Review Article

Role of Eye Platelet-Rich Plasma in the Treatment of Ocular Surface Disorders

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Abstract

The use of blood derivatives represents an alternative therapeutic approach that is gaining interest in regenerative medicine due to its potential to stimulate and accelerate tissue healing. Platelet-rich plasma is the highly concentrated form of autologous human platelets in a small amount of plasma which contains important growth factors and plasma proteins that play a significant role in the wound healing process by epithelial differentiation and collagen bundle organization.

In this article, we aim to provide an update on the current literature regarding the eye platelet-rich plasma, its methods of preparation, physiological and biochemical properties, its clinical applications, safety and efficacy as compared to other blood-derived products, etc. In ophthalmology, this product is being used in the management of symptomatic dry eyes, corneal ulcers, periocular chemical and thermal burns, idiopathic macular hole, skin rejuvenation post blepharoplasties and more recently actinic elastosis in the lower eyelid regions. The role of eye platelet-rich plasma in ocular surface disorders has been sparsely studied in literature with more studies and reports on the application of autologous and allogeneic serum eye drops therefore, it becomes very important to update ourselves with more studies in this topic to prove the efficiency of this blood-derived product.

Keywords: Platelet-rich plasma, Dry eye syndrome, Ocular surface disease, Autologous serum.

Introduction

The ocular surface may suffer from several disorders including dry eye syndrome, persistent epithelial defects (PEDs), neurotropic ulcerations, limbal deficiency and corneal dystrophies among others. Dry eye syndrome is the most common disorder, and its prevalence has tripled in the last decade. These disorders are characterized by impaired tissue repair processes.[1-5] A reduction in epitheliotrophic factors compromises the integrity of the surface epithelia, leading to the formation of epithelial defects that may persist and progress as a result of the compromised wound healing process.[6] Conventional therapeutic options include intensive artificial tear supplements, punctual occlusion, therapeutic contact lenses and appropriate management of adnexal disease. Surgical procedures, as keratoplasty or amniotic membrane transplantation, are used every day to restore the ocular surface but they are no suitable for all patients.

Many researchers have been trying to find a substance that would be similar in biological properties to natural human tears which would help in the regeneration of the severely affected ocular surface in addition to providing epithelial integrity. Such substances are blood-derived products that contain identical growth factors, vitamins, nutrients and cytokines which are found in natural tears to support epithelial cell homeostasis, augmentation and cell migration. Several types of blood-derived therapy like autologous serum eye drops (ASE), E-PRP, and umbilical cord serum have been described in the literature.[2,7]

The role of E-PRP in ocular surface disorders has been sparsely studied in the literature for which this article is focused on, i.e., to review the guidelines for the methods of preparation, its indications and uses, risks and benefits involved, and finally the safety and efficiency of the product

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in the treatment of various ocular surface disorders. The present article is a narrative review describing the application of E-PRP in ophthalmology and more specifically in ocular surface conditions.

The use of E-PRP for the treatment of dry eye, post-LASIK ocular surface syndrome, dormant ulcers, and for ocular surface reconstruction after corneal perforation etc. have been reported in peer-reviewed studies. The role of platelet-rich plasma in ocular surface disorders has been studied by many authors and, though sparsely, has been thoroughly analyzed in this review article. The use of PRP was reported by Rezende *et al.* in 2007 for the treatment of neurotrophic ulcers, and also in subsequent studies for the treatment of symptomatic dry eye and persistent epithelial defects among other uses.[8]

What is E-PRP and How it Acts?

