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Review Article

Update on the role of Eye platelet-rich plasma (E-PRP) in the treatment of ocular surface disorders

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ABSTRACT

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 plays a significant role in 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 and therefore, it becomes very important to update ourselves with more studies in this topic to prove the efficiency of this blood derived product. Moreover, the role of other platelet derived products like platelet rich growth factors, platelet lysate in ocular surface disorders have also been discussed.

1. Introduction

Ocular surface disorders broadly includes those conditions in which the ocular surface(conjunctiva, cornea, eyelids, lacrimal glands) is severely affected as in dry eye disease, non-healing corneal ulcers, neurotrophic keratitis, recurrent corneal erosions, post-LASIK Ocular surface problems, Ocular cicatricial pemphigoid(OCP), keratoconjunctivitis sicca(KCS), blepharitis and meibomian gland dysfunction (MGD), allergic eye diseases, chemical and thermal burns graft-versus host disease etc.[1] It is often hard to believe that conventional therapy for these disorders are not enough and require multi-factorial approach. Many researchers have been trying to find out a substance which would be similar in biological properties as natural human tears which would help in regeneration of the severely affected ocular surface in addition to providing epithelial integrity. Such substances are the blood-derived products which contain the identical growth factors, vitamins, nutrients and cytokines which are found in natural tears to support epithelial cell homeostasis, augmentation and cell migration. The first description of this finding was given by Ralph and colleagues in a case series of 6 patients in whom they utilized a mobile perfusion pump to deliver plasma to the ocular surface.[2] Several types of blood derived therapy like Autologous Serum Eye drops, E-PRP, and Umbilical Cord Serum have been described in literature. The role of eye PRP in ocular surface disorders has been sparsely studied in literature for which this article is focussed 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 in the treatment of various ocular surface disorders. The present article is a narrative review describing the application of Eye Platelet rich plasma in ophthalmology and more specifically in Ocular surface conditions.

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The treatment of Ocular surface conditions is tailored according to the individual patient's needs which include artificial tear drops, increasing the secretion of or conserving tears, or targeting the associated inflammation in the ocular surface. There has been a lot of research to find this ideal therapeutic eye drop similar to normal healthy tears which should have exceptional lubrication properties, the accurate biochemical makeup, and the optimal level of growth factors, cytokines, and vitamins to sustain the ocular surface epithelium and preserve health. It should be comfortable, non-toxic, non-infectious, and economical and could be manufactured in large quantities. The most remarkable and recent research has been focussed in the direction of blood derived products that include platelets. The use of Eye Platelet rich plasma for 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 have been studied by many authors, though sparsely, have been thoroughly analyzed in this review article and compiled in the form of Table 1. The number of peer-reviewed articles related to Eye-PRP, Platelet rich in growth factors (PRGF), and Platelet lysate for the treatment of ocular surface disorders which have been published within the period 2000-2020 is shown in the Figure 1.

2. What is E-PRP and how it Acts?

E-PRP is Eye platelet rich plasma which is a portion from 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.[5]

The major effects of PRP are -

1. PDGF (platelet-derived growth factor), the first growth factor to appear in the wound increases the number of repaired cells, stimulate angiogenesis, and support the development of new blood vessels and the activated macrophages. 2. TGF (Transforming growth factor) is responsible for chemotaxis and controlling epithelial proliferation and maintaining cells in an indifferent state.
2. ECGF (epidermal cell growth factor) accelerates corneal epithelial proliferation.
3. VEGF (vascular endothelial growth factor) plays a role in angiogenesis.
4. FGF (fibroblast growth factor 2) takes part in vascular proliferation.

3. How is E-PRP different from other Hemo-derivatives?

There are different varieties of blood derived products with variable amount of growth factors and platelets described in literature some of which are the Autologous serum eye drops (ASE), Platelet rich in growth factors (P-GRF), Tutopatch or Autologous Fibrin Membrane combined with clot of PRP, Platelet Lysate, allogenic serum, umbilical cord serum (UCS) and more recently the E-PRP. The existing difference between the above hemo-derivatives is based on the method of preparation, mechanism of action, efficacy in various ocular surface conditions.

However, E-PRP has been shown to have superior efficacy and easy method of preparation among all the hemo-derivatives.

