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USE OF PLATELET-RICH PLASMA IN ORTHOPEDIC TREATMENTS

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Abstract: Platelet-rich plasma, a concentrate of blood platelets, has enormous potential in therapeutic modality due to several advantages. The volume of plasma found in PRP (platelet-rich plasma) has a concentration of platelets five times greater than that found in normal blood. It can be obtained through single or double centrifugation, it is extremely important that the PRP is always autologous, thus avoiding the risk of rejection. PRP has been applied in the most diverse areas: aesthetics, dentistry, regenerative medicine, biotechnology, ophthalmology and orthopedic treatments. It also manifests anti-inflammatory properties, anabolic effects and gelling capacity. Through CF (growth factors) released by the platelets it contains, PRP assists in the processes of osteoinduction and osteointegration. Furthermore, studies reveal promising results in its use after total knee arthroplasty, as well as in other orthopedic treatments.
Keywords: Platelet Rich Plasma, Use of Platelet Rich Plasma, Platelet Rich Plasma in Orthopedics.

INTRODUCTION

BLOOD AND ITS COMPONENTS

Blood is a fluid tissue composed of a heterogeneous mass of differentiated cells: red blood cells, white blood cells and platelets, which are suspended in plasma. In general, circulating blood cells have specialization and an average lifespan of years (lymphocytes), months (red blood cells) or a few hours (granulocytes and monocytes).

Within a given volume of blood, 45% represents the cellular portion and the remaining 55% is plasma, the liquid portion. Blood has several functions, such as: transporting nutrients to organs and tissues, water and thermal regulation of the body, transport of gases (red blood cells), coagulation (platelets and plasma proteins), defense of the body (white blood cells), maintenance of aqueous, ionic and acid-base balance (AZEVEDO, 2013).

Among the blood components we can mention: plasma, formed mainly by water, where organic and inorganic substances are dissolved and are essentially made up of proteins (immunoglobulins, enzymes, clotting factors, lipoproteins, albumin and transport proteins), lipids, salts organics and glucose. White blood cells, also known as leukocytes, have specific morphological characteristics and their quantity in the blood varies from 4,000 to 10,000 per mm^3. Red blood cells, also called erythrocytes or erythrocytes, represent the majority with values between 4.5 and 5.5 million per mm^3 of blood, varying according to gender or age. Platelets or thrombocytes are small elements present in the circulation, with great importance for clotting, and their quantity varies from 150,000 to 450,000 per mm^3 of blood (AZEVEDO, 2013).

PLATELETS AND THEIR FUNCTIONS

Platelets circulate in the blood and are highly specialized and effectors of hemostasis. Despite being mainly associated with stopping bleeding after vascular damage, platelets act in several processes, interacting with immune response cells, initiating and amplifying inflammation, participating in angiogenesis, tumor progression and metastasis. This makes it clear that they have functions in the inflammatory process and can interfere with the immune response (OLIVEIRA et al., 2013).

Originating from bone marrow cells called megakaryocytes, platelets are characterized by enucleated cytoplasmic fragments and their main function is to release CF and form clots, thus being of paramount importance in the blood coagulation process (CAMARGO et al, 2012).

Platelets act by releasing various CFs, which stimulate angiogenesis, generating vascular growth and proliferation of fibroblasts, which result in increased collagen production. Therefore, platelets play a major role in wound healing, re-epithelialization and the hemostasis process. Represented by a complex of substances, mostly of protein origin, CF together with neurotransmitters and hormones play a considerable role in intercellular communication (ABREU, 2018).

The CF binds to the target cell's membrane receptor, initiating a cascade of modulatory signaling, in which each kinase activates the next through phosphorylation, causing several changes in cellular functions, continuing the tissue regeneration process (CARVALHO, 2016).

Stimulating the production of extracellular matrix and collagen by small amounts of plasma, the three main platelet CFs associated with the healing process are: platelet-derived growth factor (PDGF), transforming growth factor beta (TGFβ) and endothelial growth factor vascular (VEGF) (ABREU, 2018).

One of the main FC released by the platelet is PDGF, which stands out for stimulating wound healing and tissue repair through the stimulation of chemotaxis, collagen and DNA synthesis (FERRACIOLLI, LAPOSY, NOGUEIRA, et al, 2018).

