

Neurotrophic Ulcer after Cataract Surgery: New Treatment

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Abstract

85-year-old woman after cataract surgery on left eye develops neurotrophic keratitis with recurrent corneal ulcers that do not respond to conventional and expanded treatment (artificial tears, eye ointments, eye occlusions, Casicol[®], therapeutic contact lens). The initial visual acuity 0.1, we decide to start therapy with eye drops PRGF (Plasma Rich in Growth Factors) and Casicol[®] with for 12 weeks. The complete closure of the ulcer is achieved and improvement of visual acuity 0.8, as well as improvement in symptoms of dry eye. It has not recurrences of corneal ulcer during the two years of follow up.

Keywords: PRGF (Plasma Rich in Growth Factors); Neurotrophic keratitis; Recurrent corneal ulcer; Regenerating Agent (RGTA); Casicol[®]

Abbreviations: PRGF (Plasma Rich in Growth Factors); Regenerating Agent (RGTA); Intraocular Pressure (IOP); Best Corrected Visual Acuity (BCVA); Neurotrophic Keratitis (NK)

Introduction

Neurotrophic keratitis (NK) is a degenerative corneal disease, due to a partial or total loss of trigeminal nerve fibers, this can lead hypesthesia or anesthesia complete cornea [1]. There are multiple etiologies causing: NK from infectious (herpes simplex, herpes zoster), corneal diseases (burns, contact lens use, dystrophies, corneal surgery), use of topical medication (anesthetics, timolol, betaxolol), paralysis of the V cranial nerve and systemic diseases (diabetes mellitus, multiple sclerosis, vitamin A deficiency). The most common cause is secondary to infectious etiology (herpes virus), but it is increasingly frequent neurotofica keratitis due to corneal surgery (LASIK: laser *in-situ* keratomileusis, PRK: Photorefractive Keratectomy, cataract) [2,3].

Denervation of the corneal surgical procedures is the result of alterations in epithelial wound healing, increase epithelial permeability, decreased epithelial metabolic activity, loss of cytoskeleton structure with cell adhesion; these factors determine the extent of regeneration neuronal [4]. After cataract surgery often find dry eye syndrome, which requires chronic treatment with artificial tears, topical corticosteroids, including autologous serum or ciclosporina [2]. There is a feedback between the tear film instability and reduced corneal sensitivity nerve injury, which perpetuates the corneal damage leading to develop neurotrophic keratitis [5,6]. Factors related to impairment of corneal surface after cataract surgery are: large incision, incision in clear cornea, abnormal tear film prior to surgery, use of eye drops with preservatives [2].

Treatment for NK depends on the clinical stage; Stage 1: Use preservative-free artificial tears, ocular surface treatment of associated disease, discontinue topical medication; Stage 2: Lens therapeutic corneal or scleral contact, tarsorrhaphy, eyelid surgery, botulinum

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toxin, amniotic membrane transplantation (AMT); Stage 3: Cyanoacrylate glue, tarsorrhaphy and conjunctival flap, lamellar keratoplasty or penetrante [7]. The prognosis depends of the cause of the neurotrophic keratitis and associated ocular diseases.

New therapies have been proposed for corneal ulcers neurotrophic keratitis: The matrix RGTA (Re-Generating Agent, polycarboxymethyl glucose sulfate), an eye drop containing a matrix similar to heparan sulfate, allowing adhesion of growth factors natural corneal surface. In an animal experimental model PRK showed that RGTA can be effective in modulating repair of corneal ulcers, getting epithelial tissue regeneration and recovery inervacion [8]. RGTA creates a microenvironment that allows closure and healing of epithelial defects in a period of 8 weeks on average [9].

It has developed a corneal tissue regenerative therapy, which is approved by the local regulatory authority [10] and the FDA (Food and Drug Administration); it is the PRGF (Plasma Rich in Growth Factors) a medical product for human use, derived from the blood of the patients. The PRGF is a blood derivative obtained by centrifugation; in ophthalmology the supernatant fraction of the plasma is used, it does not contain leukocytes, it is activated with calcium citrate and remove proinflammatory products through heating process [11].