Ralph and colleagues in 1975 first described the use of blood-derived therapy for ocular surface disorders in a case series in which they created a mobile ocular perfusion pump which could deliver serum or plasma to the ocular surfaces of 6 patients.[6]

Human tears contain EGF, TGF-beta, Fibronectin, vitamin A and a variety of chemokines, which contribute to the tear film milieu that maintains the ocular surface.[8] ASE has similar biochemical properties as those of human tears. The concentrations of Epidermal growth factor are similar in serum (0.7–10ng/mL) and tears (0.5ng/ mL), while vitamin A concentrations are much higher in serum (46mg/mL) than in tears (0.02mg/ mL).[7]

Autologous serum contains cytokines derived from leukocytes and monocytes, which may be detrimental to patients with immunological disorders.[7] Thus, the platelet concentrate is beneficial 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. The concentration of Fibronectin in serum is 205μg/mL and in tear film it is 21ng/mL, TGF-β concentrations are five times higher

in serum than in tears. Therefore, many ophthalmologists prefer to use a 20% dilution of ASE to more closely match the TGF-β concentration in natural tears in order to prevent problems with epithelial cell proliferation.

Fox et al. have demonstrated the efficacy of 50% diluted autologous serum eye drops (ASE) in the treatment of keratoconjunctivitis sicca[8] and Tsubota et al. described the efficacy of 20% ASE drops.[9] ASE like other blood derivatives being a body fluid has the danger of spreading infectious disease. Nakamura et al. have reported that when ASE was combined with antibiotics the biological effect decreases.[10]

There is a mention in literature about PRP prepared by double centrifugation which has to be activated before using it. This was known as the PGRF i.e. the plasma rich in growth factors as described by Marx et al.[11] PRGF preparation required specially designed devices (Endoret system centrifuge, Endoret Ophthalmologic Kit) whereas E-PRP preparation uses commercial tubes to obtain the blood and typical laboratory centrifuge to separate plasma and is prepared by one step centrifugation technique using sodium citrate as an anti-coagulant. While PRGF requires sodium calcium chloride as a clot activator, liquid E-PRP requires calcium chloride for the activation when clots are needed for surgical procedures, such as corneal perforation treatment.[12]

PRGF was first used in the treatment of persistent corneal epithelial defects and dry eyes.[13,14]

Another form of platelet derived product is the Platelet lysate which is obtained from PRP diluted to a final concentration of 30% (v/v), then aliquoted in 1.5-mL sterile vials, freezed at -80C for at least 60 min (thermal shock) and thawed at 4 1C, to induce platelet lysis and PDGF release. A sample for bacterial and fungal detection is collected at the time the product is prepared. The final product is then freezed again at - 20°C and stored in patients' own freezer for a maximum of 45 days.[15,16]

Another hemoderivative is the autologous fibrin membrane which came into picture lately as a tectonic element along with solid PRP in the surgical management of corneal perforations. The major difference from E-PRP is that it is prepared from platelet poor plasma. After centrifugation, 5 ml of Platelet poor plasma is placed in a beaker previously sterilized with 500 ml of 10% calcium chlorite and 1 ml of previously prepared autologous thrombin. The mix is incubated at 37*C for 1 h. After the incubation, the fibrin membrane obtained is circular, with a diameter of between 18 and 22 mm, and its thickness 1 mm and can be used over large corneal perforations.

4. How is E-PRP Prepared?

E-PRP is prepared under strict sterile conditions inside a laminar flow hood using sterile and disposable materials. Whole patient's blood is collected under aseptic conditions using 3.2% sodium citrate as anticoagulant and introduced into a centrifuge. After one-step centrifugation (10 min 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. PRP is aspirated and 3–4 ml aliquots are transferred into new sterilized amber glass bottles with eye drop applicators. The bottle meant for clinical use is kept in the refrigerator at 4*C for 1 week, and the rest of the bottles in the freezer at-20*C.[14]

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. The difference between eye drop and a clot preparation is that in eye drop, there is 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.

More recently, few authors have done a research on E-PRP activated by chitosan and tried on rabbit eye model simulating severe dry eyes and proved that TEMPO-oxidized sacchachitin nanofibers (TOSCNFs) effectively promoted the healing effect on severe cases of corneal damage, and also enhance the clinical application and medical potential of PRP in ophthalmology.[17]

5. Clinical application of E-PRP in Ocular Surface Disorders

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

6. Non-Healing Corneal Ulcers

Non healing corneal ulcers are the refractory persistent corneal epithelial defects which 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. There are quite a few studies describing efficacy of ASE in non-healing corneal ulcers.

Lopez-Plandolit and associates saw a PED healing rate of 85% of patients (17 of 20 eyes) in an average of 10.9 weeks on treatment with PRGF.[18] Point to consider is that 6 of the patients had been previously treated with ASE but not much effective. One patient required an amniotic membrane graft, thus making it somewhat difficult to assess whether there was an isolated effect of PRGF or the combined tectonic effect of the AMG.

