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EMPLOYMENT OF PLATELET RICH FIBRINE AND LEUKOCYTES (L-PRF) IN POST EXTRACTION: A LITERATURE REVIEW

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ABSTRACT

Fibrin Rich in Platelets and Leukocytes (L-PRF), is an autologous biomaterial, a second-generation blood product consisting of leukocytes, platelets and a dense three-dimensional network of fibrins that are simple and without biochemical manipulation of blood tissue used for healing. This study aims to describe the use of platelet and leukocyte-rich fibrin (L-PRF) in post-extraction alveoli through a literature review. The use of platelet and leukocyte-rich fibrin (L-PRF) in alveoli after a tooth extraction is well described and documented in the widely consulted literature, especially with regard to reduced bone absorption, infection, pain, local splicing and wound healing. healing time and bone remodeling are a great option to be used mainly after dental extraction when rehabilitation with implant placement is intended. L-PRF presents itself as an autogenous biomaterial with great versatility, low cost, easy acquisition and wide use in the most diverse areas of dentistry. Its disadvantages are relatively small compared to its major advantages.

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INTRODUCTION

Tissue engineering is a multidisciplinary field based on recent advances in medicine and surgery, molecular and cellular biology, polymer chemistry and physiology. Its primary purpose is the development and manipulation of molecules, cells, tissues, or organs grown in the laboratory, artificial implants, tissue generated without laboratory capable of replacing, stimulating or supporting the function of defective or injured parts of our body (OLIVEIRA, *et al*., 2010). In this sense, tissue engineering combines three key elements: matrix (three-dimensional structures that support growth, collagen cell, bone mineral), signaling molecules (growth factors (CF) and leukocyte cytokines) and cells (osteoblasts, fibroblasts or other adequate populations for tissue regeneration) (RAJA *et al*, 2008). Tissue engineering principles have found wide applicability in various branches of dentistry, such as periodontics, oral and maxillofacial surgery, and oral implantology, in the early 2000s when there was a significant development of tissue engineering within platelet concentrates where new generations emerged (BELT, CASTILIO, 2015).

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Fibrin Rich in Platelets and Leukocytes (L-PRF), is an autologous biomaterial, a second-generation blood product consisting of leukocytes, platelets and a dense three-dimensional network of fibrins that are simple to process and without the biochemical manipulation of blood tissue used for healing. , which accumulates inflammatory cytokines (IL-1β, IL-6, TNF-α, IL-4), several key CFs are the main ones: Transforming Growth Factor □ (TGF□-1), Platelet-Derived Growth Factor (PDGF) and Insulin-Like Growth Factor (IGF), Vascular Endothelial Growth Factor (VEGF) (EHRENFEST *et al*., 2006). The three-dimensional membrane composition of L-PRF creates an environment of slow degradation and gradual release of CF such as TGF□-1, PDGF, and IGF, VEGF and TSP-1 for at least seven days until the fibrin network disintegrates. Thus, L-PRF can anticipate the healing event and contribute to cell proliferation and movement (EHRENFEST *et al*., 2006b; EHRENFEST *et al*., 2009). The slow and progressive dispensation of L-PRF polymerization increases the incorporation of these chemical mediators into fibrin meshes increasing the life span of these fibrin meshes which are released and used only at the time of initial scar matrix restructuring, causing a long-term effect. The gelatinous consistency of the L-PRF film favors the stability of the clot

and the grafting material (CORREA, CASTILIO, 2015). The L-PRF film has its applicability widely indicated in the area of implant dentistry, periodontics, lesions, regenerative endodontics, alveoli, among others due to its high potential for tissue restructuring (DE ALMEIDA *et al*., 2017). The main advantages of using L-PRF are: rapid gingival tissue healing, angiogenesis, immunological control, high ability to transform adult stem cells into cells specific for gingival tissue growth and epithelial lining of the lesion; high capacity for tissue restructuring and regeneration capacity of tissue vascular network (DE ALMEIDA *et al*., 2017). According to Choukron *et al*. (2006), these factors are essential in achieving rapid tissue healing due to the successful development of neovascularization, intense rapid closure of lesions, scar tissue restructuring and scarcity of infectious events. Therefore being configured as an ideal material for use in post-extraction alveoli because it can ensure rapid healing, prevent infection, improve the capacity of local vascularization. This study aimed to describe the use of platelet and leukocyte-rich fibrin (L-PRF) in post-extraction alveoli through a literature review.

