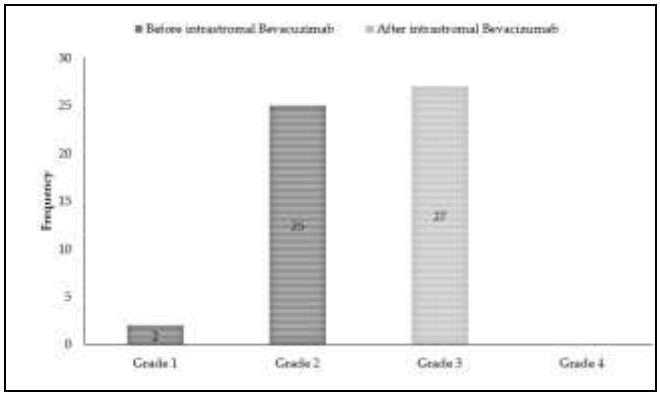

Figure-II: Reduction of Grade Severity in Patients with Grade 3 Corneal Neovascularization

DISCUSSION

Corneal neovascularization is a vision-threatening condition for which various medical and surgical treatment options have been explored. Apart from anti-VEGF treatment, none target the specific molecular mediators of angiogenesis.

VEGF is secreted in response to any ocular injury by the different cellular components like corneal endothelium, fibroblasts, macrophages, and limbal vascular endothelial cells into the cornea. 11 VEGF enhances the proliferation, migration, and invasion of endothelial cells. It regulates angiogenesis and vascular permeability by activating two receptors, VEGFR1 and VEGFR2.8. Bevacizumab binds to all VEGF isoforms and prevents VEGF from binding to these receptors, thus inhibiting vascular permeability and angiogenesis.

Various other drug administration approaches of Bevacizumab have been researched with some success, like topical administration12 and subconjunctival administration. 13 The disadvantage of topical administration is the low penetration and absorption of the drug through the intact epithelium because of the high molecular weight of Bevacizumab 14. There is also the added issue of patient compliance when instilling drops in the eye as prescribed. Subconjunctival administration of Bevacizumab has been linked with side effects such as thinning of corneal epithelium and conjunctiva.15, 16, 17 This route of administration also allows only limited duration of action within the cornea and has been shown to have limited effect on mature neovessels.18

In contrast to the above-mentioned modes of administration of Bevacizumab, intrastromal administration is effective in causing regression of mature neovascularization. This could perhaps be due to less rapid clearance by the normal limbal vasculature and a resulting longer duration of action.19 The injection procedure itself causes minimal discomfort to patients and appears to be associated with minimal systemic risk.

Our study on intrastromal administration of Bevacizumab has shown regression and downgrading of corneal neovessels after a single dose of injection. All the patients completed their follow-up with no reported systemic side effects, and no local side effects such as thinning of cornea or conjunctiva were observed. Our study results are complimented by various studies published since 2008 outlining the success of intrastromal Bevacizumab in treating corneal neovascularization. All these studies have shown partial to complete regression of corneal neovascularization with low complication rates.20-23

A single-center retrospective series by Gupta et al. noted the effects of intrastromal Bevacizumab on 14 eyes of 14 patients with chronic deep corneal

neovascularization. 14.2% of eyes had complete regression of neovascularization, avoiding the need for future corneal transplants. Persistent neovascularization was noticed in 21.4%. Minimal adverse effects were noted: temporary epithelial defect in two eyes and self-limited intrastromal hemorrhage in one. No neovascularization or graft rejection recurrence was seen in the transplant group (mean follow-up 3 years).20

Yeung et al. examined twelve eyes of twelve patients, all receiving intrastromal and subconjunctival Bevacizumab. At an average follow-up of 6.4 months, all twelve eyes achieved corneal neovascularization regression, although this was only partial.21 Similar to our study, all eyes had a very low side effect profile, further highlighting the safety of ISB.

Vieira et al. examined six eyes of six patients - five patients exhibited corneal neovascularization regression at a mean follow-up of 8.47 months. Only intrastromal Bevacizumab was used in their study. No adverse effects were noted.22

Sarah et al. examined 25 eyes of 22 patients with corneal neovascularization who received intrastromal Bevacizumab, with two eyes also receiving subconjunctival Bevacizumab . No significant side effects were noted in their cohort; 15 of 25 eyes achieved total regression, five partial, and three did not respond.23

Ranibizumab is another anti-VEGF agent used to reduce corneal neovascularization. Studies have shown that topical ranibizumab has better drug penetration and a better effect on corneal neovascularization than topical Bevacizumab because of its significantly lower molecular weight.24 However, only Bevacizumab is used in our setup because of its cost-effectiveness and the prevalence of patients with low socioeconomic status.

In recent years, a combination of two treatments has also been researched for corneal neovascularization. Studies report the effect of combined treatment with anti-VEGF and fine needle diathermy. 17, 25 Diathermy is used to occlude the limbal feeding vessels. The results showed a significant reduction in corneal neovessels, but 21.4% of patients had corneal hemorrhage compared to 4% subconjunctival hemorrhage in our study.

LIMITATIONS OF STUDY

One of the limitations of our study is that the grading of severity of corneal neovascularization was done by the degree of invasion of neovessels in the cornea from the limbus and did not indicate vessel density or area/quadrants of cornea involved. Our study does not record the effect of repeated doses of Bevacizumab injection, which may be required to eliminate corneal neovascularisation, as we aimed to assess downgradation rather than complete regression after a single dose. A longer follow-up time could help us record the long-term efficacy of Bevacizumab on complete regression of corneal neovascularization and side effects.

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CONCLUSION

Intrastromal administration of a single dose of Bevacizumab reduced the invasion area of corneal neovessels at the end of six weeks. The degree of reduction of neovascularization was also dependent on the Grade of neovascularization. Intrastromal Bevacizumab is an effective treatment for corneal neovascularization with minimum local and systemic side effects.

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Authors Contribution

Following authors have made substantial contributions to the manuscript as under:

KA & MKN: Conception, study design, drafting the manuscript, approval of the final version to be published.

SMM & MR: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

DJ & MW: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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