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Case Report

Mixed Etiology Neurotrophic Keratopathy Management with Platelet-Rich Plasma: Case Report

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Abstract

Objective*: To evaluate the efficacy of platelet-rich plasma (PRP) eye drops in the treatment of neurotrophic keratopathy (NK) secondary to type 2 diabetes mellitus and herpes simplex virus (HSV) infection.*

Methodology*: A case report of a 66-year-old male patient with a history of diabetes and previous herpetic neurotrophic ulcer presented with painless blurred vision in the left eye. Treatment with PRP eye drops was initiated, and the patient was followed up for one month. Visual acuity, corneal ulcer size, and other clinical parameters were monitored.*

Results*: A case report of a 66-year-old patient with a history of diabetes and previous herpetic neurotrophic ulcer who presented with a neurotrophic ulcer. He was managed with platelet-rich plasma (PRP) eye drops and was followed up for one month to monitor the evolution.*

Conclusion*: PRP therapy shows promise as a treatment for NK, offering early application, relatively low cost, and demonstrated efficacy in promoting corneal healing and regeneration.*

Key Words: *neurotrophic keratopathy, platelet-rich plasma, herpes simplex virus, corneal ulcer.*

Introduction

Neurotrophic keratopathy is a condition related to alterations in corneal nerves that lead to a deterioration of sensory and trophic function, causing degradation of the corneal epithelium, affecting the integrity of the tear film, epithelium, and stroma.[1] It produces corneal lesions such as persistent epithelial defects, corneal ulcers, infection, and, if left untreated, can lead to melting and corneal perforation, as well as irreversible visual impairment.[2] This degenerative corneal disease is caused by a deterioration of trigeminal corneal innervation, leading to a decrease or absence of corneal sensation. [3,4]

Among the etiology of this pathology are viral infections (herpes simplex and herpes zoster keratoconjunctivitis), chemical burns, physical injuries, and ocular surgery (LASIK, keratoplasty, cataract surgery), intracranial tumors (neuromas, meningiomas, and aneurysms), systemic diseases such as diabetes, multiple sclerosis, and leprosy that can decrease sensory nerve function or damage sensory fibers, leading to corneal anesthesia.[3,5]

The diagnosis is based on medical history, ocular examination, and tests to evaluate the decrease in corneal sensitivity and nerve damage.[1] Once the diagnosis is made, neurotrophic keratitis can be staged according to Mackie's classification. Stage 1 is characterized by a cloudy cornea, corneal edema, and superficial punctate keratopathy. Stage 2 includes persistent/recurrent epithelial defect (sometimes with a rolled edge), Descemet membrane folds, and stromal inflammation. Stage 3 includes a frank corneal ulcer that can lead to stromal melting and, ultimately,

corneal perforation.[6, 12]

Dua et al.[1] proposed a modification of Mackie's classification, incorporating corneal esthesiometry. They consider mild disease as epithelial changes only without epithelial defect, superficial punctate keratopathy, and tear film instability, with reduced or absent sensation in one or more quadrants of the cornea; moderate disease as epithelial defect with corneal anesthesia; and severe disease as stromal involvement, corneal ulcer or perforation, and corneal anesthesia.[1]

Treatment depends on the stage of the disease, but aggressive lubrication and topical antibiotics are typically required to prevent secondary bacterial infections.[7] Large epithelial defects or ulcers may require therapeutic contact lenses, temporary tarsorrhaphy, conjunctival flap surgery, amniotic membrane transplantation, or consideration of corneal neurotization surgery.[8, 9]

Other therapies include recombinant human nerve growth factor (rhNGF)[11], substance P, autologous serum drops, umbilical cord serum, platelet-rich plasma, and topical insulin eye drops.[7,8] This report describes a case of mixed etiology neurotrophic keratopathy that was treated with platelet-rich plasma eye drops with positive results.

