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JCIMCR OPEN ACCESS Journal of Clinical Images and Medical Case Reports

ISSN 2766-7820

Case Report

Open Access, Volume 6

Topical losartan treatment for corneal scarring after infectious keratitis: Case report

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Received: Jun 05, 2025
Accepted: Jul 07, 2025
Published: Jul 14, 2025
Archived: www.jcimcr.org

DOI: www.doi.org/10.52768/2766-7820/3683

Abstract

Background: Corneal opacity CO is estimated to be the cause of 5.1% of all cases of blindness and is among the top 5 causes of blindness worldwide. The lifetime burden of corneal blindness is significant because it tends to affect younger people compared with other conditions such as cataract and glaucoma. Each year 350000 children are born with or develop infections that lead to corneal blindness. Major causes of corneal opacification include trachoma, infectious keratitis, xerophthalmia, ocular trauma and the use of traditional eye medicines. Overall infectious keratitis IK is reported the most common problem.

Case presentation: A 15-year-old boy was brought to the emergency department with chief complaints of diminution of vision, pain, redness and purulent discharge in the left eye. On slit lamp biomicroscopy, paracentral corneal thinning measures about 2 mm in width surrounded by ring infiltrates measured 5.9 x 6.1 mm, with diffuse corneal edema. anterior chamber showed inferior hypopyon 3 mm. The patient was treated with topical fortified antibiotics until the resolving of the infection. However, he was left with central corneal scarring for which we initiated a trial of topical 0.08% losartan 6 times daily conjunction with 0.5% loteprednol 4 times daily. The trial lasted for 6 months during this period we noticed a significant reduction in scarring density and improvement in uncorrected visual acuity.

Conclusion: Topical application of 0.08% losartan after eradication of the infectious agent showed high efficiency and safety with good result regarding eye comfort and restoration of vision.

Keywords: Corneal opacity; Infectious keratitis; Topical losartan therapy.

Abbreviations: CO: Corneal Opacity; IK: Infectious Keratitis; ECM: Extracellular Matrix; GAG: Glycosaminoglycans; PDGF: Platelet-Derived Growth Factor; A-SMA: A-Smooth Muscle Actin; TGF-B: Transforming Growth Factor Beta; MMP: Matrix Metalloproteinases; PTK: Photo-Therapeutic Keratectomy; DALK: Deep Anterior Lamellar Keratoplasty; PK: Penetrating Keratoplasty; ARB: Angiotensin receptor blocker.

Introduction

Corneal opacity CO is estimated to be the cause of 5.1% of all cases of blindness and is among the top 5 causes of blindness worldwide. The lifetime burden of corneal blindness is significant because it tends to affect younger people compared with other conditions such as cataract and glaucoma. Each year 350000 children are born with or develop infections that lead to corneal blindness [1]. Major causes of corneal opacification include trachoma, infectious keratitis, xerophthalmia, ocular trauma and the use of traditional eye medicines. Overall infectious keratitis IK is reported the most common problem [2].

Molecular and cellular mechanisms of corneal scarring

Stromal corneal opacification is primarily the result of cellular and molecular alterations within the corneal stroma, particularly involving keratocytes and the extracellular matrix (ECM). The corneal stroma, which accounts for about 90% of the cornea's thickness, is composed of highly organized ECM, mainly collagen fibers, and keratocytes, which are the resident cells of the stroma. Under normal conditions, keratocytes maintain the transparency of the cornea by producing and maintaining the integrity of the ECM, contributing to its regular structure. However, in response to injury, infection, or inflammation, keratocytes undergo significant changes, leading to ECM disruption and the formation of scar tissue, which results in corneal opacification.

Role of keratocytes in corneal transparency and response to injury

Keratocytes are specialized fibroblast-like cells responsible for the synthesis and turnover of ECM components, such as type I, III, and V collagen, proteoglycans, and glycosaminoglycans (GAGs). The regular arrangement of these ECM components is critical for maintaining the cornea's transparency. Under normal conditions, keratocytes are relatively quiescent but become activated in response to mechanical injury, inflammation, or infection. Upon injury, keratocytes undergo a process of activation, during which it transforms into a more migratory and proliferative phenotype. This activation is driven by various signaling molecules, including cytokines (such as TGF-β) and growth factors (like platelet-derived growth factor, PDGF). Once activated, keratocytes acquire the characteristics of myofibroblasts, which are responsible for the synthesis of excessive ECM components, particularly collagen, leading to scar tissue formation.