The PRGF contains many growth factors, proteins and molecules involved in the migration, growth, differentiation and tissue repair, among these factors are: Epidermal Growth Factor (EGF), Platelet-Derived Growth Factor (PDGF), Nerve Growth Factor (NGF), Transforming Growth Factor b1 (TGF b1), Vascular Endothelial Growth Factor (VEGF), Insulin-like Growth Factor-I (IGF-I) and fibronectin and immunoglobulins IgG and IgM. There is extensive pre-clinical and clinical data supporting the use of PRGF in ophthalmology for the following pathologies: Dry Eye Disease (DED), ocular surface syndrome after LASIK, dormant corneal ulcers, Graft Versus Host Disease (GVHD) and Corneal ulcers [12-14].

We present a case report of a patient with cataract surgery (phacoemulsification) has developed a NK stage 3, that no clinical improvement achieved with standard treatments. However shows a satisfactory clinical improvement subjectively and objectively, to be treated simultaneously with PRGF and RGTA.

Case Presentation

Female patient, 85 years old. She underwent surgery on her cataract (phacoemulsification more implant intraocular lens-IOL in sulcus) in left eye (LE) in April 2012. She was evaluated at another hospital for feeling itchy eyes, red eye pain, identified a corneal ulcer (*first episode*) in the LE, received treatment (November 2012) with ophthalmic gel carbomer, preservative-free artificial tears, gentamicin ointment and eye occlusion. However due to persistent pain and red eye, go to our eye clinic for evaluation in December 2012. As important medical history patient has breast cancer (tumor resection required treatment in 2011 and chemotherapy with clinical recovery, being stable mammary tumor pathology at the time of going to our medical consultation).

In the initial eye exam the Best Corrected Visual Acuity (BCVA) of Right Eye (RE): 0.7 and BCVA in LE: 0.1. Intraocular Pressure (IOP) in RE: 14 mm Hg, IOP LE: 15 mm Hg. Endothelial count in RE: 1396 cells in LE: 1290 (Figure 1). Biomicroscopy (BMC) in LE: blepharochalasis, mixed hyperemia, diffuse epitheliopathy, fluotest positive nasal area (*60% of corneal surface*), IOL in sulcus. Fundus in LE: macular no alterations or optical disk objectified by OCT (Optical Coherence Tomography) (Figure 2). She received two PRGF cycles (one cycle= 2 drops, 4 times a day for 6 weeks), achieving complete healing of corneal ulcers and improvement of BCVA LE: 0.7.

The patient remained stable until February 2014, when consultation sharp pain in LE, LE with BCVA: 0.3, objectify corneal ulcer (*second episode*) with 40% of corneal surface, test OSDI: 43.75, VAS (Visual Analog Scale) in frequency: 97%, VAS in severity: 85%; ulcer cultivation is done and conjunctival exudates (results are negative), treatment begins with: Acyclovir 800 mg orally, gentamicin ointment, PRGF (one cycle), artificial tears free-preservatives, moxifloxacin eye drops.

In the June of 2014 the patient reported improvement in clinical symptoms of dry eye, however persistent itching sensation, BCVA of LE: 0.4, test OSDI: 25.5, VAS frequency was 20%, VAS Severity: 20% BMC LE: calm eye, no hyperemia, no swollen eyelids and monoblock

IOL in the ciliary sulcus that causes UGH syndrome (Uveitis-Glaucoma-Hiphema).

In December 2014 a great improvement was observed in the eye symptoms and complete closure of the ulcer, the BCVA in LE: 0.8, BMC in LE: Minimum residual walleye, OSDI test: 16.6, VAS frequency: 10%, VAS severity: 10%, dermatoblefarochalasis in LE (causes evaporative dry eye syndrome), no inflammation, no keratitis. Then RGTA was prescribed 1 drop per month for 5 months, showing stability in the ocular surface and symptoms of LE.

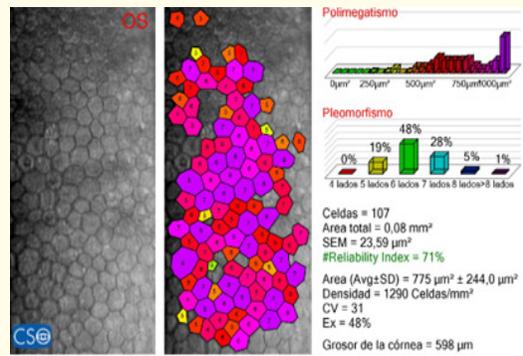


Figure 1: Left Eye Specular Microscopy, Low Density Cells.

