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The use of platelet rich-plasma in Ophthalmology: a literature review

O uso do concentrado de plaquetas na oftalmologia: uma revisão de literatura

Marina Viegas Moura Rezende Ribeiro[1], Vinícius Falcão de Melo[2], Maria Eduarda Fragoso Calado Barbosa[3], Marina Umbelino de França Tozzi[3], Matheus Soares Baracho Ramos[3], Natália Maria Sampaio Ribeiro Soares Gaia[3], Victor Machado Guimarães Santos[3], Willian de Oliveira Neri[3], Fabiano Timbó Barbosa[1], Êurica Adélia Nogueira Ribeiro[4]

Abstract

The aim of this review is to list the ophthalmological conditions in which platelet concentrate (CP) has been used, as well as its biochemical and physiological properties. The CP has both anticatabolic potential, present in autologous serum, and substances with anabolic properties, which together are responsible for its benefits in the treatment of ocular surface diseases. There is currently a shortage of clinical trials in this area, both in ophthalmology and other medical areas, with more studies and reports on the use of autologous serum. In ophthalmology, CP has been used in the treatment of symptomatic dry eye, corneal ulcers and ocular burns, among other applications, being an effective alternative in several ocular pathologies; therefore, it's evident the importance of more studies in this topic to prove the efficiency of this product.

Keywords: *Platelet-rich plasma; Growth factors; Dry eye syndrome; Platelet concentrate; Platelets; Eye diseases*

Resumo

Esta revisão tem por objetivo elencar as condições oftalmológicas em que tem sido utilizado o concentrado de plaquetas (CP), assim como as suas propriedades bioquímicas e fisiológicas. O CP possui tanto o potencial anticatabólico, presente no soro autólogo, quanto substâncias com propriedades anabólicas, que em conjunto são responsáveis pelos seus benefícios no tratamento de doenças da superfície ocular. Atualmente há um lapso de ensaios clínicos neste tema, tanto na oftalmologia como em outras áreas médicas, existindo mais estudos e relatos sobre o uso de soro autólogo. Em oftalmologia, o CP tem sido usado no tratamento do olho seco sintomático, úlceras corneanas, queimaduras oculares dentre outras aplicações, sendo uma alternativa eficaz em diversas patologias oculares; portanto, é evidente a importância de mais estudos nesse tema, para comprovar a efetividade do produto.

Descritores: Plasma rico em plaquetas; Fator de crescimento; Síndromes do olho seco; Concentrado de plaquetas; plaquetas; Oftalmopatias

[1] Universidade Tiradentes, Maceió, AL, Brazil.
[2] Doctor, Resident in Ophthalmology Cervi, Maceió, AL, Brazil.
[3] Medicine Student, Universidade Tiradentes, Maceió, AL, Brazil.
[4] Postgraduate Program in Health Sciences, Universidade Federal de Alagoas, Maceió, AL, Brazil.

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Introduction

The search for better alternative ophthalmologic treatments in pathologies, mainly of the ocular surface, has been increasing considerably over the last decades, with emphasis in the use of the platelet concentrate (PC), which is defined by Marx (2001) as a volume of plasma containing a platelet count above the baseline of whole blood.[1]

In recent years, its interest in clinical use as biomaterial has increased in regenerative medicine, given its ability to repair different tissues. Among the publications described there are clinical applications including oral and maxillofacial[2,3] and periodontal[4-6] surgeries, cosmetic plastic surgery,[7] orthopedic surgery,[8,9] dermatology,[10,11] scalp[12] and acute traumatic lesions of musculoskeletal tissues.[13]

In ophthalmology, the area discussed in the present study, the use of PC was reported by Rezende et. al. in 2007 for the treatment of neurotrophic ulcers,[14] and also in subsequent studies for the treatment of symptomatic dry eye and persistent epithelial defects,[15,16] among other uses. The present study is a narrative review describing the use of platelet concentrate in ophthalmology.

Comparison: autologous serum x platelet concentrate

The autologous serum presents characteristics that are very similar to tears, such as pH, osmolarity, vitamin A and immunoglobulin A.[17] Zhou et al. showed that the tear has several individually varying components, such as albumin, lactoferrin, lysozymes, aldolase, amylase, fibronectin and substance P.[18]

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.[17]

The use of autologous serum was first described in search of a lubricant eye drop free from harmful preservatives,[19] later showing that due to the presence of growth factors and vitamins, it could also have a true epitheliotrophic potential.[20] Thus, serum was used as a novel therapeutic approach for ocular surface disorders such as persistent epithelial defects or severe dry eye untreatable with conventional therapy.