A similar study done by Sanchez-Avila RM et al. in 2018 have shown that PRGF eye-drops could be a safe and effective therapeutic option for patients with stages 2-3 of Neurotrophic Keratitis, showing high rates of resolution of corneal ulcer in shorter times thereby reducing further complications.[19]

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.[20] 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.

Chiang et al. evaluated the efficacy and safety of allogenic serum from the patients' relatives in the treatment of persistent corneal epithelial defect (PED) in 36 patients with PED and found out that all patients showed complete healing after a maximum of two months without any adverse effects.[21]

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.[22]

Wróbel- Dudzińska D et al. evaluated the efficacy of autologous PRP in 25 patients with non-healing corneal ulcers five times/day for 3 months or till complete healing. They found that there was 80% healing of the ulcers and 100% improvement in BCVA and subjective symptoms.[23]

7. Dry Eye Syndrome

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.[24]

The definitive therapy for dry eyes is tear substitutes, although the anticipated results are not very optimal and often ineffective. Therefore, the need for additional therapeutic strategies based on blood derived products came into picture. Autologous serum eye drops (ASE), Platelet rich plasma (PRP) and plasma rich in growth factors (PRGF) have also been documented as successful treatments for moderate to severe dry eye. PRP has been reported to be superior to ASE, due to its higher concentration of growth factors, anti-inflammatory cytokines, and other platelet derivatives, which could be beneficial for the required ocular surface restoration in moderate to severe forms of dry eye.[25–27]

Silvia Lo´pez-Plandolit et al. in 2011 studied the efficacy of PRGF in 16 patients with moderate to severe dry eyes who did not respond to previous treatments. After 30 days of treatment they found significant improvement in dry eye questionnaire scoring but surprisingly did not correlate with the degree of squamous metaplasia measured by impression cytology. A Prospective, Interventional, Non-Randomized Study done in 2017 by Alio et al. studied 386 patients with moderate to severe dry eye disease treated with 6 weeks of monotherapy with E-PRP, have reported 87 percent improvement in dry eye symptoms and 29% patients improvement of at least 1 line of BCVA.[30] 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. They found that PRP treatment was more superior to Sodium Hyaluronate regarding improvement in visual acuity, decrease in hyperemia, osmolarity, conjunctival and corneal staining.[28]

8. Post LASIK Ocular Surface Syndrome

In present times, the most common refractive procedure done is LASIK and the most common cause of postoperative dissatisfaction among patients is ocular surface discomfort which may have medico-legal implications. LASIK results in surface ablation which may result in corneal denervation, alteration in corneal shape and changes in tear film quantity and quality.[29] It is also seen that there is 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.[30] They concluded that PRP drops promote epithelial status after LASIK but have no positive effect on recovery of corneal sensitivity, most likely due to the limited bioavailability of growth factors in corneal stroma when the substance is topically administered.

Alio et al. in 2007 did a pilot study in a small group of 26 eyes to study the efficacy of 4 weeks 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.[31]

Later in 2017 they have 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.[32] They reported that there was relief in dry eye symptoms, healing of punctate keratitis, improvement in conjunctival hyperemia and increase in 1-line corrected distant visual acuity after the treatment.

In a retrospective case series of 32 patients with post-LASIK Ocular surface syndrome, Sanchez-Avila, RM et al tried using PRGF four times daily for 6 weeks(1 cycle)-6 months(4 cycles), and compared with conventional regimen of Antibiotic, corticosteroids, Autologous serum, Artificial tears and have shown that PRGF could be a safe and therapeutic alternative in such patients. However, future randomized clinical studies will be necessary to properly confirm this preliminary results.[33]

9. Peri-ocular Chemical and Thermal Burns

More than two-thirds of facial burns involve the eye or periocular area and 7.5-27% of all patients treated for burns have ocular involvement. Eighty-four percent of these are due to chemicals and 16% due to thermal injury.[34]

Most ocular sequel including corneal ulcerations usually are seen secondary to post burn eyelid deformities. Marquez et al. in 2007 studied 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.[35]

Early wound debridement and skin grafts may be successful but unsuitable patient condition for surgical procedure and inadequate donor graft area make it often impossible for skin grafting, therefore there is a need to find an alternative which would improve the wound healing, be readily available, less expensive and wouldn't affect the morbidity of the patient. Such a substance is the PRP which can be used as an adjunct to the split skin grafts when used for eyelid reconstruction. Advantages of its use is that it can be readily available, effective, reduces scar hypertrophy, less wound healing period, less pain and pruritus etc.[36]

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 therapy, corneal transparency and visual acuity showed significant improvement in group I patients compared to group II.[37]

