ARTIGO DE REVISÃO

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PLASMA RICH PLASMA AND THE TISSUE REPAIR PROCESS IN CHRONIC WOUNDS

PLASMA RICO EM PLAQUETAS E O PROCESSO DE REPARAÇÃO TECIDUAL EM FERIDAS CRÔNICAS

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ABSTRACT

Objective: To verify the topical use of platelet-rich plasma in the tissue repair process of chronic wounds. **Method:** narrative review in the Scielo, Lilacs and Medline databases through controlled health descriptors. The search resulted in the selection of a sample made up of 10 studies, according to inclusion and exclusion criteria. Data analysis was performed based on an analysis of thematic categorical content. **Results:** It was evident that scarcity of research that addresses the theme and discrepancy between studies found, since some claim that platelet-rich plasma is effective and others report that there is no clinical efficacy. As a result, it can be concluded that these false negatives may occur because they do not have a specific protocol for obtaining platelet-rich plasma, which may alter the concentration of platelets. **Conclusion:** There is a need for more studies with a sample and longer observation time, as well as to see the need to establish a procurement protocol that must be followed in all surveys. Studies need to be carried out with a sample and longer observation time, as it is necessary to establish a procurement protocol that must be followed in all surveys in order to arrive at a more solid result.

Keywords: Platelet-Rich Plasma; Wound Healing; Tissues; Wounds and Injuries; Skin Ulcer.

RESUMO

Objetivo: Verificar o uso tópico do plasma rico em plaquetas no processo de reparação tecidual de feridas crônicas. **Método:** revisão narrativa nas bases de dados Scielo, Lilacs e Medline através dos descritores controlados em saúde. A busca resultou na seleção de uma amostra formada por 10 estudos, conforme critérios de inclusão e exclusão. A análise dos dados foi realizada a partir de uma análise de conteúdo categorial temática. **Resultados:** Ficou evidente a escassez de pesquisas que abordem a temática e a discrepância entre estudos encontrados, visto que uns afirmam que o plasma rico em plaquetas é eficaz e outros relatam não haver eficácia clínica. Mediante isso, pode-se concluir que esses falsos-negativos podem ocorrer por não ter um protocolo específico para obtenção do plasma rico em plaquetas, podendo alterar a concentração de plaquetas. **Conclusão:** Estudos precisam ser realizados com uma amostra e tempo maior de observação, como se faz necessário estabelecer um protocolo de obtenção que deve ser seguido em todas as pesquisas para que se possa chegar a um resultado mais sólido.

Palavras-Chave: Plasma Rico em Plaquetas; Cicatrização; Tecidos; Ferimentos e Lesões; Úlcera Cutânea.

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REVISTA ENFERMAGEM ATUAL

INTRODUCTION

A wound is represented by the lost of skin continuity, and it could reach deeper skin structures such as muscles, tendons and bones, being caused by any kind of trauma, being it physical, chemical, mechanical or triggered by a clinical condition that activate the organic defense for counter-attack.[1] They can be classified according to evolution, which could be acute or chronic; according to the presence of infection, which could be not contaminated clean, clean contaminated, contaminated or unclean and infected; according to how deep it is and/or the cause, being classified as intentional or not intentional; and surgical or traumatic.[2]

Chronic wounds are those which do not heal spontaneously and require a bigger time period than 12 weeks to heal and, frequently, show relapses and infectious process or even when associated with systemic pathologies could harm the healing process[3-6]. Among the surgical wounds, diabetic ulcers, vein ulcers and pressure lesions are highlighted, which generally are harder to treat and affect the patient's quality of life and the financial costs of health in Brazil[4,7]. Due to that, wounds are considered an issue of public health, tackling, specially, about 4% of the elderly population worldwide[8-9].

In the face of the complexity, the healing process of wounds is a dynamic process that involve cellular and molecular phenomena that interact so that the tissue repair can happen[10]. It is regulated by events of coagulation, inflammation, formation of granulated tissue, epithelialization and tissue remodeling, which are mediated and modulated by cytokines and growing factors[11].