ECM remodeling and disorganization

The ECM in the corneal stroma is a highly organized structure that allows light to pass through without scattering. It consists of a precise network of collagen fibrils and proteoglycans, with a particular organization that maintains corneal transparency. In the healing process following corneal injury, the ECM undergoes significant changes, including increased deposition of collagen and proteoglycans, but with a marked loss of the regularity and alignment of these components.

Collagen disorganization: In normal stroma, the collagen fibrils are uniformly spaced and arranged in a highly ordered pattern, which is essential for the cornea's optical properties. In response to injury, keratocytes-turned-myofibroblasts begin to produce an excess of type I collagen and type III collagen, which are more fibrous and less organized than the normal lamellar architecture. This disorganization of collagen fibrils is a key feature of stromal scarring and results in light scattering, causing opacity [3].

Proteoglycan accumulation: The balance of proteoglycans in the stroma is also disrupted during wound healing. In a scarred cornea, there is often an accumulation of proteoglycans such as decorin and lumican, which are normally found in smaller quantities in the healthy stroma. These molecules contribute to ECM rigidity and further disrupt the transparent arrangement of collagen fibers [4]. The accumulation of these ECM components results in increased refractive index mismatches, leading to opacity.

Loss of transparency: The changes in the ECM, including the altered composition of collagen and proteoglycans, disrupt the regular spacing and alignment of fibrils, impairing the ability of the cornea to refract light properly. This results in a loss of corneal transparency and the formation of visible scars in the stromal tissue, which can significantly affect vision [5].

Myofibroblast activation and excessive scar tissue formation

The transformation of keratocytes into myofibroblasts is a central event in corneal wound healing and scar formation. Myofibroblasts are contractile cells that express both fibroblast and smooth muscle-like markers, such as α-smooth muscle actin (α-SMA). This transformation is largely regulated by transforming growth factor-beta (TGF-β), a potent profibrotic cytokine that is upregulated in response to injury.

TGF-β signaling: TGF-β is one of the primary mediators of fibrosis in the cornea. Upon injury or inflammation, TGF-β is released and binds to its receptors on keratocytes, triggering a cascade of signaling events that activate the transcription of genes associated with fibrosis. This process leads to the differentiation of keratocytes into myofibroblasts, which begin producing an excessive amount of collagen and other ECM proteins, contributing to fibrosis [6].

Excess collagen production: Myofibroblasts continue to secrete large amounts of collagen, particularly type I collagen, which forms thick, disorganized fibrils in the stromal scar. These excessive deposits of collagen disrupt the fine lamellar arrangement of the normal stroma, leading to visual impairment.

Scar contraction and tissue remodeling: Myofibroblasts also exhibit contractile properties that allow them to pull the wound edges together. This contraction, while important for closing the wound, can result in the formation of a contracted scar, further disrupting the regular structure of the corneal stroma and exacerbating opacity.

ECM degradation

Matrix Metalloproteinases (MMPs): While ECM deposition is essential for wound healing, excessive degradation of the ECM by matrix metalloproteinases (MMPs) also plays a critical role in corneal scarring. MMPs, such as MMP-1 (collagenase) and MMP-2 (gelatinase), are enzymes that break down collagen and other ECM components. Their activity is tightly regulated, but

during inflammation, their expression is often upregulated.

MMP overexpression and ECM breakdown

In the healing cornea, there is an initial increase in MMP activity, which allows for the remodeling of the ECM. However, an overactive MMP response can lead to excessive degradation of the ECM, resulting in the loss of the original lamellar structure and further contributing to scarring [3]. This imbalance between ECM deposition and degradation is a hallmark of corneal fibrosis and opacity.

Fibrotic scarring and clinical implications

The final outcome of this complex process is the formation of a fibrotic scar in the corneal stroma. This scar is characterized by disorganized collagen, abnormal proteoglycan accumulation, and the presence of myofibroblasts. The extent of the scarring determines the degree of opacity and the impact on vision. In severe cases, significant scarring can lead to corneal blindness.

Treatment of corneal scarring

Finding an appropriate therapeutic technique to heal a scarred cornea efficiently has proven difficult. Restoring useful vision is the primary concern of patients with corneal scarring. Options for the treatment of corneal opacities are limited and can range from conservative to invasive therapies. Conservatively, watchful waiting can be recommended particularly in opacities that are asymptomatic and in peripheral cornea. Other therapies employed are vision correction through scleral lenses, prescription glasses or rigid gas permeable (RGP) contact lenses, Photo-Therapeutic Keratectomy (PTK) for superficial opacities. Corneal transplantation, such as Deep Anterior Lamellar Keratoplasty (DALK) or Penetrating Keratoplasty (PK) can be performed for sever opacities. However, the long-term success of surgical transplantation of allogeneic corneal tissue is associated with major limitations, chiefly that of low donor supply and requirement for strict adherence to topical immunosuppression to prevent graft rejection, with some studies reporting a rejection of up to 41% in pk [7]. Therefore, there is a need for a therapeutic method that can effectively harness the body's signaling cascade to halt fibrosis and heal the corneal wound.