PLATELET-RICH PLASMA (PRP)

Platelet-rich plasma (PRP), a concentrate of blood platelets, has great potential in therapeutic modality due to several advantages such as: antibacterial, anti-inflammatory and analgesic properties; abundance of growth factors it has, as well as ease of obtaining and preparing (El ABRAS ANKHA, 2018).

PRP has seven growth factors (CF) and three proteins (vitronectin, fibronectin and fibrin) that act in the processes of connective tissue formation and epithelial migration, characterized by cell adhesion molecules (ABREU, 2018).

Fractionation is a process for obtaining platelet concentrates by centrifuging the patient's own blood (autologous), followed by extracting the active part, which is rich in platelets. It is recommended to store the platelet concentrate at a temperature between 20ºC and 24ºC with agitation. Durability is approximately three to five days (PORFÍRIO, COSTA, RIERA, 2015).

PRP can be obtained through single or double centrifugation between 200 and 2000g for three to five minutes (Figure 1). Studies suggest that, for the safe preparation of PRP, it is important to use recombinant human, autologous or extra purified thrombin (ZABALIA, 2015).

It is extremely important that PRP is always autologous, thus avoiding risks of rejection, and other biological risks such as hepatitis, AIDS, among others; as well as the impossibility of forming active CFs. Blood collection must be aseptic, preferably in tubes that contain citrate as an anticoagulant (ABREU, 2018).

The volume of plasma found in PRP has a concentration of platelets five times greater than that found in normal blood. It is immunoreactive and non-toxic. As it is also autologous, it excludes the likelihood of immunogenic reactions caused by allogeneic or xenogenic preparations and the transmission of diseases (CAMARGO et al, 2012).

PRP TREATMENT

With its increasing use in regenerative medicine, PRP has been used in periodontal, plastic, maxillofacial, orthopedic surgeries and widely applied in burns and tissue repair of chronic wounds (ABREU, 2018)

Through the local and gradual release of proteins and CF, the use of PRP has unique characteristics regarding healing, tissue remodeling and angiogenesis. The properties of platelets that it possesses promote improved integration of grafts, both cutaneous, cartilaginous, bone, and adipose tissue (HERMETO, 2010).

PRP, obtained through blood centrifugation, is among the multiple substances that can be used in the topical treatment of venous ulcers. Can be applied in the form of a spray, perilesional injection or gel, PRP works to improve chronic ulcers by enhancing their re-epithelialization through cell cycle regulatory proteins such as CDK4 and cyclin A (ABREU, 2018).

Aiding biotechnology, in aesthetics, PRP is a non-invasive, safe and tolerable method, which can promote the postponement of the skin aging process. This is due to the fact that, through the stimulation of CF and activation of angiogenesis, as well as the induction of collagen production by stimulation of fibroblasts, PRP increases the capacity for tissue regeneration. Recent research has revealed that PRP has a beneficial effect on skin rejuvenation. The hypothesis is that it probably stimulates the synthesis of hyaluronic acid, which enables the absorption of water, guaranteeing turgor, greater firmness and hydration to the skin, thus helping in the synthesis of collagen fibers (FERRACIOLLI, LAPOSY, NOGUEIRA, et al, 2018).

Also used to soften scars, PRP improves the appearance of the skin. In this case, its mechanism of action is based on causing mild inflammation in the skin, which will trigger the healing cascade and the synthesis of FC that help in the formation of new vessels for tissue repair (GÓMEZ, ROMERO, RUBIANO, 2017).

In the treatment of musculoskeletal injuries, PRP can be applied as main or adjuvant treatment (managed after surgical repair or reconstruction) (PORFÍRIO, COSTA, RIERA, 2015).

PRP contains some leukocytes inside, which provides natural resistance to infectious processes, reducing the risk of infections in the area being treated. Furthermore, activated PRP, due to its anti-apoptotic effects, increases the survival of hair follicle cells and prolongs the anagen phase, stimulating hair growth (MARQUES, et al, 2016).