Some studies show that in chronic wounds there is reduction of the growing factors (FC) by decrease of production and decrease in liberation, or even by its fast metabolism, due to protainases present in the wound, originated by bacteria or cells. In diabetic ulcers and vein insuffiency, however, the decrease of FC is due to the kidnapping mechanism by the fibrin that surrounds the capillaries, and with that, the plasma rich in platelets (PRP) can be used to put back these growing factors[12].

The PRP is a product originated by the laboratorial processing of autogenous blood, rich in growing factors that come from alpha-platelets granules. It is a organic, not toxic and not immunerreactive, that has been used to accelerate the wound repair, from the various growing factors it holds. The FCs don't get inside the cell or its core, eliminating the possibility of any mutagenic effects. On the other hand, it stimulates the normal healing of the tissue, promoting a higher speed for the healing process. The use of PRP is safe, not showing any tendency to tumor activation[13].

So, the research emerged from the following question: what is the effect of the

REVISTA ENFERMAGEM ATUAL

topical usage of PRP in the healing process of chronic ulcer?

Considering the importance of studies about growing factors involved in the healing process of chronic skin lesions, this study was developed with the objective of verifying the topical usage of plasma rich in platelets in the process of the tissue repair of chronic wounds.

METHOD

This study is a narrative review, which is defined as the one that condensates previous researches and takes global conclusions from a specific body of literature, allowing the construction of wide analysis, contributing for discussions about methods and research results and resulting in a new learning[14].

Six steps were taken for the elaboration of this study: elaboration of northing question, search in literature, data collection, critical analysis of the studies included, discussion of the results and presentation of the review[15].

The research was conducted in the month of August of 2020, using the descriptors of MeSH®: Plasma Rich in Platelets. Healing process. Wounds and lesions. With this definition, searches were made with association of terms, from the boolean operator AND, on *Scientific Eletronic Library Online* (SCIELO), on Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS) [Latin-American and Caribbean Literature in Health Science] and on Medline.

From the search that was made 60 studies were identified, 30 on MEDLINE, 9 on SCIELO and 21 on LILACS. The criteria of eligibility for inclusion in this sample contemplated studies that approached the proposed theme; studies with humans and complete text available. A temporal cut was not considered in the searches because there was a lack of the theme in question.

From the search results, the work of elimination of articles was executed, eliminating the ones not related to the theme in study, such as studies with animals, full articles not available for free and duplicates. After analysis, 3 studies from MEDLINE, 5 studies from LILACS and 2 studies from SCIELO stayed, adding up to 10 studies that were adequate to the criteria of inclusion, composing the final sample of this review.

For the data analysis, the method used was analysis of categorical thematic content that, according to Bardin (2010, p. 131), is the one in which “the information collected have exposed the core of meaning that make up a communication, in which presence or frequency have meaning to the analytic object proposed”. So the articles were read and analyzed, with its results categorized in a sequential manner, considering the process of obtaining the plasma rich in platelets until its components and application on the healing of wounds. With that, the research aimed at a

REVISTA ENFERMAGEM ATUAL

better understanding by steps of the PRP in the process of tissue repair of chronic wounds.

RESULTS

The production about PRP is very wide, but it has more emphasis in the area of oral, musculoskeletal and joint surgeries and esthetic medicine. Apart from that, this theme has been more spoken about when it comes to the repair of chronic skin lesions.

However, most studies are clinical trials with animals, which made it harder to the search for the review analysis. As it can be observed, after utilization of filter and rigorous analysis, contemplating the criteria of inclusion delineated, it came to ten articles, which are described in Chart 1, with the variable: title, author, year and periodic.