Autologous serum has been described not only as a lubricant of the ocular surface, but also as a supplier of various substances essential for the reconstruction of epithelial damage, including vitamin A, epithelial growth factor, fibronectin and a variety of cytokines. With these epitheliotrophic factors, serum facilitates proliferation, migration and differentiation of the ocular surface epithelium.[22] 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.[23]

Therefore, this product has been effective in the treatment of persistent epithelial defects,[20] neurotrophic ulcers,[24] superior limbic keratoconjunctivitis,[25] and dry eye conditions such as graft versus host disease[26] or after refractive surgeries such as LASIK (Laser Assisted in situ Keratomilesius).[27]

Autologous serum and platelet concentrate have similar compositions, since they have various growth and healing factors present in the blood.[16,28] However, autologous serum contains proinflammatory cytokines derived from leukocytes and monocytes, which may be harmful to patients with immunological disorders or diseases.[21,29] Thus, the platelet concentrate 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.[30]

In addition, PC becomes more effective when presenting higher indexes of growth factors such as: EGF (epithelial growth factor), vitamin A, neural growth factor (NGF), Insulin type I growth factor[16,28] and platelet factor IV.[31]

Ribeiro et al. also demonstrated in 2016 how the factors mimic the physicochemical properties of natural tears,[31] which was also demonstrated by Quinto et al. regarding their importance in the stability of the corneal and conjunctival epithelium and their mechanical and lubricating properties, and also the epitheliotropic and antimicrobial effects.[17]

Growth factors are in high concentrations in PRP as anabolic agents to aid or enhance the healing of damaged tissues, being proteins that play an essential role in tissue repair and regeneration processes.[13]

Methods for obtaining the platelet-rich concentrate

The Platelet Concentrate consists of a platelet suspension in plasma prepared by double centrifugation of a whole blood unit, and also by apheresis.[32]

Platelet Concentrates obtained from whole blood can be produced from platelet-rich plasma or the whole blood leuco-platelet layer by different methods.

The first method consists of two-stage blood centrifugation. In the first stage, a light centrifugation is performed to obtain the platelet rich plasma (PRP). In the second stage, this plasma is centrifuged again, this time in high rotation, to obtain the platelet concentrate.[33]

The second method is based on the extraction of the buffy coat or leucoplatelet layer, usually with the use of automated plasma extractors and the use of top and bottom bags. The whole blood is subjected to centrifugation in order to separate the leucoplatelet layer. The supernatant plasma is transferred to a satellite bag through the top outlet of the bag, and the red cell concentrate is extracted through the bottom outlet of the bag. The leucoplatelet layer remains in the original bag.[33]

Apheresis is a process by which whole blood is collected from a donor or patient and separated into components, allowing one or more components to be retained while the remaining elements return to the donor or patient. Depending on the component removed, it may be classified as plasmapheresis, cimepheresis or selective apheresis (when only one substance present in the plasma is retained, and not the whole plasma). It can be used for therapeutic purposes or to obtain a blood component for transfusion purposes. The therapeutic apheresis procedures are aimed at removing a pathogenic element from the blood, such as an immunoglobulin, plasma protein and platelets.[34]

Transfusion or autologous donation is the procedure in which the donor-recipient binomial occurs in the same individual. It is an alternative for the use of blood or components in patients undergoing surgeries (elective or emergency), preventing the use of homologous blood and possible consequences of its use, as transmission of diseases. In this category, preoperative autologous transfusion accounts for the majority of cases.[35]

How to prepare platelet-rich concentrate eye drops

The patient makes the autologous donation, which can be of whole blood or apheresis.[32] Each PC unit contains approximately 5.5 x 10^{10} platelets in 50-60 ml of plasma, whereas the apheresis units contain at least 3.0 x 10^{11} platelets in 200-300ml of plasma, and it should be stored at 22 ± 2°C under constant stirring.[33]

For use and storage, it is reported that eye drops are transferred to 4 ml vials, and patients should be instructed to store it

in the refrigerator at -20°C until needed. The eye drops in use should be kept under refrigerated conditions at 4°C, and should be used for one week to keep all their properties.[15]

In addition to eye drops, PC can also be used in the injectable formulation and as fibrin bioadhesives or fibrin membrane, with sealant property.[36] The solid formulation is prepared with 1 ml of PC and 50 ml of calcium chloride 10%, after which it is incubated at 37°C for 30 minutes, thus obtaining a platelet concentration of two to three times the concentration in the blood.[37]

In addition, Alio reported in 2015 the existence of the autologous fibrin membrane obtained after centrifugation, in which 5 ml PC were placed in a pre-sterilized tube with 500 ml of calcium chlorite 10% and 1 ml of autologous thrombin previously prepared . The mixture was incubated at 37°C for 1h.[37]

