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Case Report

Bi-weekly Subconjunctival Injection of Bevacizumab for Corneal Neovascularization after Burn Injury

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Purpose: We report two cases of corneal neovascularization (NV) after burn injury successfully treated by subconjunctival bevacizumab injections at 2-week intervals.
Case summary: Three bi-weekly subconjunctival injections of bevacizumab were administered to two patients with corneal NV after burn injury. In our first patient, corneal NV was markedly reduced by bevacizumab injection. The patient exhibited with a clear cornea and improved visual acuity (20/30) after treatment. Eleven weeks after the last injection, the cornea remained clear, with clinical regression of smaller vessels; the improvement in visual acuity was maintained. In the second case, the diameter of the vessels, hemorrhagic lesions, and corneal edema decreased/regressed, with improvement of the visual acuity to 20/25; these improvements persisted for 12 weeks after the last subconjunctival injection.
Conclusions: Our results suggest that bi-weekly subconjunctival injection of bevacizumab is well-tolerated and effective for inhibiting chronic corneal NV after burn injury.
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Key Words: Bevacizumab; Burn; Neovascularization

INTRODUCTION

Corneal neovascularization (NV) is a major cause of diminished corneal clarity, which reduces vision.[1] Corneal NV can occur in response to a wide variety of insults, including infection, inflammation, ischemia, degeneration, trauma, and loss of the limbal stem cell barrier. This can lead to tissue scarring, edema, lipid deposition, and persistent inflammation, which may be associated with significant visual impairment, penetrating keratoplasty and a poor visual prognosis.

With recent advances in our understanding of the cornea at the molecular level, it is now known that an avascular state in the cornea is maintained by the balance between angiogenic and antiangiogenic factors at the limbus.[2] Corneal NV results from a shift toward angiogenic factors. Vascular endothelial growth factor (VEGF) is one of the most important regulators of corneal angiogenesis. Thus, VEGF suppression could inhibit corneal NV, thereby improving vision and the likelihood of transplant survival.[3]

Bevacizumab is a recombinant humanized monoclonal antibody against VEGF that neutralizes all isoforms of human VEGF.[4] Bevacizumab was originally approved for the treatment of metastatic colorectal cancer; however, intravitreal bevacizumab has been used off-label for the treatment of neovascular ocular diseases. Promising results have been achieved using topical and subconjunctival bevacizumab to treat corneal NV with various etiologies, such as pterygium, lipid deposits, and herpetic keratitis.[5] However,

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questions remain regarding the optimal timing, interval, and dose of bevacizumab for treating corneal NV.

The present study reported two cases of NV after burn injury successfully treated by subconjunctival bevacizumab injected at 2-week intervals. To our knowledge, no previous reports have focused on either the interval of injection of bevacizumab in burn patients, or the treatment outcomes.

CASE

Case 1

Patient 1 was a 65-year-old man with second- and third-degree acid burns on both arms and legs, and the face (to 8% of the body surface area). At the first ophthalmologic examination, his best-corrected visual acuity (BCVA) was 20/100 in the left eye, and the intraocular pressure (IOP) was 10 mmHg in the left eye. The anterior chamber was deep and clear. The conjunctival and corneal findings were ischemia and epithelial defects in the inferior region, respectively. There were no abnormalities of the lens, vitreous, or fundus. The injury to the left eye was grade IV according to the classification of Dua et al.[6] Both eyes were treated four times a day with 0.5% levofloxacin eye drops and 0.1% fluorometholone solution. The administration of 0.1% sodium hyaluronate ophthalmic solution every hour continued even after the anterior eye findings had resolved.

After 2 weeks, the pain returned. Clinical examination revealed cicatricial ectropion of the lower lid of the left eye, with lid margin keratinization, tarsal scarring, and some symblepharon formation. The BCVA in the left eye was 20/100. Slit lamp examination of the left eye showed superficial corneal NV between the 6 and 9 o'clock positions along with corneal edema, peripheral epithelial defect, and severe conjunctival hyperemia (Fig. 1A)

A single dose of 2.5 mg (0.1 mL) of bevacizumab was injected into the subconjunctival area, 1-2 mm behind the limbus near the corneal NV. He underwent three consecutive subconjunctival injections of bevacizumab in the left eye at bi-weekly intervals (Fig. 1A-C). Topical bevacizumab was reapplied after 2 months. The epithelial defect of the conjunctiva resolved 30 days after the start of treatment. The corneal epithelial defect resolved on day 20.