Acquired by "in vitro" addition of thrombin and calcium gluconate to platelet-rich human plasma, biocuratives release FC through platelet degranulation, thus acting directly on the healing process. The topical application of growth factors in direct contact with the wound surface promotes stimulation and acceleration of healing, revealing itself to be a promising therapeutic possibility (ZABALIA, 2015).

The possibility of using PRP in tissue engineering as a 3D scaffold in the form of a gel to support cells in cell culture brings numerous advantages. It is easily reabsorbed after transplantation as it is a biological material, is low cost, easy to obtain and rich in growth factors, especially PDGF and TGF, which stimulate the synthesis of extracellular matrix (MOROZ, 2009).

Applications of PRP in ophthalmology reveal good results in the treatment of dry eye syndrome and secondary tear dysfunction (RIBEIRO, MELO, et al, 2017).

When used in the form of eye drops in humans, PRP showed a reduction in the corneal healing time of refractory ulcers and an improvement in epithelial regeneration (PERCHES et al, 2015).

In dentistry, PRP has been used in oral and maxillofacial surgery to promote bone repair, thus promoting adequate bone regeneration. Furthermore, it also helps in the reconstruction of bone defects and alveolar ridges, as well as in lifting the sinus floor of the maxillary sinus (CAMARGO et al, 2012).

PRP IN ORTHOPEDIC TREATMENTS

Due to the promising results of the first standardized applications using PRP in the 90s in the plastic-reconstructive and dermatological fields, several orthopedic applications began in the 2000s. These were initially pertinent to osteoarthritis, bone trauma and musculoskeletal diseases (MANFREDA et al, 2019).

PRP has been used successfully in bone treatments since 1994 (GOLOS et al, 2014).

Showing great effectiveness in cartilage repair and having properties indicated for the treatment of chondral defects, PRP manifests anti-inflammatory properties, anabolic effects and gelling capacity. Its platelets contain alpha granules, storage units that transport FC in inactive form, together with fibronectin and plasma proteins, thus enabling cell adhesion and repair of connective tissues and assisting in the processes of osteoinduction and osteointegration (YAMADA et al, 2016).

With the presence of biological mediators, matrix, osteocomponent cells, efficient blood support and vascularization, bone tissue has significant regenerative potential, being able to repair fractures and local defects with similar structure (SILVA et al, 2009).

Triggered by an inflammatory response at the fracture site, bone union is associated with the activation of macrophages, T cells, granulocytes, osteoblasts and osteoclasts. Bone healing begins with the formation of a fracture hematoma, which can be altered by several local and systemic factors. An important medical problem is delayed bone healing after surgical intervention, for which multiple methods have been developed that influence healing. One of these is the administration of PRP into the fracture gap (GOLOS et al, 2014).

Although considered a relatively new therapeutic agent, PRP has great advantages over corticosteroids in the treatment of degenerative diseases of the TMJ (temporomandibular joint). Although the exact mechanism of action of PRP is not yet known, it has been increasingly used and famous in sports medicine and orthopedics, proving to be a promising treatment for degenerative cartilage defects and OA (osteoarthritis) (EL ABRAS ANKHA, 2018).

Studies since 2006 have shown that the use of PRP after total knee arthroplasty has promising results: improved healing, less blood transfusion, less infection and postoperative pain, less blood loss and reduced hospital stay (GUERREIRO et al, 2015).

This work is justified by the fact that platelet-rich plasma has shown several uses in the health area and has shown promise for the development of many research studies. Its use in orthopedic treatments brings the possibility of recovery in less time and reveals many other benefits, which is of great advantage to medicine and society.

The objective of this work was to analyze the use of PRP in orthopedic treatments and verify, through articles and scientific materials, the adherence to the use of PRP in recent years, highlighting the evolution in orthopedic treatments through its use.

METHODOLOGY

To prepare this work, a systematic bibliographic review was carried out. Scientific articles were selected and included works in English and Portuguese that cover scientific points about platelet-rich plasma, its functions, its applications in orthopedics, its capacity for tissue regeneration as well as the reliability, excellence and benefits of its use.