Role of losartan in the treatment of corneal scarring

"losartan is a well known angiotensin II receptor blocker (ARB)". (antihypertensive drug) and an inhibitor of pro-fibrosis TGFβ signaling. By blocking the angiotensin receptor, losartan contributes to an anti-inflammatory milieu. TGFβ is a pleiotropic multifunctional cytokine that regulates several essential cellular processes in many parts of the body including the cornea, and is considered the most important cytokine in the pathogenesis of fibrotic disease in the cornea. The influx of TGFβ triggers the keratocytes proximate to the site of injury to commence their developmental transition into myofibroblasts which excrete large amounts of disordered extracellular matrix that along with the relatively opaque myofibroblasts forms the haze or scarring fibrosis [8]. However, those cells are continually dying by apoptosis and being replaced with new myofibroblasts in the scarred cornea, even years after the original injury. losartan interrupts this process, and, myofibroblasts that are dependent on TGFβ for regeneration and survival will instead be replaced with new, normal corneal cells that restore corneal transparency [9]. Topical losartan likely can prevent or reverse scarring anywhere myofibroblasts develop in the anterior segment of the eye, including the conjunctiva in fibrotic diseases of that tissue.

Topical losartan is the first therapy that has shown promises in clearing corneas with scarring fibrosis no matter how long-term.

Case presentation

A 15-year-old boy was brought to the emergency department with chief complaints of diminution of vision, pain, redness and purulent discharge in the left eye for the previous four days. He was from a poor socioeconomic background. There was a history of preceding minor trauma involving plant matter and the use of topical corticosteroids for the past ten days before symptoms evolve. Systemic history was not significant. Various blood investigations including blood sugar, liver and kidney function tests and complete hemogram were within normal limits. Presenting visual acuity in his left eye was hand movements. On slit lamp biomicroscope, central corneal thinning measures about 2 mm in width surrounded by ring infiltrates measured 5.9 x 6.1 mm with diffuse corneal edema, anterior chamber examination showed inferior hypopyon 3 mm. There was diffuse conjunctival congestion with minimal chemosis in the absence of any features of scleritis. Corneal scraping was performed and sent for direct microscopy and cultures and sensitivity However both came back negative as no microbial growth was revealed, probably due to antibiotic therapy been used. The patient was treated with topical 5% vancomycin, 1.5% gentamycin and oral doxycycline (100 mg/day) vitamin c 1000 tablet once/day. Topical drops were administered every hour for 48 hours, then every hour during the day till the achievement of the improvement in the signs. After that, it was administered 5 times during the day. When no clinical improvement had been noticed in the following 48 hrs a topical antifungal agent (5% natamycin) was added. The patient showed a gradual improvement in the corneal thinning and the ring infiltrates over the first 8 days after initiating therapy and the hypopyon resolved completely in the first week.

Regarding other inflammatory markers purulent discharge, conjunctival congestion, corneal thinning and infiltration had shown a slow improvement over the first two weeks of treatment and the patient was discharged after three weeks.

A 20 IU insulin eyedrops were added 4 times daily to maintain ocular surface integrity and enhance wound healing and the patient was monitored until complete corneal repithelialization and eradication of infection which occurred after 4 weeks of intiating therapy.

As a result of the inflammation process the patient was left with central corneal leucomatous opacity and a visual acuity of 60/800. The patient was put on topical 0.08% losartan 6 times daily inconjuction with 0.5% loteprednol 4 times daily and monitored every week. We noticed a weekly improvement in the opacified cornea which manifested as improvement in the uncorrected visual acuity which improved in the course of two months after initiating treatment reaching 6/15 on Snellen charts.

The trial lasted for 6 months after clearance of infection; most of the improvement happened during the first 2 months and no further improvement was noted in the following 4 months regarding the opacity or the uncorrected visual acuity.