E-PRP is E-PRP which is a portion from the patients own blood having a platelet concentration above baseline. The basic idea behind using platelets rather than any other blood cells is that the circulating platelets are an important reservoir of growth factors, cell adhesion molecules, and cytokines concentrated in the alpha granules. When the platelets are activated, these growth factors are released which play a major role in hemostasis, tissue regeneration, immune response, and wound healing. Alpha granules of the platelets include over 30 known biologically active substances such as platelet-derived growth factor, transforming growth factor b1 and b2 and insulin-like growth factor 1, vascular endothelial growth factor, epidermal cell growth factor, fibroblast growth factor 2, and insulin-like growth factor etc.[3] *In-vitro* studies by Liu *et al.* have established that platelet lysate has much higher concentrations of growth factors than serum.[4] In view of the fact that growth factors are vital to corneal epithelial cell health and regeneration, many researchers have tried to use platelets and the contained growth factors as part of therapeutic eye drops. The released growth factors initiate a cascade of reactions responsible for migration, mitosis, extracellular matrix formation, and angiogenesis promoting proliferation and differentiation of corneal cells. The major effects of PRP are –

- Platelet-derived growth factor (PDGF), the first growth factor to appear in the wound increases the number of repaired cells, stimulates angiogenesis, and supports the development of new blood vessels and activated macrophages.
- Transforming growth factor (TGF) is responsible for chemotaxis and controlling epithelial proliferation and maintaining cells in an indifferent state.
- Epidermal cell growth factor (ECGF) accelerates corneal epithelial proliferation.
- Vascular endothelial growth factor (VEGF) plays a role in angiogenesis.
- Fibroblast growth factor 2 (FGF) takes part in vascular proliferation.

Autologous Serum *versus* PRP

The autologous serum presents characteristics that are very similar to tears, such as pH, osmolarity, vitamin A and immunoglobulin A. Tears and serum contain abundant common growth factors and antibacterial components enabling the nutritional factors necessary to maintain cell viability in the epithelial repair process. Thus, serum facilitates the proliferation, migration and differentiation of the ocular surface epithelium. In addition, it is known for its anti-catabolic properties by inhibiting the inflammatory cascade triggered by interleukin-1 (IL-1) when it binds to its receptors, which prevents tissue destruction.[6]

Autologous serum eyedrops (ASE) and platelet concentrate (PRP) have similar compositions since they have various growth and healing factors present in the blood. However, autologous serum contains proinflammatory cytokines derived from leukocytes and monocytes, which may be harmful to patients with immunological disorders or diseases. Thus, the PRP is advantageous for not containing these immunoglobulins of the inflammation, and also for regulating the expression of several genes in the cellular communication and differentiation, improving the biological activity of the corneal epithelial cells when compared to the autologous serum. In addition, PRP becomes more effective when presenting higher indexes of growth factors such as: Epithelial growth factor (EGF), vitamin A, neural growth factor (NGF), Insulin type I growth factor and platelet factor IV.[9]

How is E-PRP Prepared?

E-PRP is prepared under strict sterile conditions inside a laminar flow hood using sterile and disposable materials. The whole patient's blood is collected under aseptic conditions using 3.2% sodium citrate as an anticoagulant and introduced into a centrifuge. After one-step centrifugation (10 minutes at 1600 rpm), three layers are obtained. The upper layer contains platelet-poor plasma, PRP in the middle layer and at the bottom white and red cells. In 3 to 4 mL aliquots of PRP are transferred into new sterilized amber glass bottles with eye drop applicators. The bottle is kept in the refrigerator at 4°C for 1-week, and the rest of the bottles in the freezer at-20°C. The E-PRP prepared can be used in two ways- as topical eye drops for surface applications and as a clot for ocular surface reconstruction. For E-PRP clot preparation, 1-mL of the plasma nearest to the red cells is extracted, avoiding the white blood cell layer and placed into 4 well tissue culture plates and 50 µL of 10% calcium chloride are added to each well for activation. After mixing carefully with a sterile pipette, the plates are incubated at 37ºC for 30 minutes.[10]

The difference between eye drop and a clot preparation is that in eye drop, there is the endogenous release of activators of the coagulation in the site of application which results in slow release of growth factors and chemical mediators thus providing a longer effect whereas the clot can be used immediately after preparation since it is already activated (Figure 1).