Case Presentation

A 66-year-old male patient presented at our cornea department at Clínica La Luz, Lima, Peru, referred by the retina service of another ophthalmological center, with a clinical history of 2 months of painless blurred vision in the left eye. There was no associated pain, photophobia, or tearing.

The patient had been diabetic for 10 years and was being treated with insulin and metformin. Regarding ophthalmological history, he had previously experienced a neurotrophic ulcer of herpetic etiology in the left eye 2 years ago. He had a surgical history of phacoemulsification with intraocular lens implantation and a posterior vitrectomy with endolaser for tractional retinal detachment due to diabetes mellitus in the left eye

2 months ago, and a retinal detachment in the right eye 5 years ago. At the time of the examination, he was using autologous serum 1 drop every 4 hours, topical insulin 1 drop every 6 hours, 0.4% sodium hyaluronate every 2 hours, hypertonic solution 1 drop every 6 hours, acyclovir 400 mg 1 tablet 5 times a day, polyacrylic acid gel 3 times a day, and Omega-3, 1 tablet a day, without improvement.

Upon ocular examination, his visual acuity was finger counting at 30cm in the right eye and hand motion in the left eye with no significant improvement. Pupils were round, regular, and reactive to light, without relative afferent pupillary defect (RAPD). Extraocular movements were normal. Annexes showed no abnormalities. The conjunctiva of the right eye was normal, while the left eye showed ciliary redness. Corneal sensation was evaluated macroscopically using a cotton swab and was found to be reduced in both eyes. The right cornea was clear while the left cornea showed a well-defined, clean-edged corneal ulcer measuring 4 x 3 mm on the inferior aspect, surrounded by an area of corneal thinning and opacification, corneal edema with Descemet's folds, and midriatic pupil (Figure 1). No staining was observed in the right eye, while the ulcer in the left eye was stained after the instillation of sodium fluorescein (Figure 1). The anterior chambers were deep and without cells. The patient was pseudophakic in both eyes. Intraocular pressure was 12 mmHg in the right eye and 10 mmHg in the left eye.

The patient was diagnosed with mixed etiology neurotrophic keratitis secondary to herpes simplex and type 2 diabetes mellitus. Treatment was initiated with topical platelet-rich plasma 1 drop every 6 hours, topical insulin 1 drop every 6 hours, vitamin C 1 gram per day, doxycycline 100mg 1 tablet every 24 hours, 0.4% sodium hyaluronate 1 drop every 1 hour, and moxifloxacin 0.5% 1 drop every 24 hours. Anterior segment tomography (Visante) and specular microscopy were requested.

After one week of follow-up, the patient showed clinical improvement. Conjunctival injection in the left eye had decreased. The corneal ulcer in the left eye had decreased in size (2 x 3 mm) (Figure 2, 3). Acyclovir 400mg was added every 12 hours, timolol 1 drop every 12 hours, polyacrylic acid gel 1 application every 8 hours, and topical insulin was discontinued. At 2 weeks of treatment, the ulcer had decreased to 2x2mm (Figure 4). Visual acuity remained unchanged, as the patient had undergone a vitrectomy and had central corneal leucoma in the left eye. The patient was reevaluated after one month, revealing complete healing of the ulcer without staining (Figure 5). This highlights the promising role of platelet-rich plasma in the treatment of neurotrophic keratitis secondary to the mixed etiology of herpes simplex and diabetes mellitus.

