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Platelet-rich fibrin: preparation, quality definition, clinical use

Fibrina rica em plaquetas: preparo, definição da qualidade, uso clínico

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ABSTRACT

Introduction: Platelet Rich Fibrin is a platelet concentrate, extemporaneously prepared and autologous, whose purpose is to improve and accelerate the cicatrizing and repair of surgical lesions, originally used for oral surgeries. **Objective:** To analyze the preparation, quality control and clinical use of PRF, to understand and discuss the practical and regulatory aspects of its use. **Method:** This work was elaborated as an integrative review, by the survey of scientific articles and current legislation on the clinical use of PRF. **Results:** PRF consists of a matrix of fibrin with a large quantity of platelets, which release numerous pro-regenerative mediators. Its preparation is done in a surgical center or dental office, and the dental surgeon is responsible for the procedures and the final product. The used equipment and materials must be compatible with the standards approved for the PRF preparation methods. **Conclusion:** The use of the PRF by dental surgeons is regulated by the Resolution of the Federal Council of Dentistry (CFO) 158/2015, June 08, 2015. There is no regulation for the use of PRF by the Federal Council of Medicine (CFM). PRF preparation and use are not considered to be a part of Advanced Therapies.

KEYWORDS: Blood Platelet; Fibrin; Regeneration; Oral Surgery

RESUMO

Introdução: A Fibrina Rica em Plaquetas é um concentrado plaquetário, de preparo extemporâneo e uso autólogo, cuja proposta é promover uma melhor e mais rápida cicatrização e reparo das lesões cirúrgicas, tendo sido desenvolvida, inicialmente, para as cirurgias bucais. **Objetivo:** Analisar o preparo, controle de qualidade e uso clínico do PRF para compreender e discutir os aspectos práticos e regulatórios acerca da sua utilização. **Método:** Este trabalho foi elaborado como uma revisão integrativa, pelo levantamento de artigos científicos e legislação vigente sobre a utilização clínica do PRF. **Resultados:** O PRF constitui-se de uma matriz de fibrina, com grande quantidade de plaquetas, que liberam numerosos mediadores pró-regenerativos. A sua obtenção, preparo e uso ocorrem em centro cirúrgico ou consultório odontológico, cabendo ao cirurgião-dentista o compromisso com a garantia da qualidade, quanto aos procedimentos realizados. Além disso, os equipamentos e insumos utilizados devem ser compatíveis com as técnicas de preparo e uso do PRF. **Conclusões:** A utilização do PRF, pelos cirurgiões-dentistas, segue as determinações da Resolução do Conselho Federal de Odontologia – CFO nº 158/2015, de 08 de junho de 2015. Não há regulamentação para o uso de PRF pelo Conselho Federal de Medicina (CFM). A preparação e o uso do PRF não são considerados Terapia Avançada.

PALAVRAS-CHAVE: Plaquetas; Fibrina; Regeneração; Cirurgia Bucal

INTRODUCTION

Platelet Rich Fibrin is a platelet concentrate developed by Choukroun et al.[1] in France to be applied in oral and maxillofacial surgery[1]. It is an extemporaneous preparation product intended for autologous use. Its proposal is to promote better and faster healing and repair of surgical lesions.

The healing of wounds depends entirely on the initial mechanisms of tissue homeostasis. When an organism suffers an injury, the first tissue to react is the blood, since a hemorrhage represents imminent danger and is potentially harmful for the organism. The wound triggers a cascade of molecular and cellular reactions that lead to the sealing of the vascular lesion with an aggregate of platelets. Platelets not only control hemorrhage, forming a plug in the damaged tissue, but they are also responsible for triggering the next stages of tissue regeneration. For this, platelets generate a high concentration of fibrinogen and fibrinogenic enzymes in the wounded areas and release a large number of pro-regenerative mediators, particularly those of the family of growth factors[2].

Fibrinogen begins to polymerize in a dense fibrin network to seal and close the wound with a solid wall. This fibrin matrix has as its final purpose the formation of clots[3]. Platelet growth factors simultaneously stimulate and activate the vascular and perivascular resident cells of the injured tissue, as well as promote the mobilization of cells for tissue regeneration. The fibrin matrix also has the function to capture and stabilize growth factors, concentrate them at the injured site, and provide the incorporated cells for migrating into the adjacent tissues. Thus, coagulation should not be considered as a simple enhancement of the anti-hemorrhage function of the platelet clot. Coagulation leads to the rapid restructuring of a new tissue that consists of a dense matrix of fibrin, provided with platelets and leukocytes. Coagulation, therefore, is the mechanism that allows the blood to materialize in an adaptive and polymorphic solid form[4].