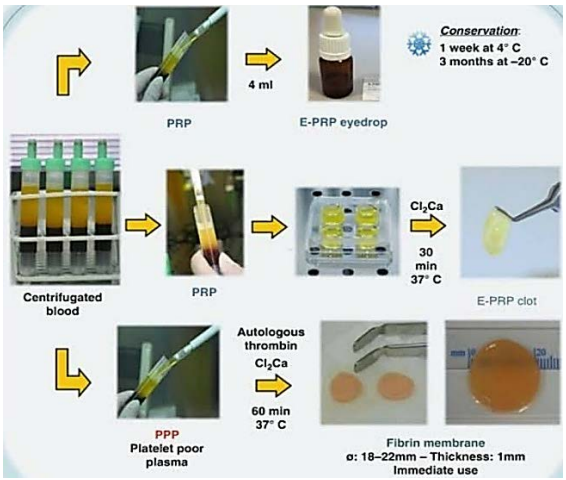

Figure 1: PRP preparation

Clinical application of E-PRP in Ocular Surface Disorders

- Dry eyes
- Non-healing corneal ulcers
- Post-LASIK ocular surface syndrome.
- Chemical and thermal burns.
- As an adjunct in ocular surface reconstruction in corneal perforation.
- Ocular surface disorders in autoimmune conditions like Stevens-Johnsons syndrome, ocular cicatricial pemphigoid, Graft-versus host disease.

Dry Eye disease (DED)

The definition of dry eye disease (DED), updated in 2007 by the International Dry Eye Workshop, is a multifactorial disease of the ocular surface and tears that produce symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface (Figure 2).[9]

The use of PRP in the treatment of dry eye syndromes was evaluated in 2 prospective observational studies by Alio *et al.* in 2007 and by Lopez Plandolit in 2011.[10-13] Alio worked with a total of 34 patients with moderate or severe dry eye syndrome. PRP was applied topically 4 to 6 times a day for 1 to 3 months, resulting in a significant improvement or disappearance of all symptoms in 82% of patients.[2] Lopez Plandolit *et al.* also demonstrated that the concentrate can be used in the treatment of severe dry eye in patients with different etiopathologies such as Sjogren's Syndrome.[13] More recently Garcia *et al.* in 2019 have published a prospective comparative randomized study including 83 patients with hyposecretory dry eyes, 44 patients treated with PRP (PRP group), and 39 patients treated with artificial tears of sodium hyaluronate.[14] They found that PRP treatment was more superior to sodium hyaluronate regarding improvement in visual acuity, decrease in hyperemia, osmolarity, conjunctival and corneal staining

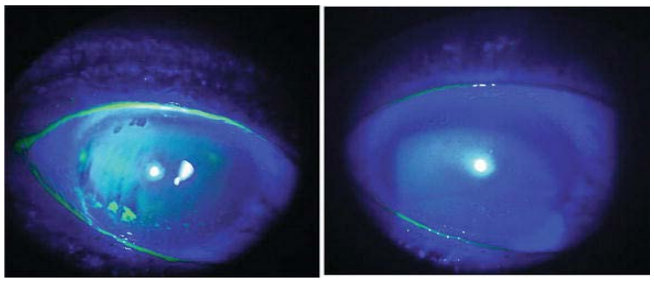

Figure 2: Before and after treatment with PRP in severe dry eye

The most frequently used therapy for treating ocular surface disorders are the drops of artificial tears. However, none of these commercially available preparations include essential components of tears, such as growth factors, vitamins, and immunoglobulins. In addition, artificial tears contain conservatives, stabilizers, and other additives, which potentially induce toxic and allergic reactions.

Non-Healing Corneal Ulcers

Non-healing corneal ulcers are refractory persistent corneal epithelial defects that usually do not respond to conventional topical therapy. The most common causes for non-healing corneal ulcers are severe dry eye syndrome, meta herpetic disease, neurotrophic keratopathy, post keratoplasty, alkali burns, and immunological disorders.