The search engines Scielo, Google Scholar, VHL and Pubmed were used, with the keywords: Platelet-Rich Plasma, Platelets, Use of Platelet-Rich Plasma, PRP in Orthopedic Treatments, Platelet-Rich Plasma in Orthopedics.

The exclusion criteria were articles that did not have full texts available, those published before 2009, and those that did not have subjects related to the topic in question.

The selected works were published between 2009 and 2019 and the searches provided approximately 514,606 results. From these results, 73,076 publications were separated a priori and only 30 articles were subsequently used as they contained the necessary material to carry out the study.

RESULTS AND DISCUSSION

PRP has been widely used in orthopedics, being applied in several areas such as dentistry, treatment of OA, late union of bones, treatments associated with bone grafts, chronic lateral epicondylitis, among many others, presenting benefits or not and may have adverse effects.

In the field of dentistry, a significant part of the studies found in the literature reveal great improvements in tissue regeneration and bone regeneration with the use of PRP, combining it with oral and maxillofacial surgery, periodontics and implant dentistry. Although many studies show promising results in the dental clinic, ranging from reduced bleeding to faster healing with better tissue regeneration, the application of PRP requires more studies to recognize its long-term effectiveness (CAMARGO et al, 2012).

With regard to the treatment of OA, through a study that evaluated the effect of the association of platelet-rich plasma with hyaluronic acid hydrogel on the regeneration of the osteochondral surface of the TMJ and the articular disc in osteoarthritis in rabbits, both did not present satisfactory results as protectors of the osteochondral surface, however, they have been shown to help prevent atypical calcification or the formation of mineralized material in the TMJ articular disc.

This association, helping to reduce the defect created in the disc, revealed favorable results in the treatment of osteoarthritis in the TMJ of rabbits (EL ABRAS ANKHA, M.V., 2018).

As joint degeneration increases, some factors can reduce the effectiveness of PRP, which we can mention: reduction of living cells and the anabolic response to growth factors, thinning of the cartilage plate, loss of chondrocytes, muscle instability and deficiency of muscle functions caused due to increased ligament laxity. It is believed that PRP has anti-inflammatory properties by regulating common homeostasis and cytokine levels and that patients with advanced stage OA benefit from it, although with a weaker response. It is difficult to assess the effectiveness of PRP due to the lack of standards regarding PRP administration. Potential improvement in chronic knee pain in knee osteoarthritis was found over a period of 12 weeks through PRP injections, with this improvement being more stable between 6 and 12 weeks (SUCUOĞLU, H., ÜSTÜNSOY, S., 2019).

To establish the real role of PRP in osteoarthritis, it is essential to carry out prospective randomized studies with correct designs (KNOP, E., PAULA, L.E., FULLER, R., 2016).

Regarding late bone union, the average time between surgical treatment and the diagnosis of delayed bone union continued by the administration of PRP was 4.05 months. Providing more efficiency in patients with bone union disorders after proximal tibial fractures, PRP was administered into the fracture gap, with satisfactory FCs (GOLOS, J., WALIŃSKI, T., PIEKARCZYK, P., 2014).

In treatments associated with bone grafts, during a study that evaluated PRP associated or not with cancellous bone in the repair of experimental bone defects, it was found through mesoscopic evaluation that PRP, when administered alone, fills the gaps in a way that occurs from the bottom to the surface and from the edges to the center, with the filling tissue being less compact than its neighbor. When PRP is administered together with the bone graft, or the second one alone, bone growth occurred in the central portion of the defects, which may be associated with the promotion of early osteogenesis and stimulation of direct bone formation due to the presence of the graft in the center. of the failure. It was also found that the CFs linked to PRP need a substrate to act and in this case the bone graft is the carrier. In other words, there is no formation of new bone by PRP alone, but its FCs provide it with osteoinductive capacity, which depends on cells present in the graft to act (SILVA, P.S.A., DEL CARLO, R.J., SERAKI-DES, R., et al, 2009).

In chronic lateral epicondylitis of the elbows, the use of PRP showed a notable reduction in pain, and its use must be considered before surgical intervention, requiring additional study with a control group (ERNESTO, C.A.P., MOURA, P.S., 2012).