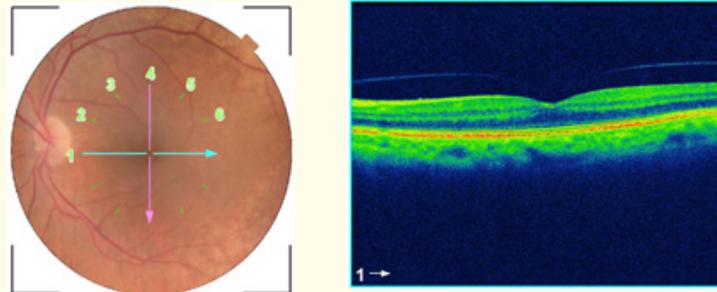
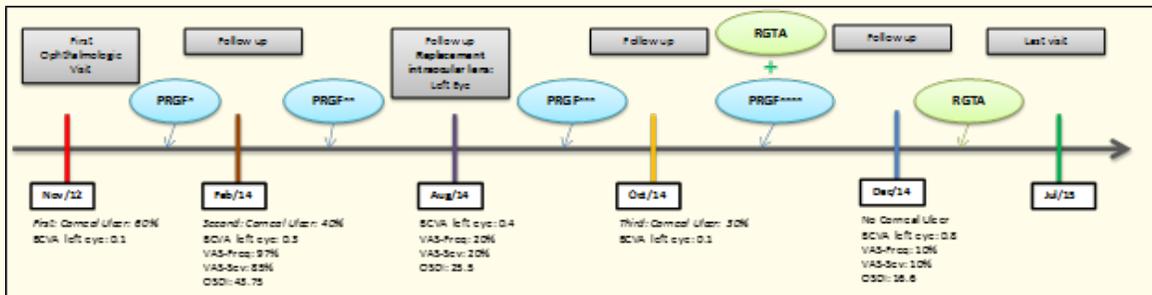


Figure 2: OCT Macular Left Eye, Retinography and Normal OCT.



*: Two PRGF cycles (one cycle= 2 drops 4 times daily for 6 weeks); **: A cycle of PRGF; ***: A cycle of PRGF; ****: Two cycles PRGF.

Figure 3: Monitoring and Treatment Of Corneal Ulcer in the Left Eye.

On the last visit (July 2015), the patient has remained stable in BCVA of LE: 0.8, the walle eye practically been resolved, she has not had corneal ulcer reopening of the LE, OSDI: 6.25, VAS Frequency: 5%, VAS Severity: 5%.

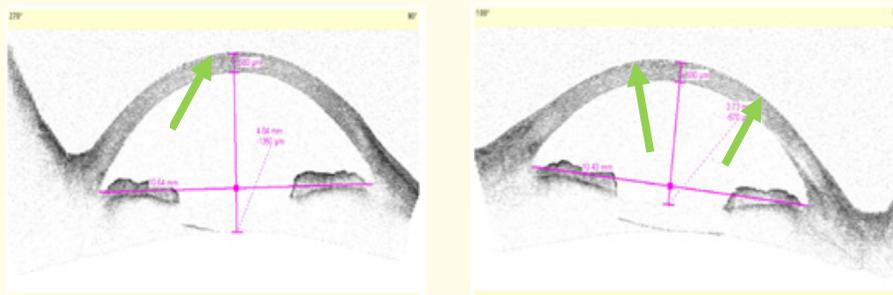


Figure 4: Anterior Segment OCT Left Eye (Visante™) in May 2015. Regeneration of the Corneal Epithelium and Stroma, Good Tissue Thickness (green arrows).



Figure 5: Photograph of Left Eye Review (July 2015). Residual Walle eye Almost Solved (Red Arrow).

Discussion

As the number of corneal refractive surgeries increases, the incidence of NK is likely to increase in the future due to delayed and abnormal nerve reinnervation [15]. Various new treatment drops modalities such as fibronectin eye-drops, nerve growth factor and serum eye-drops have been reported to improve NK, however there are very cases refractory to multiple treatments.

In the case of cataract surgery (phacoemulsification) there are few reports of persistent NK, but when present are related to the site and size of the corneal incision. There is a subsequent alteration of the tear film having a recovery period between 1 and 3 months under normal conditions phacoemulsification [2,5]. To our knowledge post-cataract surgery neurotrophic ulcers have been extracapsular [16] surgery or herpes zoster coinfection.