There is a recently published single case report by Alvarado et al. where in they have used solid PRP along with Allogenic Limbal stem cell transplant for a patient with previously diagnosed Limbal stem cell deficiency suffering a lime burn and have shown excellent improvement in BCVA postoperatively.[38]

10. Adjunct in Ocular Surface Reconstruction In Large Corneal Perforation

Corneal perforations pose an immediate danger to the ocular integrity which needs emergency surgical intervention. Small corneal perforations can be managed with bandage contact lenses and cyanoacrylate glue, fibrin glue, conjunctival flaps etc but large corneal perforations need amniotic membrane transplantation or keratoplasty procedures. Newer modalities of treatment include cultivated corneal, oral mucosal epithelial transplantation, and autologous cultivated corneal limbal epithelial transplantation.[39] Few authors have reports of using combination of solid E-PRP clot as an adjuvant to tectonic elements like autologous fibrin membrane/bovine pericardium/amniotic membrane to close a corneal perforation. The solid form of E-PRP clot has the advantage of having 2-3 times more concentrated platelets than the topical form. Alio´et al.[22] presented a case series with corneal perforations or impending perforations with amniotic membrane grafts combined with E-PRP clot and got successful outcome in 71% (10/14 eyes) which had complete resolution. 57% eyes improved in visual acuity after 1-2 weeks of surgery. The improvement in clinical outcome may be 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 decrease inflammation. The role of the Amniotic membrane was to conserve the solid clot attached at the damaged surface.

Further studies were done using bovine pericardium also known as the Tutopatch on 6 patients, with low biological risk also showed completely healed perforations after 3 months of treatment, the only drawback being that it was opaque in color and not soft for the eye.[40] Point to note is that 3 out of the 6 patients suffered with Ocular cicatricial pemphigoid.

Autologous fibrin membrane has also been tried along with E-PRP in corneal perforations by Francisco et al. in 2013 where 11 patients with corneal perforations were treated with autologous fibrin membrane along with solid E-PRP clot.[41] They reported that the fibrin membrane stays on the ocular surface for about 5 days and then gradually disappeared. The perforations were sealed in 7 days and there was no evidence of any leakage with no further relapse. Hence, they have concluded that it is a safe and effective alternative for the closure of corneal perforations with an obvious advantage of this material being 100% autologous.

11. Autoimmune Conditions

Many of the Autoimmune diseases such as Sjogrens 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. Ocular surface manifestations are also seen in Ocular cicatricial pemphigoid and Moorens' ulcer which have different pathology i.e, inflammatory other than dry eye syndrome and hence the mode of management is different.

Avila MY et al. evaluated the effectiveness of platelet rich plasma (PRP) injections to lacrimal gland at 1 month 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.[42] They suggested that PRP contains several components with known pro regenerative capabilities in secretory tissues, stem cell properties, indirect antifibrotic properties and anti-apoptotic activities. We believe, future studies must be tried in the direction of treating other autoimmune conditions like Rheumatoid arthritis, GVHD, OCP etc with these newer methods.

Kyung-Sun Na et al. in 2012 tried allogeneic serum eye drops in patients with chronic graft-versus-host disease (cGVHD) following bone marrow transplantation diagnosed with dry eye syndrome refractory to conventional treatment for four weeks. They found out that when autologous extraction is not possible for some circumstances, allogenic serum eye drops can be tried which have a positive therapeutic effect without any significant side effects.[43]

Pezzotta et al. treated with autologous plasma rich in PDGFs eye drops 23 patients affected by ocular GVHD (severity grade II to IV) unresponsive to standard medical therapy. Photophobia improved in 82.6% of patients, TFBUT in 86.9% and anterior segment score in 82.6%. The positive response was maintained over the time.[44]

Moorens ulcer is a chronic, painful peripheral ulcer of the cornea. Treatment options available are anti-inflammatory drugs (steroidal and non-steroidal), topical and systemic cytotoxic drugs, conjunctival resection and superficial keratectomy.[45] But there is no evidence to show which is the most effective amongst these treatment modalities and E-PRP has still not been tried which we believe may be an option.

Arnalich F et al. tried Tutopatch in one patient with severe ocular cicatricial pemphigoid and long history of limbal stem cell deficiency with previous limbal stem cell transplantation suffered a relapse, and a penetrating keratoplasty was performed after 1 month. We believe this case may be an eye opener for all since the prognosis in such patients is however poor after so many procedures.[46]

Sanchez Avilla et al. in 2017 have tried PRGF (Endoret) in the treatment of moderate to severe dry eye in patients with primary and secondary Sjogrens syndrome and reported that there was a significant reduction in OSDI scores and 63% improvement in visual acuity.[47]

12. Risks and Technical Issues

Regardless of the important role-played by platelet related products in the treatment of ocular surface disorders, there are few technical issues which need to be resolved and obvious risks in the clinical use.