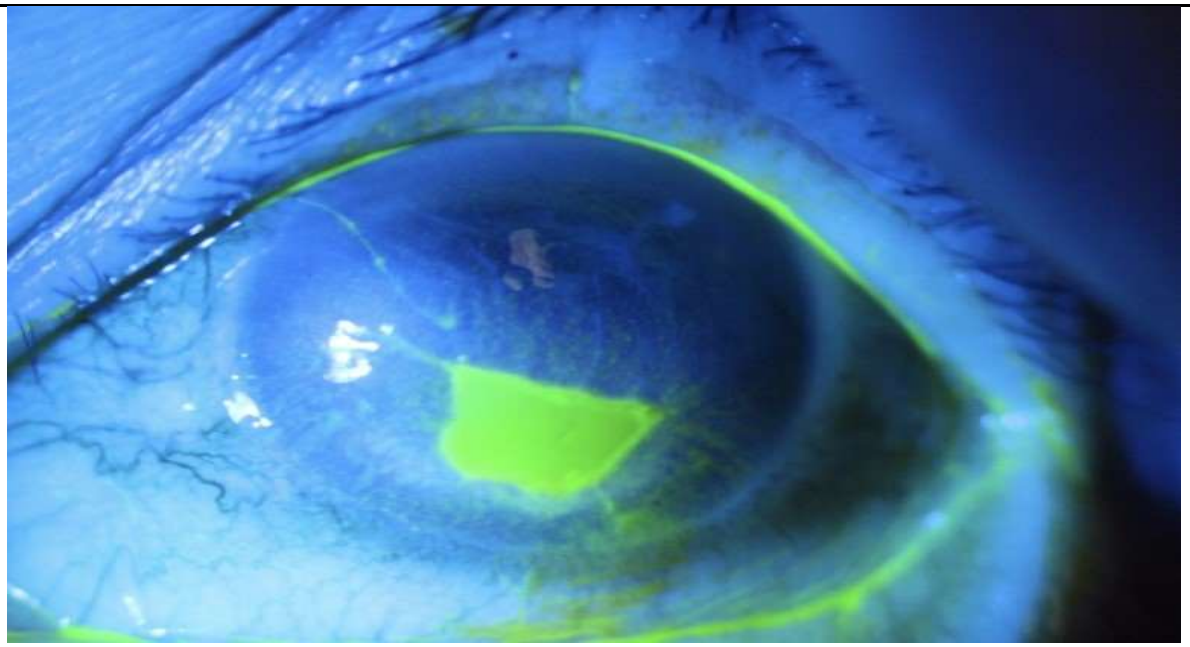

Figure 1. First-day biomicroscopy left eye: 4x3mm ulcer in the lower quadrant, with an area of corneal thinning and opacification, surrounding corneal edema with Descemet's folds.