Side effects from PRP injection are uncommon and when they occur, they are self-limited and mild. Commonly, local symptoms ranging from pain to signs of arthritis manifest as adverse events. Intra-articular infection can be avoided by performing the procedure aseptically. Allergic reactions will rarely occur as it is an autologous product (KNOP, E., PAULA, L.E., FULLER, R., 2016).

A case of atypical type I allergic reaction shortly after PRP injection was revealed by a study. Despite the scarcity of data on the anticoagulants used in preparation kits and their influence on plasma samples, the most used are citrate, heparin, citrate acid dextrose (ACD) and citrate-theophyllineadenosine-dipyridamole (CTAD). Despite preventing blood clotting, citrate-based anticoagulants do not have studies regarding calcium citrate as an allergen. It has been proven that pure autologous tissue is safe, however this safety can be significantly reduced by preparation for its use (LATALSKI, M., WALCZYK FATYGA, A., RUTZ, E., et al., 2019).

When dealing with the benefits and risks of PRP, only six systematic reviews highlighted the distinct benefits and risks of using PRP to treat clinical cases such as musculoskeletal soft tissue injuries, chronic wounds, dental implant surgery and bone consolidation. Most studies had limited methodological quality due to the few conditions for randomized clinical trials, creating a risk of bias. To support the use of PRP in various clinical situations, in which it is already used in practice even without regulation, quality research is essential (PORFÍRIO, G.M., COSTA, I.H., RIERA, R., 2015).

Unfortunately, a limitation to equalizing the work has been the changes in the ways of obtaining, preparing and applying the PRP. PRP was not effective in improving function and reducing knee bleeding after arthroplasty when compared to the control group. There was also no antibacterial effect or benefit regarding the healing of the surgical wound, which can be justified by the way it was prepared: outside the laminar flow hood, facilitating contamination (GUERREIRO, J.P.F., DANIELI, M.V., QUEIROZ, A.O, et al., 2015).

The differences in the forms of formulation and application of PRP mean that it has different purposes. This justifies the difference in results, which can be good, dangerous or ineffective. According to the study that evaluated the true effectiveness of PRP as an alternative to surgery, which is in contrast to much of the literature, treatment with PRP infiltrations for chronic patellar tendinopathies does not reveal good results. The possible justification is the number of limitations that existed, such as: uneven collection, smaller sample, smaller number of patients, wide age range (19-45 years), uneven BMI, short follow-up period and lack of control group and standardized criteria (MANFREDA, F., PALMIERI, D., ANTINOLFI, P., et al., 2019).

Being able to promote tissue regeneration through several mechanisms, PRP has several FCs, and has seen an increase in its use for orthopedic applications recently. However, there is little guidance regarding its indications and cost-effectiveness and evidence-based literature indicates that the success of its use varies depending on some factors such as: the patient's medical condition, method and composition of the preparation, type of tissue and anatomical location (HSU W.K., MISHRA A., RODEO S.R. et al., 2013).

The use of PRP in orthopedic surgery is beneficial, promoting the increase and acceleration of the healing process of musculoskeletal injuries, such as: knee osteoarthritis, lateral epicondylitis, rotator cuff injuries, ulnar collateral ligament injuries, Achilles tendinopathy and injuries to the hamstrings. However, most of the literature is level III and IV, thus showing that more research is needed in order to establish optimal concentrations of platelets, leukocytes and growth factors in order to achieve the desired effect, as well as the moment of application and the appropriate delivery method for each target tissue (MLYNAREK R.A., KUHN A.W., BEDI A., 2016).

CONCLUSION

In dentistry, PRP has shown good results, showing improvements in tissue and bone regeneration, as well as reducing bleeding.

In the treatment of OA, it showed pain reduction and anti-inflammatory effects.

PRP also showed good results when used in the treatment of late bone union and when associated with bone grafts.

Although uncommon, adverse effects may occur when using PRP, such as pain, signs of arthritis and allergic reactions.

Finally, despite currently having many studies, PRP still needs many more, in order to establish fixed standards regarding obtaining, preparation, administration and dosage, follow-up time, use of anticoagulants, among other factors. The differences presented regarding these questions have revealed different results, which prevents the correct use of it as well as the improvement of its use.

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