After cataract surgery is common to have a new diagnosis of dry eye syndrome. Dry eye syndrome is an inflammatory disease that can interfere with patient quality of life. There are many factors that might affect ocular surface environment after cataract surgery: such as benzalkonium chloride in the topical anesthetic agent, exposure to intense light from the operating microscope and corneal incisions following corneal denervation. These can act as an inflammatory trigger or disrupt the regular mechanisms neuro-regulatory [17].

RGTA mimicking biopolymer is an engineered heparan sulfates as a protector and stabilizer of the actions of heparin-binding growth factors [18]. RGTA interacts with components of the extracellular matrix, binding matrix proteins, protecting them from proteolysis, restoring the matrix environment and improving tissue healing. There is preclinical evidence of efficacy of RGTA for the treatment of ocular

surface disorders in an animal model for the rapid corneal ulcer closure was demonstrated in 7 days [8,19]. In a prospective study 11 patients with neurotrophic ulcers, receiving treatment with RGTA, eight patients displayed complete corneal healing after a mean period of 8.7 weeks (range 1 to 22 weeks) [20]. It published a case report of a patient with *Acanthamoeba* neurotrophic corneal ulcer, which was treated with RGTA (1 drop every 2 days) for 8 weeks. The corneal defect was completely repaired in 3 weeks [21]. Three cases of persistent epithelial defects (PEDs) treated with therapeutic contact lens and RGTA, achieved complete closure of the ulcer between 4-21 days of treatment [22].

PRGF technology is opening new avenues in regenerative medicine [23]. PRGF is an autologous platelet rich plasma by which it is possible to obtain different growth factor enriched formulations including a colirium, that can be used in the treatment of several disorders. For the particular case of ophthalmology, PRGF is used as eye drops, having corneal tissue regeneration properties, antibacterial properties, control cell migration and differentiation, evidenced in animal models of PRK [23,24]. PRGF is also involved in axonal regeneration, resulting in the elimination of neuropathic pain [25]. In addition, PRGF eye drops can be stored for up to 3 months without any reduction of the main proteins involved in healing ocular surface, allowing great adherence to topical ophthalmic treatment [26]. PRGF does not contain leucocytes but doubles the concentration of platelets, it is expected to have more growth factors and neurotrophic factors but without pro-inflammatory cytokines [12].

There is clinical evidence of the use of PRGF in eye diseases. In the case of DED, a study showed significant improvement in 82% of the patients showed or full disappearance of symptoms [27]. The effect of PRGF on PEDs was evaluated by means of a prospective study in 18 eyes, the results showed full recovery of the epithelial defect in 85% of cases [12]. In corneal ulcers, the PRGF has also proven effective, in a study (n= 38) showed that 92% of patients with dormant corneal ulcers improved significantly, reduced inflammation and decreased ocular pain after PRGF treatment [28].

In the clinical case described, the patients clinical condition basal (possible immunosuppression by chemotherapy) was not the most efficient molecular mechanisms to allow corneal reparaticion. That is why perhaps in single use of PRGF will work only for a short period of time and then reproduce again corneal ulcer, having no substrate (matrix), from which it could release molecules PRGF. That is why perhaps the use of RGTA to be a matrix polymer molecules replace heparan sulfate, enable the creation of an appropriate extracellular environment that can fix the PRGF growth factors and allow subsequent release of such factors ocular surface, allowing more efficient tissue regeneration.

After treatment in conjunction PRGF + RGTA, the patient in this case remained stable from the point of view ophthalmological for 7 months, without reopening the new corneal ulcer and substantially improve the ocular surface, with improvement objectified her BCVA in LE, OSDI test and improvement of quality of life (VAS Scale).

Conclusion

NK is an eye disease that can have multiple etiologies, the more often it is of herpetic origin, but can also be surgery kerato-refractive origin, where the most common is post lasik, but also it has been linked to cataract surgery, in which the most important factors are related to the site, size insicion and postoperative treatment. Treat NK depends on the clinical stage, in the case of stage 3 are used artificial tears, TCL, autologous serum and even surgery (TAM), in order to prevent corneal perprofacion.

This is the first clinical report using associated PRGF and RGTA to treat NK stage 3, showing a rapid closure of the ulcer and maintained over time. Likewise it is improving all the biological environment of the ocular surface, a fact that leads to the symptoms of dry eye and quality of life of patients. This opens a door to develop in the future prospective study with the involvement of the two therapies.

Conflict of Interest

The author has no conflict of interest when he wrote this article.

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