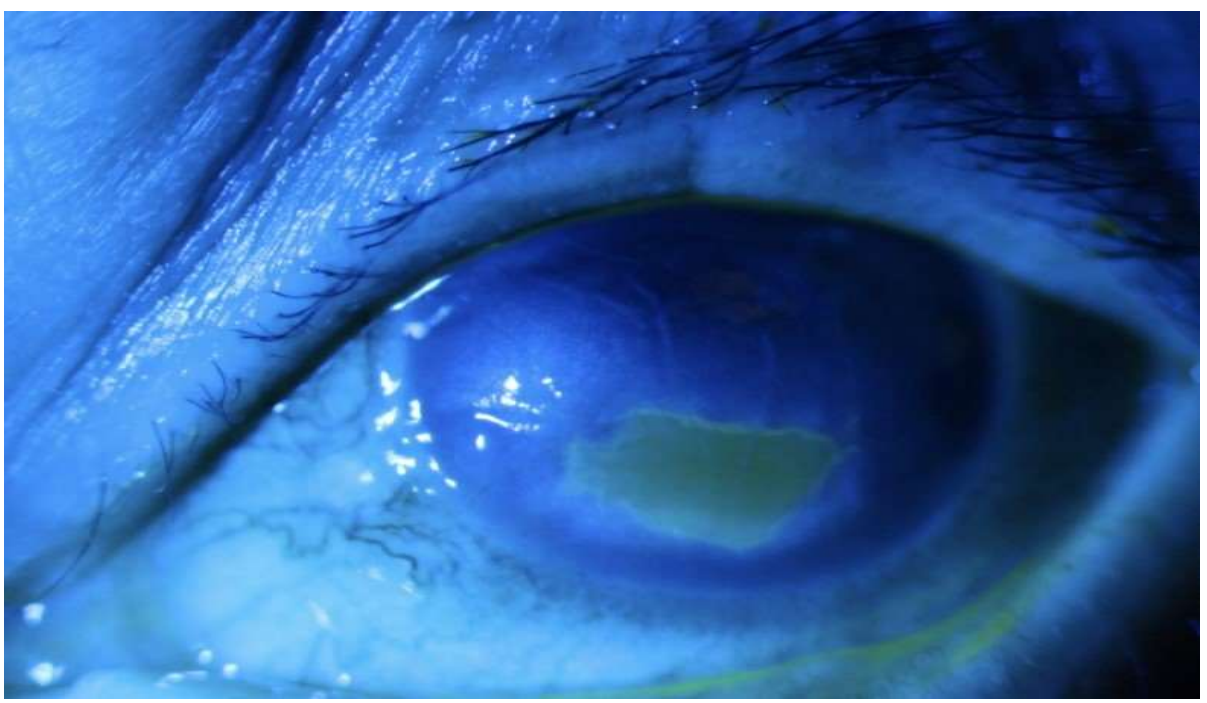

Figure 2. One-week follow-up: ulcer decreased in size (2 x 3 mm), with persistent corneal edema and Descemet's folds

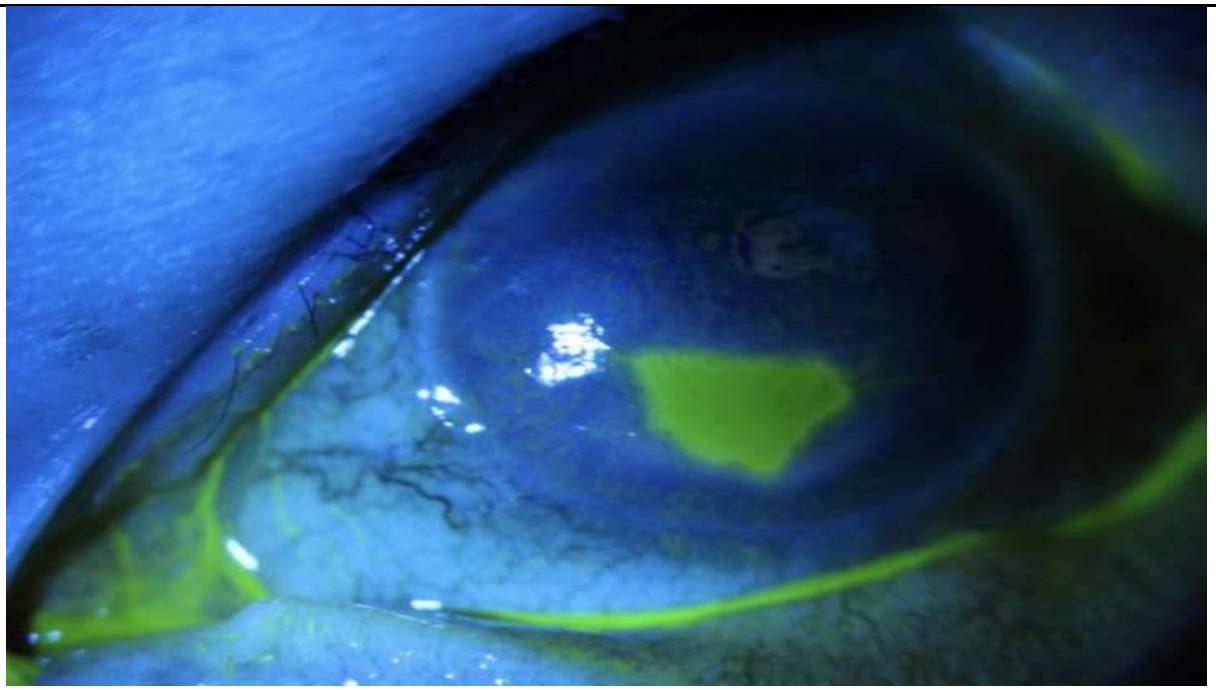

Figure 3. One-week follow-up: ulcer decreased in size (2 x 3 mm), with persistent corneal edema and Descemet's folds