1. There are no International standardized protocol and guidelines for the preparation of the platelet derived products. A recent international survey about the methods of preparation of serum eye drops showed that large procedural differences in the collection, clotting time, centrifugation, dilution, screening of infectious disease and storing are present among all the centres.[48]
2. Currently, there is still debate whether blood-derived eye drops should be considered as a blood product or as a drug.
3. The potential transmission of infectious diseases is a major risk of blood-derived eye drops, and may occur due to infectious disease of the donor or microbial contamination during the preparation or the prolonged use of the initially sterile dropper bottle.
4. Adverse events have been reported after administration of these preparations which are usually minor and resolve in few days however, large population cohorts need to be studied to confirm the results.

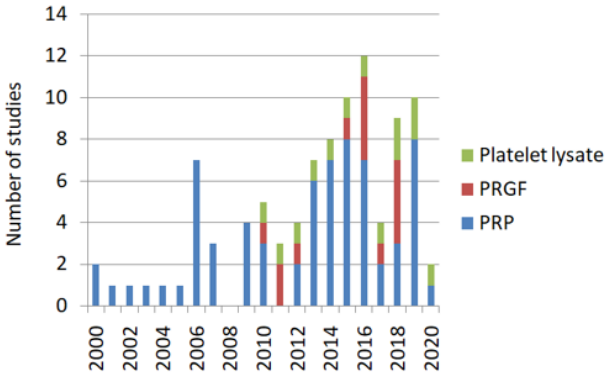

Fig. 1:

Table 1: Detailed analysis of the peer reviewed studies related to the use of platelet-derived product according to the type of Ocular surface condition

Condition	Product	Study design	Patients	Control arm	Frequency	Duration of Treatment	Concomitant therapy	Results
Non healing corneal ulcers	PRGF	Lopez-Plandolit et al 2010 Prospective	18	None	2 hrly X 3 days then variable	Until healing	Antibiotic and steroid	85% healing within 11 weeks
	PRP	Kim et al2012 Retrospective	28	ASE	Not mentioned	Till complete healing	Artificial tears substitutes	11/11 treated with PRP showed complete healing
	PRP (topical, solid)	Alio et al 2007 Prospective, non-randomized	38	None	6 times/day	21 days	None	95% success, 5%no change
	PRP	Wrobel et al 2018 Prospective, nonrandomized	25	None	5 times/day	3 months or till complete healing	Artificial tear drops, Vitamin A ointment	Complete healing 80% BCVA improved 100%
	PRGF	Sanchez et al 2018, Retrospective	31	None	4 times/day	6 weeks	Antibiotic agents, anti-inflammatory, artificial tears	97% complete healing, 53% improved BCVA
Dry eye(mod-severe)	PRP	Alio et al 2017 Prospective, non-randomized	386	None	6 times/day	6 weeks	None	Symptomatic improvement 87%, 29% improve in BCVA
	PRP	Garcia et al 2019 Prospective, randomized	83	Sodium Hyaluronate	6 times/day	4 weeks	None	PRP group more visual improvement, Fluorescein staining.
	PRGF	López-Plandolit et al 2011	16	None	4 times/day	3 months	None	Significant improvement in dry eye symptoms
Post LASIK Ocular surface syndrome	PRGF	Sanchez-Avila et al (2018), Retrospective comparative	42	Artificial tears, corticosteroids, Autologous	4 times/day	6 weeks-6 months	Antibiotic agents, anti-inflammatory agents, artificial tears	Significant improvement in OSDI, BCVA,VAS
	E-PRP	Alio et al, (2017)	80	Serum, cyclosporine	6 times/day	6 weeks	None	