Development

The evolution of platelet concentrates: Initially the study in tissue engineering developed fibrin glue in 1970 and the fibrinogen polymerization with thrombin and calcium using donor plasma; However, due to the low concentration of fibrinogen in plasma, the low stability and quality of fibrin glue, and the threat of hepatitis transmission, much allogeneic fibrin glues commercialized so far have been banned in the US since 1978. Some commercial fibrin patches, such as Tisseel® (Baxter Healthcare Corp.) are commercially available, are heat-treated products with minimal risk of disease transmission, but not totally eliminating their use is still controversial. This is due to the complexity of the protocols for their production, in the case of autologous adhesives, and the risk of cross-infection in commercially available allogeneic adhesives. In 1974 Ross *et al*. Innovated the medical sciences by pioneering the discovery of the regenerative capacity of platelets. Describe and demonstrate that when isolated in peripheral blood samples, they presented themselves as an autologous source of growth factors (CFs). The CFs contained in platel*et al*pha granules are able to stimulate cell proliferation, matrix remodeling and angiogenesis (CARDOSO, LOPES, 2015). Since 1990, medical science has recognized the importance and power of various blood components that are part of the natural restoration of homeostasis; when added to injured tissues or surgical sites, able to anticipate healing. In possession of this knowledge there have been numerous attempts to develop autologous fibrin adhesives, but without much success Tayapongsak and colleagues in 1994 described a way to achieve an autologous fibrin glue with an extremely complex protocol, its use was limited due to the complexity and high costs of the production protocol (RAJA, 2008). The use of autologous blood materials then focused on the use of platelet concentrates associated with CF. These chemical mediators obtained from platelets, in addition to their action on tissues, interact with other CF, resulting in the activation of gene expression and the production of proteins that favor cellular activity (RAJA, 2008). The use of platelet concentrates aimed at improving healing in oral and maxillofacial surgery in place of fibrin glues, such results were first described by Whitman and colleagues in 1987 (WHITMAN, BERRY, GREEN, 1997).

Other protocols were developed. The described protocols generally used double centrifugation to increase the concentration of collected platelets: the first spin, soft spin, separated the blood sample into three distinct layers and the hard spin, where there was a longer and faster spin, obtaining, again, three distinct layers (AZEVEDO, 2014). The potential risks associated with the use of PRP through these protocols was the thrombin used (usually of bovine origin) that could be associated with the emergence of antibodies to both anti thrombin and anti factors V and XI, resulting in a risk of coagulation changes. There was also the possibility of a foreign body immune reaction due to the presence of factor V in the thrombin used (AZEVEDO, 2014). The original goal of PRP autologous preparations was to concentrate platelets and CF in a plasma solution, and to make them a fibrin gel for surgical site use in order to favor the healing process (CORREIA, CASTILIO, 2015). A natural blood clot is made up of 95% red blood cells, 5% platelets, less than 1% white blood cells and numerous amounts of fibrin filaments. A PRP blood clot contains 4% red blood cells, 95% platelets and 1% white blood cells (RAJA, 2008). Therefore, the properties of PRP are based on the production and release of multiple CF and differentiation in platelet activation. These factors are essential in regulating and stimulating wound healing and play a key role in regulating cellular processes such as mitogenesis, chemotaxis, differentiation, and metabolism (RAJA, 2008).

The major watershed in the after the emergence of PRP was the technique developed by Choukroun and collaborators who were pioneers in trying to alleviate the limitations of PRP, and eventually developed a new generation of platelet concentrates (AZEVEDO, 2014). Choukroun and colleagues developed in 2000 in France a specific technique for the acquisition of PRF, a second generation platelet concentrate, an autologous scar matrix for use in oral and maxillary surgery, revolutionized dentistry with a new concept: fibrin gel, a platelet concentrate on a fibrin film with a very high lesion repair potential (MOURÃO *et al*., 2015).