This new rapidly formed tissue is the first matrix that acts as a guide for healing. It has the function of attracting more platelets and leukocytes, trapping the circulating stem cells and allowing the migration and differentiation of the surrounding cells within the network of fibrin. The matrix is then remodeled and transformed: this transient tissue serves as an initial template for the formation of a new scar tissue. The coagulation process, therefore, constitutes an important step for tissue regeneration.

In the development of new therapeutic procedures, the human sciences often seek to mimic the efficacy of the mechanisms observed in Nature[4]. Platelet concentrates were developed for surgical use, and the autogenous products were prepared by centrifuging an autologous patient's blood sample[5]. The concept of this technology is to collect and assemble the most active components of the blood sample - platelets (rich in growth factors), fibrin and sometimes leukocytes - and prepare them in a clinically usable form. Such platelet-enriched fibrin preparations may be presented in the form of solutions or gels to be injected or accommodated at the surgical site directly onto a wound or on the injured area to regenerate the damaged tissues[6].

In view of the use of PRF as a biological additive in a range of surgical procedures, the objective of the present study was to analyze scientific papers and texts of current legislation regarding its preparation, quality control and clinical use, to understand and discuss the practical and regulatory aspects regarding its use.

METHOD

This work was elaborated as an integrative review, according to the methodology described by Sobral and Campos[7], considering the survey of scientific articles and the current legislation.

The research of scientific literature was carried out by consultation based on PubMed and the Virtual Health Library (VHL), using keywords like: Platelet-Rich Plasma, *Plasma Rico em Plaquetas*, Platelet-Rich Fibrin, *Fibrina Rica em Plaquetas*, Platelets, *Plaquetas*, Regeneration, *Regeneração*. The websites of the Brazilian Health Regulatory Agency (Anvisa - portal.anvisa.gov.br), of the Brazilian Ministry of Health (portalsaude.saude.gov.br), of the Federal Council of Medicine (portal.cfm.org.br/) and the Federal Council of Dentistry (cfo.org.br/) were also consulted. This research was carried out from September 4 to December 5, 2017.

RESULTS AND DISCUSSION

The use of whole blood products for wound sealing and stimulation of the healing process began more than 40 years ago. The proposal for the application of platelet concentrates in the surgical area originated from another product called sealant or fibrin adhesive[8].

The objective of the procedures for obtaining the platelet concentrates is to obtain the blood elements that can be used to improve healing and promote tissue regeneration by centrifuging[4]. Compared with the application of a single supraphysiological dose of a recombinant growth factor, platelet concentrates have the advantage of offering multiple synergistic action factors at the site of the wound in biologically and physiologically more suitable concentrations[9]. However, such concentrations should remain within the appropriate thresholds, since a low platelet count may generate a suboptimal effect, and a high count may inhibit some of the repair processes[10].

The first proposed platelet concentrates for clinical use include Platelet Rich Plasma (PRP), which requires an anticoagulant in the blood collection tubes and can be used in liquid or gel form, formed after the addition of a coagulation activating agent and the activation of platelets[11].

Depending on the protocol used to obtain PRP, the number of concentrated platelets ranges from 2 to 5 times the physiological level[8,12]. Although it is already used in orthopedics[13], sports medicine[14] and in oral or maxillofacial surgeries[9,15], there is still no general standardization as to its production processes.

The proposed protocols for obtaining PRP are diverse, but generally they consist of collecting about 20-80 mL of blood, prior to surgical intervention, in tubes with anticoagulant, which prevents the conversion of prothrombin to thrombin and platelet degranulation[8].

At the time of preparation of the therapeutic intervention, the first centrifuging (gentle rotation) takes the whole blood to the separation in three fractions: Plasma Poor in Platelets (PPP), buffy coat, and the fraction containing red blood cells. Only the buffy coat layer is used in the second centrifuging (high rotation), in which three new fractions are obtained: PPP, PRP and red blood cells[8]. PRP is then isolated and used for the treatment of the patient.