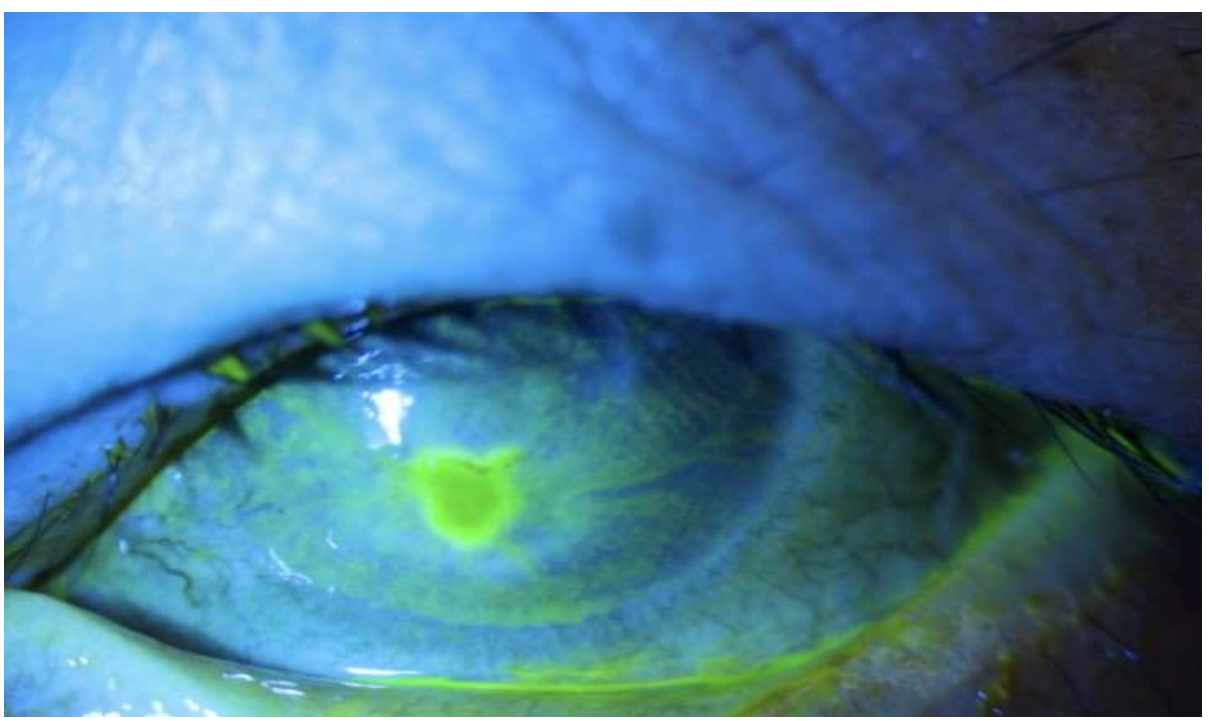

Figure 4. Two-week follow-up: Ulcer decreased to 2x2mm with persistent corneal edema and Descemet's folds