Continued on next page

Table 1 continued

	E-PRP	Javaloy et al(2013)	108	None	6 times/day	3 months	None	Symptomatic relief, improved BCVA Improved epithelial status
Chemical ocular burns	Sub conj PRP	Marquez et al (2007) Prospective randomized	10 Single Sub- conj PRP injection	Cyclopentolate, Dexamethasone Tobramycin, Retinol palmitate Gentamicin DL-Methionine	Single sub conj injection	Till complete healing seen	Conventional therapy, Antibiotic and steroid cream after injection	Significant reduction in cicatrization time, early healing in PRP group (6 days)
	Topical PRP	Panda et al (2012) Prospective randomized	20	Steroid Cycloplegics, Sodium citrate, Ascorbate	10 times/day	3 months	Steroid Cycloplegics, Sodium citrate, Ascorbate	Significant improvement in corneal clarity and BCVA in PRP group
Large Corneal perforation	PRP clot with Tutopatch	Alio et al (2013)	6	None	-	-	Systemic Antibiotic, NSAIDS	100% complete healing, 57% improved BCVA
Auto immune conditions-GVHD	Platelet lysate	Pezzotta et al (2012)	23	None	4times/day	6 months	None	TBUT improved in 87%
Sjogrens syndrome	PRP injection to lacrimal gland	Avila MY et al (2019) Prospective	15	Hyaluronic acid 5times/day	3 Inj at 1month interval	3 months	Topical Hyaluronate	Improvement in TBUT, OSDI scores
	PRGF-Endoret topical	Sanchez-Avila et al (2017) Retrospective	26	None	4 times/day	6 weeks	Antibiotic agents, anti-inflammatory, artificial tears	63% Improvement in BCVA, reduction in OSDI scores

13. Conclusion

Eye platelet rich plasma 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. Previous animal and human clinical studies have shown a good profile in terms of both safety and efficacy for different ocular surface problems. However further randomized clinical trials and international guidelines are the need of the hour which will help in more wide preparation and use of the products in our daily clinical practice.

14. Source of Funding

None.

15. Conflict of Interest

The author(s) declare(s) that there is no conflict of interest.