Two weeks after the last bevacizumab treatment, slit-lamp examination of the left eye showed a clear cornea. The corneal NV was markedly reduced, and the BCVA had improved to 20/30 (Fig. 1D). Eleven weeks after the last injection, the cornea remained clear, with clinical regression of the smaller vessels. The improvement in visual acuity was maintained (Fig. 1E).

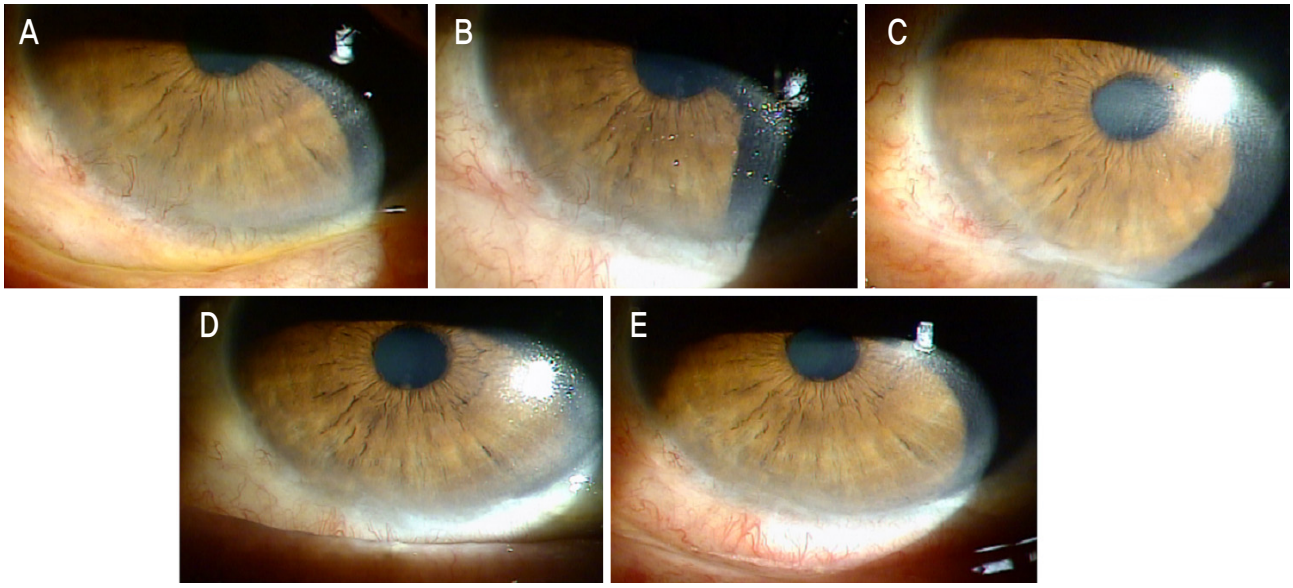

Figure 1. Photograph of the anterior segment of the eye of the first patient (chemical burn). (A) The eye before subconjunctival bevacizumab injection (0 weeks). (B-D) The eye at 2, 4, and 6 weeks after the first injection, respectively. The patient received 3 bi-weekly injections (at 0, 2, and 4 weeks). (E) Neovascularization of the cornea gradually regressed during the injection period and the cornea remained clear 11 weeks after the last injection.