In face of the study carried out in rabbits, it is believed that the treatment based on PC eye drops is indicated for cases in which the objective is a rapid corneal epithelization. In lesions with large stromal loss, the association of solid PC and amniotic membrane is recommended, as well as its use in isolation.[38]

Composition and mechanism of action of platelet-rich concentrate

Platelets are small anucleated cytoplasmic fragments of 5 to 7 μm diameter and less than 3 μm width, originating from the megakaryocytes of the bone marrow. CP is obtained from them, which must have at least 300,000 platelets per microliter.[39] However, studies differ as to the proper concentration of this product. Some authors, such as Anitua et. al, define PC as blood plasma with a platelet concentration of two to eight times higher than the normal concentration.[40]

The platelet activating factor (PAF) present in PC has a mediating role in inflammation and corneal healing after injury. In rabbits, it was evidenced that this factor activates vascular endothelial growth factor (VEGF) and also induces angiogenesis.[14]

In the blood derivative in question, there is a great concentration of substances and proteins working in cicatrisation, which are stored in distinct populations of granules easily distinguishable by electron microscopy, among them: dense granules, alpha granules and lysosomal granules. Dense granules influence cell migration and proliferation, and can determine the vascular tone.[40] Purinergic signaling was demonstrated in these granules, in which nucleotides are linked to the members of the P2Y and P2X receptor families.[41]

Whereas ATP (Adenosine Triphosphate) may act on P2X1 - a subtype of the P2X surface receptor family present in the platelet - participating in the platelet response to collagen under flow, ADP (Adenosine Diphosphate) promotes platelet aggregation. Ca^2 is a cofactor necessary for platelet aggregation and fibrin formation, and it can also modulate the proliferation and differentiation of keratinocytes.[42]

Serotonin and histamine are both components of PC. Serotonin has receptors on vascular cells, and their release leads to vasoconstriction and increased capillary permeability, whereas in histamine there may be pro and anti-inflammatory action.[40]

The alpha granules contained in platelets are the ones that contribute the most to the therapeutic effects of PC, mainly due to its degranulation. They have growth factors (GFs) inside, among them: Transformation Growth Factor β (TGF-β), Platelet Derived Growth Factor (PDGF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), platelet-derived endothelial growth factor (PDEGF), platelet factor-4, platelet-derived angiogenesis factor (PDAF), and insulin-like growth factor (IGF-1), besides adhesive proteins such as fibrinogen (Fg), fibronectin (Fn), vitronectin (Vn), and thrombospondin-1 (TSP-1), whose function is to increase the matrix / cell interaction.[43-46]

Each growth factor presents a defined period of action, although all are released together by the platelet alpha granules. Initially PDGF acts on angiogenesis and early cell differentiation, whereas TGF-B enhances cell differentiation, and in turn stimulates cell maturation. Maturation is terminated by IGF-1, which schedules the consolidation of healing by stimulating other cells.[2]

The release of GFs occurs mainly in the first hour, but continues throughout the platelet's life span (approximately seven days).[47,48] The growth factors cause a cascade of many reactions responsible for migration, mitosis, formation of extracellular matrix, and angiogenesis of cells.[48]

PDGF is mitogenic for vascularization of smooth muscle tissue and fibroblasts, whereas the alpha-transformation growth factor (TGF-α) has a similar action, but with a higher angiogenic factor in relation to EGF, which presents mitogenic induction for most epithelial tissues, fibroblasts and endothelial cells.

Vascular endothelial growth factor (VEGF) is also mitogenic for endothelial cells, but not for keratinocytes, smooth muscle or fibroblasts, as well as the insulin-like growth factor-1 (IGF-1), which acts on endothelial cells, fibroblasts, bone cells, neural tissue, and hematopoietic cells.

High-affinity neural growth factor (TrkA) and fibroblast growth factor (FGF) are mitogenic for neural tissue, whereas keratinocyte growth factor is mitogenic for epithelial cells, but not for fibroblasts or endothelial cells.[49]

Among the factors, only the tumor growth β (TGF-β-1) and (TGF-β-2) act to inhibit most cells in vitro, including keratinocytes, endothelial cells, lymphocytes, and macrophages, and inhibit or stimulate fibroblasts.[49]

In addition to the alpha granules secreting these growth factors, lysosomal granules are also observed, which function is to secrete acid hydrolases, cathepsins D and E, elastase, and other degradative enzymatic substances. [50]

Clinical use of platelet concentrate

Dry Eye

In recent years, the use of PC 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. Alio worked with a total of 34 patients with moderate or severe dry eye syndrome. PC 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.[15]

Lopez-Plandolit et al. also demonstrated that the concentrate can be used in the treatment of severe dry eye in patients with different etiopatologies such as Sjogren's Syndrome.[51]