PRP can receive activators, such as thrombin or calcium chloride, which cause platelet degranulation and fibrin polymerization, with formation of a platelet gel and release of growth factors[16]. This release of growth factors starts within the first 10 minutes, and PRP is ready to be used. Approximately 95% of factors are released within the first hour after PRP activation. This means that activated PRP should be used within the first few minutes after its activation[12,17]. However, unactivated PRP can be preserved for a longer time[12], following the standards and precautions of the blood banks, and used after its extemporaneous activation.

Platelet Rich Fibrin (PRF) is part of the second generation of platelet concentrates. Its obtained in an open protocol that is fairly simple and inexpensive. Briefly, the blood is collected in dry glass or plastic tubes, free of anticoagulants, and immediately subjected to a single gentle centrifugation[18]. Three layers are thus formed: one of red blood cells at the bottom, one of PPP in the supernatant, and one in the intervening space in which the fibrin clot forms with the platelets[19]. This clot contains activated platelets, healing-promoting and pro-regenerative factors, as well as antibodies and elements of immunity and resistance to infection, present in the blood initially collected[20]. It can be used directly as a clot to fill the lesion or, after compression, as a protective and resistant membrane[21].

The natural coagulation process occurs spontaneously and allows easy collection of a fibrin-rich clot and containing leukocytes without the need for any biochemical modification of the blood, such as the use of anticoagulants, thrombin, or calcium chloride[5]. Platelets, fibrin, and leukocytes act naturally in synergy to promote healing and tissue regeneration[22]. Leukocytes have important antiinfective and immune regulation properties and produce large amounts of vascular endothelial growth factor (VEGF), which plays an important role in angiogenesis, fundamental to the process of tissue regeneration.

PRF is an autologous fibrin matrix, with a large amount of platelets, in which the release of cytokines occurs. Platelet concentrates are expected to improve soft tissue healing in oral and maxillofacial surgeries, as well as bone regeneration[11]. The use of PRF involves minimally manipulated, autologous materials with orthologous use of platelet function in blood stasis, stimulation of healing and tissue regeneration. Fibrin promotes scar closure and the migration of the cells involved in it.

Fibrin also adsorbs growth factors, releasing them progressively. PRF gel releases, for more than 7 days, significant amounts of key coagulation and healing molecules (thrombospondin-1, fibronectin, vitronectin) and growth factors - particularly platelet-derived growth factors: TGFß1 (Transformer Growth Factor ß), PDGF (Platelet Derived Growth Factor) and VEGF[23,24].

The PRF gel thus obtained may also be associated with organic and/or mineralized materials to promote filling of regions that have undergone tissue ablation. The preparation of the final product should be done extemporaneously in the surgical environment, with rigorous asepsis precautions. All materials that enter the composition of the final product in this case must be properly authorized for clinical use and properly manipulated. These compounds, as well as pure PRF, may be used in the form of membranes, plugs or pastes, to promote filling of areas that have undergone tissue ablation, while playing a role in the blood stasis of the surgical site in which they are used and in the regeneration process. Among the indications for use in oral and maxillofacial surgeries, the following ones stand out: soft tissue management in aesthetic area, treatment of membrane perforations in maxillary sinus floor elevation, protection and stabilization of graft materials (particulates or blocks), root coverage of one or more teeth with gingival recession, association with implants[15,25]. Miron et al.[26] performed a systematic review, following Prisma guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyzes)[27], in which they evaluated the regenerative/reparative potential of PRF in a variety of clinical situations in dentistry. Thirty-five studies were included, among them: 10 on intraosseous defects, three on furcation defects, 13 on gingival recession, four on guided bone regeneration and five on maxillary sinus lift. PRF improved soft tissue formation and limited dimensional changes after tooth extraction. However, there were no well-conducted studies that could demonstrate the role of PRF in the regeneration of bone tissue, which points to the need for randomized clinical studies to evaluate PRF in bone formation.

In clinical studies in the medical field the application of PRF promoted a reduction in the size[28] and increased healing and closure of the wounds in chronic ulcers[29]. Mahapatra et al.[30] observed an increase in the number of hair follicles, after application of the PRF matrix in conjunction with transplantation of follicular units, in the treatment of androgenic alopecia.