References

1. Khanna RC. Ocular surface disorders. *Community Eye Health*. 2017;30(99):1–2.
2. Alio JL, Rodriguez AE, WróbelDudzińska D. Eye platelet-rich plasma in the treatment of ocular surface disorders. *Curr Opin Ophthalmol*. 2015;26(4):325–32. doi:10.1097/icu.0000000000000169.
3. Nurden A. Platelets, inflammation and tissue regeneration. *Thromb Haemost*. 2011;105(S 06):S13–S33. doi:10.1160/ths10-11-0720.
4. Liu L, Hartwig D, Harloff S, Herminghaus P, Wedel T, Kasper K, et al. Corneal Epitheliotrophic Capacity of Three Different Blood-Derived Preparations. *Investig Opthalmol Vis Sci*. 2006;47(6):2438. doi:10.1167/iovs.05-0876.
5. Ralph RA, Doane MG, Dohlman CH. Clinical Experience With a Mobile Ocular Perfusion Pump. *Arch Ophthalmol*. 1975;93(10):1039–43. doi:10.1001/archopht.1975.01010020815015.
6. Yamada C, King KE, Ness PM. Autologous serum eyedrops: literature review and implications for transfusion medicine specialists. *Transfus*. 2008;48(6):1245–55. doi:10.1111/j.1537-2995.2008.01665.x.
7. Geerling G. Autologous serum eye drops for ocular surface disorders. *Br J Ophthalmol*. 2004;88(11):1467–74. doi:10.1136/bjo.2004.044347.
8. Fox RI, Chan R, Michelson JB. Beneficial effect of artificial tears made with autologous serum in patients with keratoconjunctivitis sicca. *Arthritis Rheum*. 1984;27:459–61.
9. Tsubota K, Goto E, Shimmura S, Shimazaki J. Treatment of persistent corneal epithelial defect by autologous serum application. *Ophthalmol*. 1999;106(10):1984–9. doi:10.1016/s0161-6420(99)90412-8.
10. Nakamura M, Nishida T, Mishima H, Otori T. Effects of antimicrobials on corneal epithelial migration. *Curr Eye Res*. 1993;12(8):733–40. doi:10.3109/02713689308995769.
11. Marx RE. Platelet-Rich Plasma (PRP): What Is PRP and What Is Not PRP? *Implant Dent*. 2001;10(4):225–8. doi:10.1097/00008505-200110000-00002.
12. Plandolit SL, Morales MC, Freire V. Plasma rich in GFs as a therapeutic agent for persistent corneal epithelial defects. *Cornea*. 2010;29:843–8.
13. López-Plandolit S, Morales MC, Freire V, Grau AE, Durán JA. Efficacy of Plasma Rich in Growth Factors for the Treatment of Dry Eye. *Cornea*. 2011;30(12):1312–7. doi:10.1097/ico.0b013e31820d86d6.
14. Alio JL, Arnalich-Montiel F, Rodriguez AE. The Role of "Eye Platelet Rich Plasma" (E-Prp) for Wound Healing in Ophthalmology. *Curr Pharm Biotechnol*. 2012;13(7):1257–65.
15. Pezzotta S, Fante CD, Scudeller L, Cervio M, Antoniazzi ER, Perotti C. Autologous platelet lysate for treatment of refractory ocular GVHD. *Bone Marrow Transplant*. 2012;47(12):1558–63. doi:10.1038/bmt.2012.64.
16. Sandri G, Bonferroni MC, Rossi S. Platelet lysate formulations based on mucoadhesive polymers for the treatment of corneal lesions. *J Pharm Pharmacol*. 2011;63:189–98.
17. Lin HL, Wu TH, Ho HO, Chao FC, Wu MH, Liu DZ, et al. TEMPO-Oxidized Sacchachitin Nanofibers (TOSCNFs) Combined with Platelet-Rich Plasma (PRP) for Management of Dry Eye Syndrome. *Int J Nanomedicine*. 2020;15:1721–30.
18. López-Plandolit S, Morales M, Freire V, Etxebarría J, Durán JA. Plasma Rich in Growth Factors as a Therapeutic Agent for Persistent Corneal Epithelial Defects. *Cornea*. 2010;29(8):843–8. doi:10.1097/ico.0b013e3181a81820.
19. Sanchez-Avila RM, Merayo-Lloves J, Riestra AC, Cueto LFV, Anitua E, Begoña L, et al. Treatment of patients with neurotrophic keratitis stages 2 and 3 with plasma rich in growth factors (PRGF-Endoret) eye-drops. *Int Ophthalmol*. 2018;38(3):1193–1204. doi:10.1007/s10792-017-0582-7.
20. Kim KM, Shin YT, Kim HK. Effect of autologous platelet-rich plasma on persistent corneal epithelial defect after infectious keratitis. *Jpn J Ophthalmol*. 2012;56(6):544–50.
21. Chiang CC, Chen WL, Lin JM, Tsai YY. Allogeneic serum eye drops for the treatment of persistent corneal epithelial defect. *Eye*. 2009;23(2):290–3. doi:10.1038/sj.eye.6703079.
22. Alio JL, Abad M, Artola A, Rodriguez-Prats JL, Pastor S, Ruiz-Colecha J. Use of Autologous Platelet-Rich Plasma in the Treatment of Dormant Corneal Ulcers. *Ophthalmol*. 2007;114(7):1286–93.e1. doi:10.1016/j.ophtha.2006.10.044.
23. Wróbel-Dudzińska D, Alio J, Rodriguez A, Suchodoła-Ratajewicz E, Kosior-Jarecka E, Rymgayłło-Jankowska B, et al. Clinical Efficacy of Platelet-Rich Plasma in the Treatment of Neurotrophic Corneal Ulcer. *J Ophthalmol*. 2018;2018:1–7. doi:10.1155/2018/3538764.
24. The definition and classification of dry eye disease: report of the definition and classification subcommittee of the international dry eye workshop. *Ocul Surf*. 2007;5(2):75–92.
25. Alio JL, Colecha JR, Pastor S, Rodriguez A, Artola A. Symptomatic Dry Eye Treatment with Autologous Platelet-Rich Plasma. *Ophthalmic Rese*. 2007;39(3):124–9. doi:10.1159/000100933.
26. Hussain M, Shtein RM, Sugar A, Soong HK, Woodward MA, DeLoss K, et al. Long-term Use of Autologous Serum 50% Eye Drops for the Treatment of Dry Eye Disease. *Cornea*. 2014;33(12):1245–51. doi:10.1097/ico.0000000000000271.
27. Urzua CA, Vasquez DH, Huidobro A, Hernandez H, Alfaro J. Randomized Double-Blind Clinical Trial of Autologous Serum Versus Artificial Tears in Dry Eye Syndrome. *Curr Eye Res*. 2012;37(8):684–8. doi:10.3109/02713683.2012.674609.
28. García-Conca V, Abad-Collado M, Hueso-Abancens JR, Mengual-Verdú E, Piñero DP, Aguirre-Balsalobre F, et al. Efficacy and safety of treatment of hyposecretory dry eye with platelet-rich plasma. *Acta Ophthalmol*. 2019;97(2):170–8. doi:10.1111/aos.13907.
29. Toda I. LASIK and the ocular surface. *Cornea*. 2008;27(1):70–6.
30. Javaloy J, Alió JL, Rodriguez AE, Vega A, Muñoz G. Effect of Platelet-Rich Plasma in Nerve Regeneration After LASIK. *J Refract Surg*. 2013;29(3):213–9. doi:10.3928/1081597x-20130129-04.
31. Alio JL, Pastor S, Ruiz-Colecha J, Rodriguez A, Artola A. Treatment of Ocular Surface Syndrome After LASIK With Autologous Platelet-rich Plasma. *J Refract Surg*. 2007;23(6):617–9. doi:10.3928/1081-597x-20070601-13.
32. Alio JL, Abad M, Artola A, Rodriguez-Prats JL, Pastor S, Ruiz-Colecha J. Use of Autologous Platelet-Rich Plasma in the Treatment of Dormant Corneal Ulcers. *Ophthalmol*. 2007;114(7):1286–93.e1. doi:10.1016/j.ophtha.2006.10.044.
33. Sanchez-Avila RM, Merayo-Lloves J, Fernandez ML, Rodriguez-Gutierrez LA, Jurado N, Muruzabal F, et al. Plasma Rich in Growth Factors for the Treatment of Dry Eye after LASIK Surgery. *Ophthal*