Still regarding dry eye, Ribeiro et. al. (2016) analyzed the efficacy of PC treatment in 12 diabetic patients. The results showed improvement in 100% of patients in relation to symptoms such as dryness, burning sensation, itching, foreign body sensation, and redness, and regarding Schirmer's test, 41.66% of patients showed improvement, 50% did not show alterations, and 8.33% had a reduced value after the test.[31]

Options for conventional dry eye therapy include artificial tears supplies, lacrimal point occlusion, contact lenses, and appropriate management of adnexal disease. 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.[17]

Pezzota et al. also tested the effects of platelet concentrate on a total of 23 patients with ocular pathologies of graft versus host disease (grade II-IV) without response to conventional treatments. The results showed that 74% of patients (17 out of 23) were classified as responders to the treatment, showing improvement of dry eye symptoms. Photophobia was the symptom that obtained the most resolution (82.6% of patients). Clinical manifestations were also significantly improved, showing improvement in tear break-up time and corneal fluorescein stain of 86.9% and 69.6%, respectively.[52]

Corneal ulcers

The cornea is an anterior and transparent structure of the fibrous tunica of the ocular bulb. Due to its constant exposure to the environment, it is very susceptible to lesions, which justifies the fact that corneal ulcer is among the most common eye diseases.[53] The healing process of trauma repair begins immediately after epithelial lesion, with the secondary release of cytokines such as interleukins 1 (IL-1), tumor necrosis factor alpha (TNF-a) and growth factors.[54]

Thus, in order to ensure a better prognosis for patients, the use of PC in this pathology was reported by Marquez et al., Geremicca et al., and Panda et al., allowing the formation of a fibrin skeleton that can be used as a membrane in ocular ulcers.[55-57] In general, it is associated with the reduction in repair and epithelization time of the cornea and conjunctiva, with better corneal clarity and visual acuity.[55]

In a study (n = 38) of 2007, Alio et al. demonstrated that 92% of patients with corneal ulcers improved significantly, reducing inflammation and ocular pain after PC treatment.[58] In 2013,[59] Alio et al. also observed the potential benefit of platelet concentrate derived from either pure fibrinous membrane or in combination with other membranes such as amniotic[58] or Tutopach.[60] All studies showed a stable closure of corneal perforation in all patients treated with fibrinolytic platelet concentrate. In the evolution, no infection, inflammation or pain was observed in any of the patients with this treatment.[16]

In 2007, Rezende et al. also reported a case of corneal trophic ulcer not responsive to conventional treatments and showing significant clinical improvement after CP use.[14]

Lopez-Plandolit et al evaluated in a prospective study the effect of platelet-rich concentrate in 18 eyes. Results showed complete recovery of the epithelial defect in 85% of cases (17 of 20 eyes).[61] In another comparative, retrospective and non-randomized study with patients with persistent epithelial defects post infection and keratitis, Kim et al (2012) successfully reported similar results.[62]

It is advised that plasma rich in growth factors should not be used for extensive ulcers where neovascularization (mechanism of natural repair of the corneal stroma) has already occurred, since it may subsequently increase the formation of new reservoirs with subsequent corneal opacification, increasing the speed loss of sight.[52]

Other applications

The use of plasma-rich growth factors in the field of ophthalmology has been successfully extended to other ocular surface disorders, including the treatment of dry eye syndrome[63] and flap necrosis[64] after LASIK surgery. A recent study has shown that the administration of plasma-derived proteins and platelets adjacent to the lacrimal gland restored the lacrimal function of all patients.[65] In addition, a significant improvement in tear volume was observed in another study, with an increase in the tear film breaking time and a reduction of ocular dyeing after plasma treatment.[16]

In the treatment of ocular burns, the platelet concentrate was described applied subconjunctivally. In this study, it was possible to see that the injection produced a significant statistical reduction in the time of corneal healing and in the conjunctival cicatrization.[66]

It is also reported that the treatment of four patients with severe lachrymal dysfunction secondary to Sjogren's Syndrome, Stevens-Johnson Syndrome and pemphigoid with platelet concentrate, and a reduction in ocular surface stain results due to an improvement in tear and reduction of the inflammatory process secondary to Sjogren's Syndrome.[65]

Conclusion

This review demonstrates the variety of PRP applications not only in several medical specialties, but especially in several applications in ophthalmology with good results. Its biochemical and physiological properties make it an probably-effective alternative treatment for diseases, mainly of the ocular surface.

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Corresponding author:
Vinícius Falcão de MeloAL 101 Sul, CondomínioLaguna, Quadra N31, Barra Nova Marechal Deodoro, AL Brazil
Phone Nº.:+55 (82) 991944689
E-mail: viniciusfalcao_@hotmail.com