Chart 1 - Characterization of publication with titles, authors, year of publication and periodic

N	TITLES	AUTHORS / YEAR	PERIODIC
1	Efficacy and safety of autologous platelet rich plasma for the treatment of vascular ulcers in primary care: Phase III study	Sebastian et al. (2014).	BMC Family Practice
2	Platelet-rich plasma combined with skin substitute for chronic wound healing: a case report.	Knox et al. (2006).	The Journal of extra-corporeal technology
3	A case report on the use of sustained release platelet-rich plasma for the treatment of chronic pressure ulcers.	Sell et al. (2011)	The journal of spinal cord medicine
4	Role of local application of autologous platelet-rich plasma in the management of pressure ulcers in spinal cord injury patients.	Singh et al. (2014)	Spinal cord
5	De lo convencional a lo alternativo en el manejo de las úlceras venosas	Trujillo et al. (2016)	Revista Urug. de Enfermería
6	Evidências de revisões sistemáticas Cochrane sobre o uso de plasma rico em plaquetas.	Porfírio, Costa & Rieira (2015)	Rev. Diag. e Trat.
7	Application of platelet-rich plasma in the treatment of chronic skin ulcer – Case report.	Pinto et al. (2014)	Anais Bras. de Dermato.
8	Plasma rico em plaquetas na dermatologia.	Monteiro (2013)	Surgical & Cosmetic Dermatology
9	Utilização do plasma rico em plaquetas autólogo nas cirurgias de enxertos cutâneos em feridas crônicas.	Vendramin, Franco & Franco (2010)	Rev. bras. cir. Plást
10	Plasma Rico em Plaquetas e fatores de crescimento: técnica de preparo e utilização em cirurgia plástica.	Vendramin et al. (2006).	Rev. do Colégio Bras. de Cirurgiões

REVISTA ENFERMAGEM ATUAL

Fonte: Data from research, 2020.

The articles were analyzed considering the objective, methodology and results found by the authors, as it is shown in Chart 2.

Chart 2 - Characterization of publications with objective, methodology and results

N	OBJECTIVE	METHODOLOGY	RESULTS
1	Evaluate the efficiency potential and safety of plasma rich in platelets autologous for treatment of vein ulcers in comparison to conventional treatment	Random Multicentric Study	It was observed the decrease of healing time in comparison to conventional treatment, but it is still not possible to recommend this treatment due to the lack of rigorous studies.
2	Report the use of PRP therapy singly and in combination with a skin substitute genetically modified as skin graft rich in platelets in wound.	Case Report	The combination brought dramatic results, eliminating tunneling and reducing the wound's dimension, but indicates that more studies are needed.
3	Show results of the utilization of PRP and PRP activated by $CaCl_2$ for liberation supported by FC and cytokines to stimulate the healing process in pressure ulcers.	Case Report	The treament with PRP consistently resulted in the formation of granulated tissue and improved the vascularization for each of the three patients treated, while reducing the area and general volume of the ulcer.
4	Evaluate the local application of PRP in relation to the healing process of pressure ulcers in one (case) versus saline curative in another PrU (control) in the same patient.	Prospective Study	The area of the surface of the wound of the pressure lesion (case) decreased significantly.
5	Analyze bibliographic information about the use of alternative and conventional ways for the management of vein ulcers.	Review of Documentary	It was verified that the conventional methods are: handling sclerotherapy, negative pressure, plasma rich in platelets, larva therapy, a paste of zinc oxide of initialization.
6	Mapping evidence of Cochrane systemic reviews about osteoarthritis treatment.	Narrative review with systemic search of literature	There are no evidence suggesting autologous PRP benefits the treatment of chronic wounds.
7	Report the efficiency of PRP application in the treatment of chronic skin ulcer.	Case Report	The treatment with FC could result in a smaller time of healing and recovering of member function, improving the patient's quality of life.