Case 2

The second case was of a 45-year-old man with a scald burn on his face and ocular trauma to his right eye, caused by plastic debris expelled from a high-temperature steam compressor. At the first ophthalmologic examination, his BCVA was 40/100 in the right eye, with an IOP of 15 mmHg. Slit-lamp examination revealed many foreign bodies in the conjunctiva, diffuse and superficial corneal punctate epitheliopathy, and corneal edema. He underwent several procedures for foreign body removal and symblepharon lysis and was treated with 0.5% levofloxacin eye drops every 6 hours and 1% prednisolone eye drops every 12 hours. A therapeutic soft contact lens was fitted for epithelial healing of the cornea. After 1 week, the BCVA was 20/30 in the right eye, and the IOP was 17 mmHg. Slit-lamp examination showed a large (7-mm-diameter), round inferior epithelial defect, with circumferential thinning of the cornea and Descemet's membrane. Topical bevacizumab was reapplied after 3 weeks. The corneal epithelial defect resolved 30 days after treatment initiation.

In this patient, corneal thinning and the large epithelial defect diminished. However, superficial NV of the cornea developed in the area of concern. There was no response to a single subconjunctival injection of dexamethasone and 1% fluorometholone eyedrops four times a day during the 2-month treatment period (Fig. 2A). The patient was informed about the potential risks and benefits of off-label use of bevacizumab. A subconjunctival injection of 2.5 mg (0.1 mL) of bevacizumab was administered to the right eye at 2-week intervals, and treatment with 0.5% levofloxacin eye drop treatments was maintained. After three consecutive injections, residual blood vessels persisted; however, the diameter of the vessels, hemorrhagic lesions, and corneal edema had regressed, with improvement in the visual acuity to 20/25 (Fig. 2A-D). These improvements persisted for 12 weeks after the last subconjunctival injection (Fig. 2E).

DISCUSSION

Subconjunctival bevacizumab can successfully treat corneal NV in both animals and humans.[5,7] In animals, VEGF inhibition reduces corneal NV and improves corneal graft survival. Previous results of subconjunctival bevacizumab for ocular surface NV have been promising; however, the reported outcomes have been somewhat variable, and corneal NV is still the most common undesirable outcome of burn injury.

The concentration of bevacizumab in the anterior segment of rabbit eyes reached its maximum at 1 week after subconjunctival administration, and the half-life was less