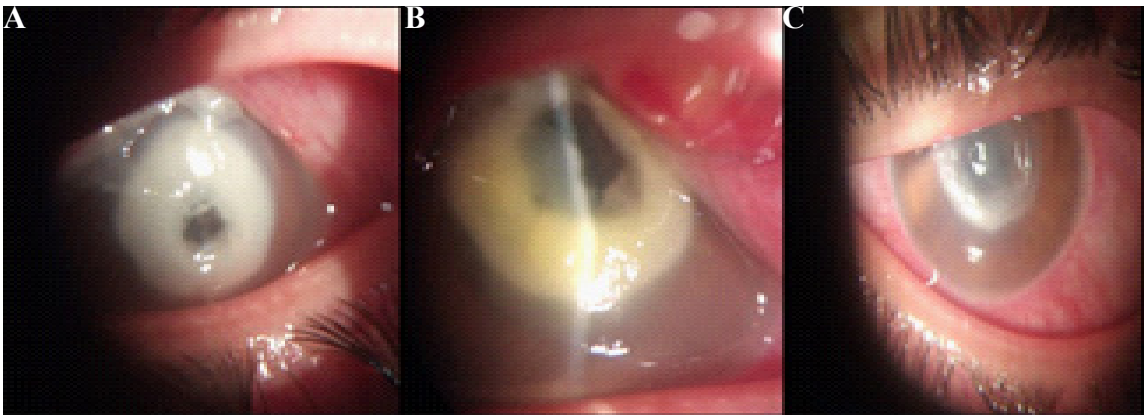

Figure 1: Slit lamp examination of the left eye **(A)** the case at presentation showing corneal thinning and ring infiltrate **(B)** and **(C)** improvement during course of treatment.

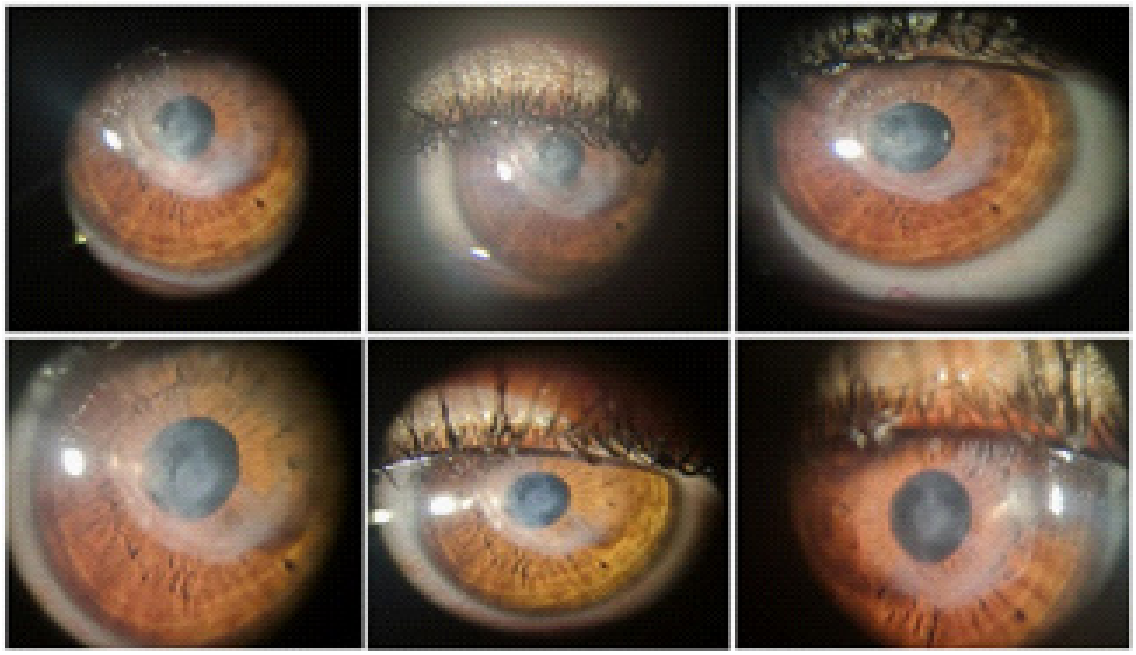

Figure 2: Slit lamp examination of the left eye showing decreasing in opacity after initiating 0.08% losartan treatment.

Conclusion

Topical losartan has been shown to effectively improve the case of corneal opacification and restore transparency post infectious keratitis. Therefore, it can potentially help in the treatment of scarred cornea for different causes. Further studies with large case numbers and long follow up should be the main focus of future researches.

Declarations

Patient consent: Written informed consent was obtained from the patient for participation and publication of this paper and any accompanying images.

Funding and competing interests: The authors declare that there is no conflict of interest regarding the publication of this paper. This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data availability: The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Contributor: MM described the ocular changes, prepare the drops and wrote the manuscript. AQ contributed in writing the manuscript. TD supervision and review. All authors read and approved the final manuscript.

Acknowledgement and fundings: The authors don't have any acknowledgement to state. No financial support was received.

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