The efficacy of PRP in the treatment of PED has also been compared with that of ASE in a clinical study by Kim *et al.* in 28 eyes with PEDs from post-infectious inflammation. All 11 eyes treated with PRP showed complete healing, whereas only 12 of 17 achieved the same in the ASE group. Faster healing rates were seen in the PRP group.[15]

Alio *et al.* treated with PRP 40 eyes affected by dormant corneal ulcers, and showed that inflammation and subjective symptoms, particularly pain, improved in all patients while vision remained stable or improved in all the cases.[2]

Post LASIK Ocular Surface Disorder

LASIK results in surface ablation which may result in corneal denervation, alteration in corneal shape and changes in tear film quantity and quality. It is also seen that there is a definitive loss of conjunctival goblet cells thus adding to the problem. The first-line treatment with artificial tears is not quite adequate and additional methods such as punctal occlusion, treatment of meibomian gland dysfunction, or anti-inflammatory therapy are often tried. Javalio *et al.* in 2013 did a randomized controlled trial on 108 myopic eyes receiving LASIK to investigate the effect of E-PRP on the recovery of corneal sensitivity after LASIK.[16] They concluded that PRP drops promote epithelial status after LASIK but have no positive effect on the recovery of corneal sensitivity.

Alio *et al.* in 2007 did a pilot study in a small group of 26 eyes to study the efficacy of 4 weeks of topical E-PRP in post-LASIK symptomatic ocular surface syndrome and concluded that there was 85% improvement in the dry eye symptoms and

punctate keratopathy.[7] Later in 2017 they studied 156 eyes of 80 patients affected by post-LASIK chronic ocular surface syndrome who were treated with autologous E-PRP 6 times a day as monotherapy for 6 weeks. They reported that there was relief in dry eye symptoms, healing of punctate keratitis, and improvement in conjunctival hyperemia.[17]

Ocular Chemical and Thermal Burns

More than two-thirds of facial burns involve the eye or periocular area. In 84% of these are due to chemicals and 16% due to thermal injury. Most ocular sequelae including corneal ulcerations usually are seen secondary to post-burn eyelid deformities. Subconjunctival application of platelet-rich plasma in ocular burns and reported a shorter healing period of the corneal and conjunctival epithelium and reduction in conjunctival cicatrization.[18]

Panda *et al.* treated 20 eyes affected by grade III to V chemical injury: 10 eyes (group I) received PRP eye drops along with standard medical treatment while 10 eyes (group II) received standard medical treatment alone. After 3 months of therapy, corneal transparency and visual acuity showed significant improvement in group I patients compared to group II patients.[11,12]

Adjunct in Ocular Surface Reconstruction in Corneal Perforation

Corneal perforations pose an immediate danger to the ocular integrity which needs emergency surgical intervention. Few authors have reports of using a combination of solid E-PRP clot as an adjuvant to tectonic elements like autologous fibrin membrane/amniotic membrane to close a corneal perforation. The solid form of E-PRP clot has the advantage of having 2 to 3 times more concentrated platelets than the topical form.

Alio´*et al.* presented a case series with corneal perforations or impending perforations with amniotic membrane grafts combined with E-PRP clot and got successful outcomes in 71% (10/14 eyes) which had complete resolution. A total of 57% eyes improved in visual acuity after 1 to 2 weeks of surgery. The improvement in clinical outcome was most likely due to the prolonged synthesis and constant release of growth factors by the ERP clot and thereby adding to the corneal wound healing processes and further decreasing inflammation.[17]

Autoimmune Conditions

Many of autoimmune diseases such as Sjogren's syndrome, lupus, and rheumatoid arthritis, chronic Graft host disease cause aqueous deficient dry eye disease (ADDED) characterized by an insufficient volume of tears due to dysfunction of the lacrimal gland and obstruction of the lacrimal ducts.[4] Many other ancillary products have been tried for such conditions.[19]

Avila MY *et al.* evaluated the effectiveness of PRP injections to the lacrimal gland at 1month intervals for 3 months in the treatment of severe dry eye in patients with Sjogren syndrome and found improvements in corneal staining, TBUT time, OSDI scores, etc. They suggested that PRP contains several components with known pro-regenerative capabilities in secretory tissues, stem cell properties, indirect antifibrotic properties, and antiapoptotic activities.[20]

Conclusion

E-PRP is a very good option for the treatment of cornea and ocular surface disorders, being an ample source of growth factors and cytokines and mimicking both the composition and function of human natural tears. This review demonstrates the variety of PRP applications in ophthalmology with good results. Its biochemical and physiological properties make it an effective alternative treatment for diseases, mainly of the ocular surface.

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