Since the first protocol, established by Choukroun et al.[1], others have been developed with the proposal to modify the fibrin structure, as well as the cells that are part of the obtained matrix, in order to improve the performance of PRF in the processes of tissue regeneration. Modifications have been proposed regarding the relative power and the centrifugation time, since those are key elements to modify the structure and composition of the PRF matrices[31,32,33].

In the first PRF protocol developed by Choukroun, blood is centrifuged at approximately 2700-3000 rpm for 12 min or at approximately 400 *g* immediately after collection[34,35].

The Advanced PRF (A-PRF) was developed with the proposal to increase the number of lymphocytes, as well as platelets in the fibrin network. For that, they used a lower spin speed (1500 rpm), for 14 min[31,36]. Ghanaati et al.[31] compared the obtained cells and their distribution in the fibrin matrix, obtained from the protocols for PRF and A-PRF. They verified that the cell types were distributed differently depending on the different centrifugal forces used. In the PRF clot, a dense fibrin network was formed, with minimal spaces between the fibers. Cells were observed throughout the clot, decreasing, however, in the distal parts of the clot. The clots obtained with the A-PRF protocol showed a looser structure, with more interfibrous spaces, and more cells present in them. They were distributed more evenly along the clot compared to PRF, with some cells seen in the more distal portion of the clot. T and B lymphocytes, stem cells and monocytes were found in both groups within the first 25% -30% of the proximal part of the clot. Platelets were observed throughout the clot in both groups, although in group A-PRF, more platelets were found in the distal part far from the buffy coat portion.

The decrease in the rotation speed and the increase in the centrifuging time in the A-PRF group provided a greater presence of neutrophil granulocytes in the distal part of the clot. In the PRF group, most neutrophils were found at the interface between the red blood cells and the buffy coat layer. It is expected that they will contribute to the differentiation of monocytes into macrophages and thereby create a synergistic relationship between the cells, allowing mutual stimulation for tissue regeneration[31].

Another modification of A-PRF was proposed by Fujioka-Kobayashi et al.[37], where the suggested spin speed and centrifuging time were 1300 rpm and 8 min. According to the authors, this modified protocol, called A-PRF +, allows the increase of the anchored cells in the PRF matrix.

Mourão et al.[38] proposed an alternative for the production of platelet-rich fibrin for use in their liquid (injectable) or polymerized (clot) form. To produce i-PRF, blood is collected in plastic tubes without anticoagulant and centrifuged at 3,300 rpm for 2 min. Another protocol proposed to obtain liquid PRF consists of centrifuging the tubes for 2400-2700 rpm for 2 min. The collected supernatant is called Concentrated Growth Factors (CGF)[39].

We can verify that different structures of the fibrin matrix, as well as of the cells anchored thereto, can be obtained depending on the use of different protocols, in which the speed as well as the centrifuging time can vary. For the definition of the most appropriate protocol to be used each clinical situation should be considered specifically.

Furthermore, the characteristics of the centrifuge may interfere with obtaining the PRF clot[40]. This requires special attention in the application of a particular protocol in the centrifuge that is different from the one in which the protocol was developed.

The Resolution of the Federal Council of Dentistry n. 158, of June 8, 2015[41] regulates the use of PRP and PRF, denominated as Autologous Platelet Aggregates, for non-transfusion purposes in the scope of Dentistry. The portion of blood containing the platelet components, without addition of any product, including anticoagulant or coagulant, is called PRF. PRP is considered to be the portion of blood that contains platelet components, with the addition of any product, including anticoagulants or coagulants. According to Paragraph 3, the processing of human blood to obtain PRP in a closed system and the manipulation of blood to obtain PRF can be performed in a surgical center or dental office by a qualified dental surgeon in accordance with RDC/Anvisa n. 63, of November 25, 2011[42], which provides for the Requirements of Good Operation Practices for Health Services, or any other resolution that replaces or supplements it. According to this Resolution, Chapter II on Good Operation Practices, Section I – On Quality management, Art. 5:

> The health service must adopt measures to establish a quality policy involving structure, process and result in the management of its services.
>
> Single paragraph. The health service must use Quality Assurance as a management tool.