REVISTA ENFERMAGEM ATUAL

8	To describe what is PRP and show some of the publications that exist in dermatology.	Integrative Review	The publications approach various themes, such as its use in the treatment of chronic wounds in diabetic patients, in the evaluation of the speed of epithelialization of areas that could be donated for skin grafts and closing of chronic ulcers due to vascular insuffiency, among others.
9	To evaluate the results of PRP application in surgeries of skin graft in chronic wounds.	Random Prospective Study	There was a better integration of the grafts in the side that received PRP than in the other side of the same wound, but without PRP.
10	To establish a cheap and efficient method for the preparation of plasma rich in platelets and growing factors for utilization in plastic surgery.	Laboratory Research	The use of a strength and time of centrifugation in two steps had a platelet concentration different from the sample.

Fonte: Data from research, 2020.

DISCUSSION

For discussion, three categories were identified: process of acquisition of plasma rich in platelets, PRP components and PRP in the Healing Process Chronic Wounds.

Category 1: Process of acquisition of plasma rich in platelets (PRP)

The plasma rich in platelets is obtained through the blood of the patient through steps to reach cellular separation: blood sampling, centrifugation, separation of the plasma rich in platelets, activation of coagulation by adding calcium chloride and topical application of PRP after gelation[7,16]. In another way, 50 to 60 ml of blood are collected through peripheral vein puncture that are distributed in 20 test tubes of 5ml, containing a solution of sodium citrate to 3,2%, that are later centrifuged to 400g to 1500rpm for 15 minutes, in room temperature. About 1,2 ml of plasma are collected by tube and associated to 5 ml of calcium chloride and, approximately, five minutes later, the gel is formed[7,17,18].

The acquisition of PRP can also be seen in centrifugation of 10 min to 2000 rpm, with blood immersed in three basic components: red blood cells, platelets and plasma poor in platelets, that have been distributed in the low layer – where the erythrocytes are –, the middle layer – where the platelets are – and in the top layer, where the plasma poor in platelets was. The layer of red blood cells is removed and the remainder was shaken for several seconds and submitted to 10min to a second centrifugation to 2000 rpm, in which the supernatant was plasma poor in platelets and the lower layer was

REVISTA ENFERMAGEM ATUAL

concentrated in platelets. The result was put in two tubes of vacuum of 5 ml, which received 2ml of calcium chloride (10%) for PRP activation, after that shaken for 5-10s for the formation of the gel[19,20].

Considering the ways shown for PRP acquisition, it can be observed that there isn't a specific protocol, which can cause variations and differences in the platelet concentration and, consequently, in growing factors.

From a relation between the blood sample and the strength and time it was observed that in the first centrifugation higher platelet concentration were obtained when using a strength of 300g for 10min, in which it was obtained an average 4,54 times higher than the blood sample. In the second centrifugation were reached when using the strength of 640g for 10min, obtaining an average 4,96 times higher than the blood sample[17].

Category 2: Plasma Rich in Platelets Components

The healing properties of PRP are based by the platelets, that have growing factors with an important part in tissue repair. These factors could contribute to the formation of tissue and epithelialization, with the platelets having at least five of these: growing factor derived from platelets (PDGF), platelet factor 4, transformative growing factor β, angiogenesis factor derived from platelets and epidermal growing factor derived from platelets, that when are liberate stimulate and modulate multiple biological processes that are important for the wound's healing[16,17,20,21,22].

In another studies, it was observed that after the activation with calcium, the platelets secrete high concentrations of PDGF, epidermal growing factors (EGF) and transformative growing factors (TGF) were secreted along with cytokines pro and anti-inflammatory such as interleukin 4 (IL-4), IL-8, IL-17, tumor necrosis factor alfa (TNFα) and interferonalpha (INFα).

Category 3: PRP in the Healing Process of Chronic Wounds

The PRP is used as treatment in many types of lesions, such as corneal ulcers, vasculitic, neuropathic, diabetic foot and skin grafts, among others[16,22]. It has growing factors that help accelerate the healing process of wounds and can have properties to fight infections. These growing factors contribute to the formation of tissue and epitheliazation, making the use of PRP valuable in the healing process of chronic wounds, because they have a decrease of growing factors and could show infection, which end up harming the healing process. Besides that, PRP could help fight infections using white blood cells and liberating platelets of bactericidal factors[21-22].