Res. 2018;60(2):80–6. doi:10.1159/000487951.
34. Sarabahi S, Kanchana K. Management of ocular and periocular burns. *Indian J Burns*. 2014;22(1):22–32. doi:10.4103/0971-653x.146997.
35. Marquez-De-Aracena R, Montero-De-Espinosa, Munoz M, Pereira G. Subconjunctival application of plasma platelet concentrate in the treatment of ocular burns, Preliminary results. *Arch Soc Esp Oftalmol*. 2007;82:475–82.
36. Unal M. Platelet-Rich Plasma in Burn Treatment. In: Kartal SP, Bayramgurler D, editors. Hot Topics in Burn Injuries. Intech Open; 2018. p. 87–104.
37. Panda A, Jain M, Vanathi M, Velpandian T, Khokhar S, Dada T. Topical Autologous Platelet-Rich Plasma Eyedrops for Acute Corneal Chemical Injury. *Cornea*. 2012;31(9):989–93. doi:10.1097/ico.0b013e3182114661.
38. Alvarado-Villacorta R, García-Carmona KP, Martínez-Pardo ME, Vázquez-Maya L. Allogeneic Limbal Epithelial Transplantation Modified With Solid Platelet-Rich Plasma for Bilateral Limbal Stem Cell Deficiency. *Cornea*. 2020;39(10):1311–4. doi:10.1097/ICO.0000000000002321.
39. Nakamura T, Kinoshita S. New hopes and strategies for the treatment of severe ocular surface disease. *Curr Opin Ophthalmol*. 2011;22(4):274–8. doi:10.1097/icu.0b013e3283477d4d.
40. Alio JL, Rodriguez AE, Martinez LM. Bovine Pericardium Membrane (Tutopatch) Combined With Solid Platelet-Rich Plasma for the Management of Perforated Corneal Ulcers. *Cornea*. 2013;32(5):619–24. doi:10.1097/ico.0b013e31825a6d9a.
41. Alio JL, Rodriguez AE, Martinez LM, Rio AL. Autologous fibrin && membrane combined with solid platelet-rich plasma in the management of perforated corneal ulcers: a pilot study. *JAMA Ophthalmol*. 2013;131(6):745–51.
42. Avila MY, Igua AM, Mora AM. Randomised, prospective clinical trial of platelet-rich plasma injection in the management of severe dry eye. *Br J Ophthalmol*. 2019;103(5):648–53. doi:10.1136/bjophthalmol-2018-312072.
43. Na KS, Kim MS. Allogeneic serum eye drops for the treatment of dry eye patients with chronic graft-versus-host disease. *J Ocul Pharmacol Ther*. 2012;28(5):479–83.
44. Pezzotta S, Fante CD, Scudeller L, Cervio M, Antoniazzi ER, Perotti C. Autologous platelet lysate for treatment of refractory ocular GVHD. *Bone Marrow Transplant*. 2012;47(12):1558–63. doi:10.1038/bmt.2012.64.
45. Alhassan MB, Rabiu M, Agbabiaka IO. Interventions for Mooren's ulcer. *Cochrane Database Syst Rev*. 2011;doi:10.1002/14651858.CD006131.pub2.
46. Arnalich F, Rodriguez AE, Luque-Rio A, Alio JL. Solid Platelet Rich Plasma in Corneal Surgery. *Ophthalmol Ther*. 2016;5(1):31–45. doi:10.1007/s40123-016-0051-9.
47. Sanchez-Avila RM, Merayo-Lloves J, Riestra AC, Anitua E, Muruzabal F, Orive G. The Effect of Immunologically Safe Plasma Rich in Growth Factor Eye Drops in Patients with Sjögren Syndrome. *J Ocul Pharmacol Ther*. 2017;33(5):391–9. doi:10.1089/jop.2016.0166.
48. Marks DC, van der Meer and PF. Serum eye drops: a survey of international production methods. *Vox Sanguinis*. 2017;112(4):310–7. doi:10.1111/vox.12502.

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