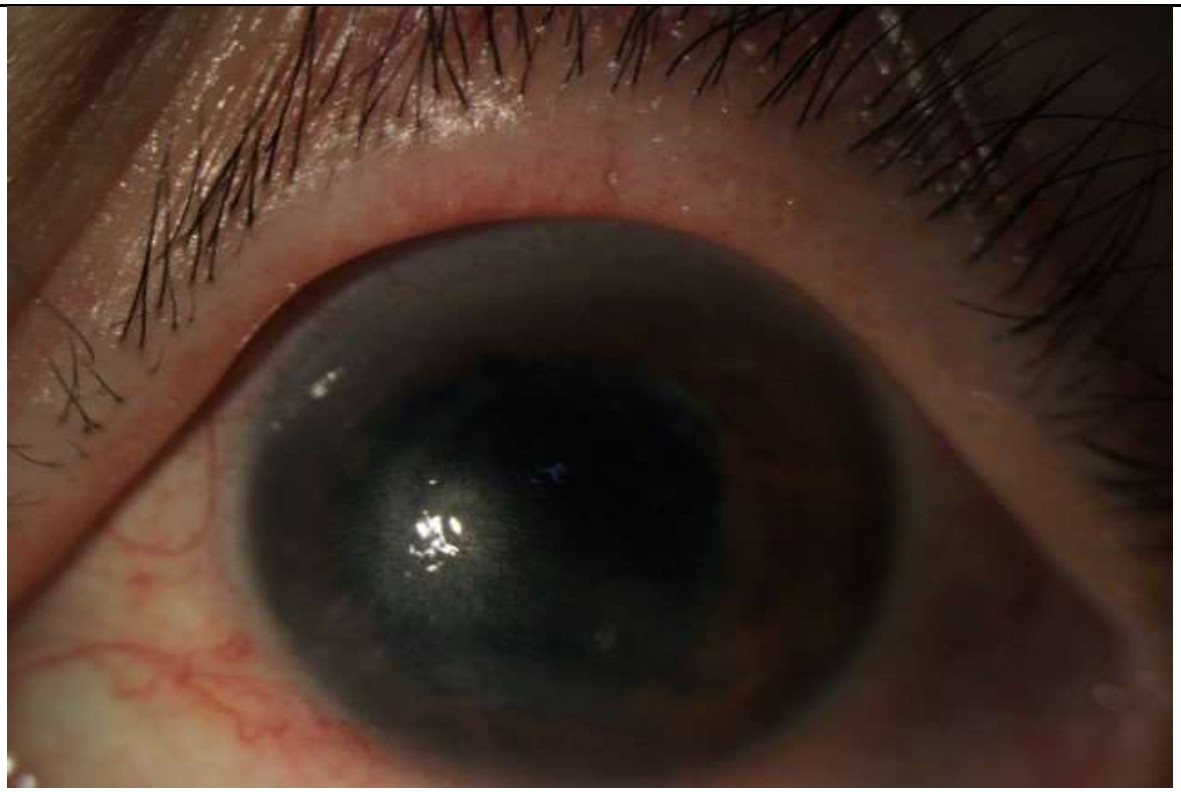

Figure 5. One-month Follow-up: complete healing of the ulcer without staining

Discussion

In this case report, we highlight the role of platelet-rich plasma (PRP) in the treatment of mixed neurotrophic keratitis secondary to previous herpes simplex virus (HSV) infection and diabetes mellitus. It is known that injury to the trigeminal nerve leads to a deficiency of neuropeptides, neurotransmitters, and growth factors that maintain ocular surface homeostasis.

The main objective is to treat this disease according to its etiology and promote corneal healing to prevent corneal perforation. Initially, preservative-free artificial tears are administered, and in cases of severe ulcers, such as the present case, topical antibiotics are introduced to prevent secondary infections.[2,8] Topical glucocorticosteroids are avoided when viral infection is suspected, as they increase viral replication, prolong stromal healing time, and increase the risk of corneal perforation.

The therapy for neurotrophic keratitis is based on promoting corneal healing; therefore, reserves of growth factors and cytokines, such as blood derivatives, appear to be an optimal option. Thus, eye drops containing autologous serum, umbilical cord serum, and platelet-rich plasma (PRP) have been implemented.