Another study reports the disagreement when it comes to the effect

REVISTA ENFERMAGEM ATUAL

exercised by the leukocytes, when one attributes the antibacterial effect and immunological, others believe that the presence of these cells has an inflammatory and malefic effect. The first growing factor liberated is glycoprotein PDGF that stimulates the proliferation of fibroblasts for collagen formation and elastin from the cellular matrix in the process of conjunctive tissue repair. Another growing factor – vascular endothelial growing factor – induces the mitogenesis, angiogenesis and activation of macrophages in chronic wounds[7,17,19,22,23].

It can be observed results in Pressure Lesions (LP), vein and diabetic ulcers, with the formation of granulated tissue, vascularization and epitheliazation. It is believed that therapy with PRP is a promising technique that could reduce the economic impact for the patient and for the health system, because its cost of acquisition is reasonably low[7,16,19].

The decrease of costs could be associated with the decrease of the time of the healing process when compared to conventional treatment, and besides that, contribute to the improvement of the patient's quality of life[7,16,19,24].

Besides evidence about the efficiency of PRP, most studies are limited to small groups and other could not determine a benefit, which generates a discussion about false-negatives and what PRP needs in concentration of active platelets enough to help in the healing[16,20,21]. As it has been observed in some studies, this efficiency depends on the quantity of white blood cells presents in the PRP, which have influence on the liberation of growing factors, and could make it harder to compare and evaluate clinical results when the patient is submitted to different concentrations of PRP components[22].

It has been observed that some authors can't find pre-clinical evidences of the use of PRP in LP, but there were few studies that showed that it led to reactivation and accelerated the healing process of the LPs[19]. In diabetic ulcers it was also observed the acceleration of the healing process, with an average of 12 weeks of treatment and variations of 8 to 40 weeks[20].

Since the researchers couldn't reach an agreement on the adequate values for acquisition of the plasma, this could be one of the difficulties found for the evaluation and comparison of results of scientific works. Because of this, it is highlighted the concern in obtaining a standardization for the acquisition of these components[22]. This discrepancy makes some professionals fear making use of these new treatment because of the lack of scientific basis that makes it easier for an integral approach[24].

However, it must be pointed out that, due to the fact that it is autologous, there is no counter indications for its utilization and

REVISTA ENFERMAGEM ATUAL

it has no risks for transmission of infectious diseases, but the handling should be done with caution, and utilizing aseptic techniques so that there isn't contamination. Besides, it is a minimally invasive technique and very well accepted by the patients that could be used weekly[18,23].

Another important fact that should be highlighted is that in autologous PRP treatment, no complication was observed, however 2% to 5% of patients could show adverse effect such as pain or local edema, or a decline in the hemoglobin levels[19,20]. However, PRP turned out to be an alternative treatment or as adjuvant in another therapeutic, which could be implanted in public hospitals, because it is low cost, although it needs trained personnel for the plasma acquisition[18,24].

CONCLUSION

The research has determined that in spite of PRP being a technique used in esthetic procedures, buccomaxillary facial and musculoskeletal surgeries, it still is considered "news" in the process of tissue repair, but it presents itself as a promising therapy in many types of skin lesions.

It can be observed that there are few studies and a good amount of them are international studies, which have shown divergences among them about the efficiency of PRP, but most of them showed that PRP application is an effective, safe and easily acquired technique.

This acquisition is made in a simple manner and with small costs, because there is no need for high technologies, just a centrifuge, some materials and capacitated personnel that follow aseptic techniques so that there is not a contamination of the product. Due to that ease and low cost, this therapeutic could be easily implanted in the health system.

However, it becomes clear that there is a need of more studies with a sample and higher time of observation, and also to see the need to establish an acquisition protocol that should be followed in every study to improve the viability of its practical application.

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