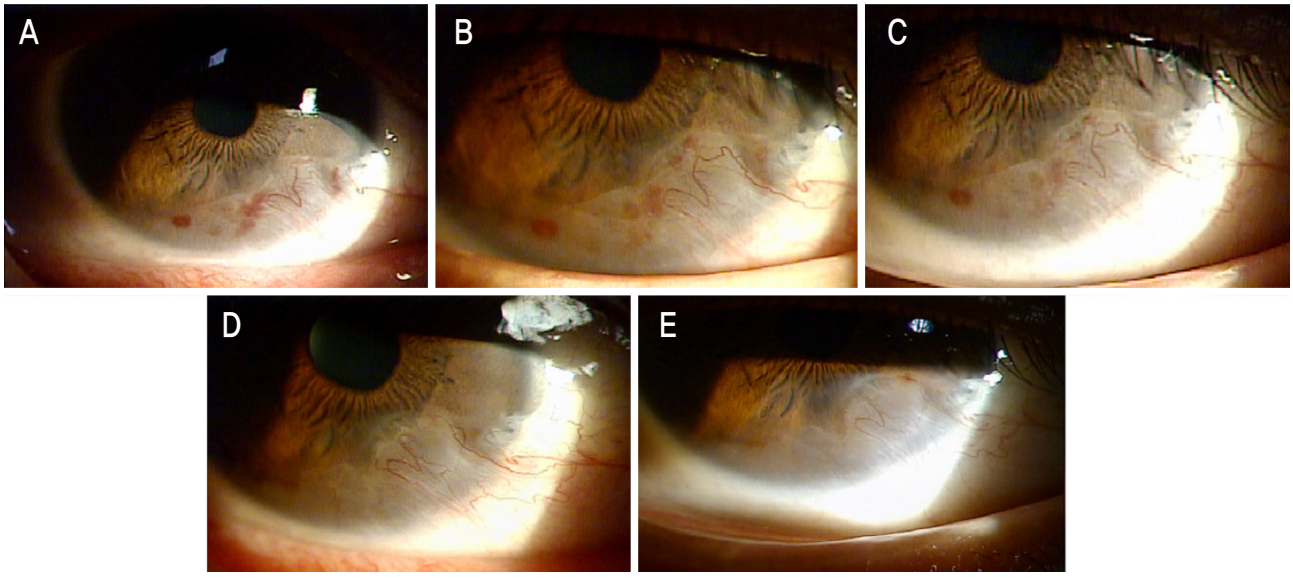

Figure 2. Photograph of the anterior segment of the eye of the second patient (scald burn). (A) The eye before subconjunctival bevacizumab injection (0 weeks). (B-D) The eye at 2, 4, and 6 weeks after the first injection, respectively. The patient received 3 bi-weekly injections (at 0, 2, and 4 weeks). (E) The diameter of the neovascular vessels and hemorrhagic lesions of the cornea regressed gradually over the injection period, and the cornea remained clear 12 weeks after the last injection.

than 2 weeks.[8] An optimized treatment regimen is one of the most important factors for achieving good outcomes when using bevacizumab to treat corneal NV; however, previous studies have not considered this in detail. In a report of three patients with corneal vascularization who had undergone penetrating keratoplasty within the previous 7 months, regression of the vessels was observed after the injection; this effect peaked at 1-week post injection, but the vessels rapidly returned over the following 2 weeks.[9] This finding is similar to results reported in burn patients, whereby initial success was followed by rapid regrowth of vessels; thus, it seems that a single injection is unlikely to have lasting benefits in cases of chronic corneal vascularization after burn injury.[10,11] The effects of bevacizumab are often transient, owing to the short half-life of the drug, and treatment often needs to be repeated.[11,12] Thus, bi-weekly subconjunctival injection of bevacizumab has been used. Faramarzi and Feizi[13] evaluated the efficacy of subconjunctival injections of bevacizumab (2.5 mg/0.1 mL), at 2-week intervals, for the treatment of ocular surface squamous neoplasia, and reported decreased size and vascularity of lesions. Nava-Castañeda et al.[12] obtained promising results in patients with corneal pterygium recurrence after three injections administered at 2-week intervals. Following this preliminary study, we administered bi-weekly subconjunctival injections of bevacizumab in patients with corneal NV after burn injury. Regression of vessels was seen after three injections, along with improved visual acuity; these effects were maintained for 3 months after the last injection.

The severity of corneal burn is determined by the degree of limbal stem cell damage. Severe injury to these stem cells can lead to apoptosis.[14,15] When anti-angiogenic factors inherent to the corneal epithelium are missing, the cornea repairs itself in an abnormal manner via the conjunctival epithelium, thus becoming vascularized.[14,15] Therefore, when the burn affects the limbus of the cornea, subconjunctival injection of bevacizumab can reduce corneal NV.

Hurmeric et al.[16] designed an animal study to compare the effects of bevacizumab injected immediately versus 3 days after injury. With immediate injection, better anti-angiogenic responses were achieved.[16] Also, subconjunctival bevacizumab injection has a greater effect on new than old or stable vessels.[7] This may be because bevacizumab occludes new vessels. Thus, we recommend immediate subconjunctival injection of bevacizumab in patients with corneal burns.

Mello et al.[17] demonstrated that subconjunctival administration of bevacizumab efficiently reduces corneal NV, without inducing persistent epithelial defects in cases of chemical burns. In our study, no serious side effects were observed. However, delayed corneal epithelial healing was described in a previous study with higher doses of topical bevacizumab.[18] Thus, there is a possibility of severe local side effects, such as loss of epithelial integrity or progression of thinning, when high or multiple doses are used. As such, care should be taken when using high-dose bevacizumab or a frequent administration schedule.

Although our results were encouraging, better outcomes would likely have been achieved if conjunctival bevacizumab had been injected at the first visit. Also, as the regression of corneal vessels is clinically important, it should be studied in a randomized clinical trial with a larger sample size and longer follow-up. In conclusion, bi-weekly subconjunctival injection of bevacizumab was used in this study for treating patients with corneal NV after burn injuries. The data indicated that subconjunctival injection of bevacizumab is well-tolerated and effective for inhibiting chronic corneal NV.

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