PRP is an autologous blood derivative without preservatives, rich in proteins and growth factors that enable cells to differentiate, proliferate, and migrate, thus stimulating tissue healing and regeneration.

PRP has been shown to contain cytokines (e.g., PF4 and CD4OL, which control antibody-mediated immunity and cell-mediated immunity activity)[14], as well as growth factors such as PDGF (platelet-derived growth factor), TGF-β1 and β2 (transforming growth factor), IGF-1 (insulin-like growth factor-1), VEGF (vascular endothelial growth factor), EGF (epidermal growth factor), FGF-2 (fibroblast growth factor-2), and IGF[13, 16]. However, most of PRP's efficacy is attributed to PDGF, which stimulates angiogenesis, collagen synthesis, and regeneration. TGF, secreted during platelet degranulation or actively produced by macrophages, acts as a paracrine growth factor, responsible for epithelial chemotaxis and proliferation. Another important protein contained in platelet alpha granules is EGF (epithelial growth factor). It accelerates corneal epithelial proliferation and has an anti-apoptotic function.

VEGF (vascular endothelial growth factor) and FGF-2 (fibroblast growth factor-2) participate in angiogenesis, as a result of which new vessels deliver nutrients and progenitor cells to the wound.[16]

The growth factors bind to their transmembrane receptors in the damaged tissue, triggering a cascade of reactions: activation of endogenous signaling proteins, expression of genes responsible for cell proliferation, formation of cell matrices, and collagen synthesis. All these mediators trigger processes of cell differentiation, proliferation, migration, angiogenesis, and therefore, the regeneration of damaged tissue. Additionally, platelets secrete antibacterial proteins that have an antibiotic effect. [17]

In a study by Alio et al[10]. different varieties of platelet-rich plasma were used in 40 patients with non-healing corneal ulcers. Complete healing of the ulceration was observed in 23 patients, with significant improvement in 15 patients, and 2 patients, the treatment did not produce any result. In most cases, a reduction in inflammation and pain was observed. Additionally, visual acuity improved in approximately 60% of cases. The product was well tolerated, and no adverse side effects were reported.[6, 7] The treatment of recurrent corneal erosions (RCE) with platelet-rich plasma (PRP) eye drops was also evaluated. Lee et al. reported that the mean frequency of corneal erosion recurrence was 0.06 ± 0.08 per month in the group treated with PRP eye drops and 0.39 ± 0.24 per month in the conventional treatment group ($p = 0.003$).

Regarding our study, we had significant limitations such as the limited sample size, which could restrict the generalizability of the results, and the concomitant use of acyclovir and insulin in the treatment protocol. Additional studies are required to validate and confirm the efficacy of platelet-rich plasma treatment for

corneal ulcers.

Conclusion

Platelet-rich plasma (PRP) therapy has emerged as a promising approach for the management of neurotrophic keratopathy (NK) secondary to type 2 diabetes mellitus and herpes simplex virus (HSV) infection. This treatment modality offers several advantages, including its early application, relatively low cost, and demonstrated efficacy in promoting corneal healing and regeneration. However, despite these promising results, the use of PRP for NK remains largely investigational and is not yet considered a standard therapeutic option.

Further research is needed to validate the long-term efficacy and safety of PRP therapy for NK. Additionally, studies evaluating long-term visual outcomes and comparing PRP therapy with other conventional treatments are essential to establish its position in the management algorithm for this challenging condition. While initial findings are encouraging, more extensive clinical trials are necessary to determine the optimal protocols, patient selection criteria, and potential complications associated with PRP therapy for NK.

In conclusion, while PRP shows promise as a treatment for NK, its use should be approached with caution and reserved for cases refractory to standard therapies. Collaborative efforts between ophthalmologists, researchers, and industry partners are essential to further explore the potential of PRP in the treatment of NK and establish evidence-based guidelines for its clinical use.

Disclosure

The authors report no conflicts of interest in this study.

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