In its Section III, on Organizational Conditions, Art. 17:

> The health service must provide physical infrastructure, human resources, equipment, supplies and materials necessary for the operation of the service according to the demand, type of assistance provided and current legislation.

Also, according to its Section VIII, Technology and Processes Management, Art. 54:

> The health service must perform the management of its technologies in order to meet the needs of the service, maintaining the conditions of selection, acquisition, installation, operation, distribution, disposal and traceability.

Therefore, it is up to the dental surgeon, responsible for the health service, to comply with RDC n. 63/2011[42], of which we highlight the commitment to the quality assurance of the procedures performed. Furthermore, the equipment and inputs used must be compatible with PRF preparation and use techniques.

In order to obtain PRP in a closed system, the kits to be used must be registered as health products, according to Anvisa's RDC n. 185, of October 22, 2001[43]. The requirements of safety and efficacy should also be followed[44].

According to Paragraph 4 of CFO Resolution n. 158/2015[41], the processing of human blood in an open system to obtain PRP for autologous use in Dentistry should be performed exclusively in Cell Processing Centers (CPCs), duly licensed by the competent Health Regulatory Agency, in accordance with the current legislation and with the agreement between the services documented in writing and proving the outsourcing. In that case, the determinations should be followed, as well as the controls,

defined by Anvisa's RDC n. 214, of February 7, 2018[45], which may include the platelet count and the microbiological control of the material to be applied. The protocol for obtaining PRP involves minimal manipulation of the patient's blood, which determines, therefore, that it be performed at the Cell Processing Center. According to RDC n. 214, of February 7, 2018, the Cell Technology Centers are now known as Cell Processing Centers.

According to the Report n. 20/2011 of the Federal Council of Medicine (CFM)[46], the use of PRP in non-hemotherapy procedures is considered experimental. CFM Resolution n. 1.499, of August 26, 1998[47], prohibits physicians from providing services of therapeutic practices that are not recognized by the scientific community. According to CFM Resolution n. 2,128, July 17, 2015[48], the practice of using PRP is still considered experimental and its use is restricted to clinical experimentation within the protocols of the Research Ethics Committee (CEP)/National Commission of Ethics in Research (CONEP), to be conducted in institutions duly qualified for this purpose and that comply with the norms of the Ministry of Health for the manipulation and use of blood and blood products in the country.

Regarding the PRF, the CFM does not regulate or make specific reference to the use of the PRF. Thus, clinical use of PRF in the medical field should be performed as clinical research, and should be approved by the CEP/Conep system.

The technological revolution in biomedical research has led to the development of new clinical procedures and biological medical products for human use, currently classified as "Advanced Therapies".

Anvisa's resolution n. 1.731, of September 9, 2016[49] defines Advanced Therapies as: (I) Advanced cell therapy products; (II) Tissue engineering products; and (III) Gene therapy products. These products consist of somatic cells or their non-chemically defined derivatives with therapeutic or preventive properties, through their main metabolic, pharmacological and/or immunological mode of action for autologous or allogenic use in humans. These products are subjected to extensive manipulation and/or perform in the recipient a distinct function from that performed in the donor. The manipulation of advanced therapy products should take place at the Cell Processing Center, according to Anvisa RDC n. 214/2018[45], which deals with Good Practices in Human Cell Therapeutics for Therapeutic Use and Clinical Research or according to the documents that replace it.

The PRF preparation from the patient's blood and its therapeutic use are performed in the same surgical act. PRF is a surgical adjuvant, having the function of an improved blood clot, and this is a way to mimic and amplify a natural phenomenon: blood coagulation and its participation in tissue regeneration[4]. The difference between the natural blood clot and the PRF is that the latter is more homogeneous and stable, easier to manipulate and to place in the indicated site, and may be associated with synthetic or biogenic materials[25]. The material is obtained and is intended for autologous use after blood collection and centrifuging, maintaining its primary function of blood stasis and coagulation. It is obtained through minimal manipulation in blood collection tubes for gel formation.

CONCLUSIONS

The use of the PRF by dental surgeons follows the determinations of Resolution CFO 158/2015[41]. There is no regulation for the use of PRF by CFM. The preparation and use of PRF is not considered an advanced therapy.

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Conflict of Interest

Authors have no potential conflict of interest to declare, related to this study's political or financial peers and institutions.