Thus Choukroun and collaborators eventually created a new material that could not be considered either fibrin glue or a classic platelet concentrate, PRF, eliminated the possible risks associated with the use of bovine thrombin (AZEVEDO, 2014). The technique does not require anticoagulant, thrombin or any other gelling agent. Blood is centrifuged without any addition and forming a film from an autologous blood sample without the addition of external factors, PRF, an autologous platelet-rich fibrin concentrate acquired in a small volume of plasma from sample collection. venous blood in collection tubes (MOURÃO *et al*., 2015). Fibrin gel is based on a concept of continuous release therapy of HR and protein by the gel and induces fibroblast collagen synthesis, which can speed up wound healing and tissue healing process (VASCONCELLOS, TEIXEIRA, CROSS, 2008). With continuous advances and research in the area, Choukroun and collaborators based on the concept of Ros *et al*., Developed L-PRF, a second generation blood product or immune processing and platelet concentrate that is simple and without biochemical manipulation of blood. which is determinant for the conformation of the fibrin network consisting of leukocytes, platelets in a dense three-dimensional fibrin network, a high density fibrin 3D tissue capable of generating a system that accumulates inflammatory cytokines (IL-1β, IL-6, TNF -α, IL-4), VEGF, PDGF, epidermal growth factors (EGF family), fibroblast-derived growth factors and IGF-I (EHRENFEST *et al*., 2006; GUEDES, 2017).

According to Guedes (2017), the L-PRF was developed with the objective of obtaining bone regeneration but its superior qualities indicate a much higher potential. Concentrates can also be divided into two major referenced groups: PRP and PRF.PRP is the first group of the precursor group and consists of a modification of fibrin glue (produced in the 1970s by Matras) resulting from the donor's own two-stage centrifugation of the blood that contains the HRs that influence healing, tissue adjustment, and cell regulation mechanisms that include chemotaxis, differentiation, and metabolism. Generally, PRP is used as a gel achieved by mixing PRP (resulting from double autologous whole blood centrifugation) with thrombin and calcium chloride. Obtaining PRP is divided into two more protocols: P-PRP and PRP-L (GUEDES, 2017). The PRF, belonging to the second generation of platelet concentrates, or second group with single centrifugation and no biochemical handling of blood developed by Choukroun *et al*. The technique of Choukron and collaborators presents two distinct protocols: PRF and L-PRF (GUEDES, 2017).For a better understanding of the community and scientist, scholar and researchers have performed a terminology system of platelet concentrates (EHRENFEST *et al*., 2012).The evolution of fibrin concentrates are classified into four categories according to their leukocyte content and fibrin architecture:

- Pure Platelet Rich Plasma (P-PRP): As the PRP, Vivostat, Anitua PRGF or Nahita PRP cell separator, P-PRP refers to the inactive liquid form of this product, and its activated version, respectively called P-PRP gel;
- Platelet Rich Leukocyte Plasma (L-PRP): Curasan, Regen, Plateltex, SmartPReP, PCCS, Magellan, Angel or GPS PRP; being its active form called L-PRP gel;
- Platelet Rich Fibrin (P-PRF): such as Fibrinet;
- Platelet-Rich Fibrin and Leukocytes (L-PRF): like Choukroun's PRF (EHRENFEST *et al*., 2012b).

The Applicability of Fibrin-Rich Platelet and Leukocyte (L-PRF) Post Extraction Alveoli: After an extraction, a set of inflammatory events for local repair arises where the alveolus is filled with blood due to ruptured blood vessels of the periodontal ligament, and a fibrin network is immediately formed. At this stage, platelets lead to clot creation, then there is the presence of erythrocytes and neutrophils. If the primary clot is retained, alveolar healing will follow a natural course (FIGUEIRA, GONÇALVES, 2015). Between the third and fourth day, the emergence of epithelialization and the creation of immature connective tissue is observed. Some small clot fragments are already replaced by granulation tissue. One week after the immature bone trabeculae event are already visualized, and an initial angiogenesis stage is noted (FIGUEIRA, GONÇALVES, 2015). Alveolar bone healing during post-extraction repair is associated with tissue remodeling resulting in bone volume loss, approximately 50% both vertically and horizontally. Such resorption occurs mainly within the first three months and triggers the deformation of the lip that causes aesthetic and functional difficulties. Post-extraction bone resorption in both the maxilla and mandible is a major challenge for oral rehabilitation. This resorption and loss of the physiological alveolar process after tooth removal is a natural, undesirable phenomenon that can impair the installation of prostheses and implants (GUEDES, 2017). For this physiological condition, Del Corso, Toffler (2010) suggest using the L-PRF technique, which acts on bone formation and maintenance in post-extracted teeth alveoli, thus minimizing the loss of height and thickness of the alveolar process.

The 4 fundamental events that structure L-PRF is:

- Angiogenesis,
- Immunity,
- Stem cell chemotaxis and
- Epithelization (diniz, 2017).

Diniz (2017) lists the main advantages of L-PRF

- L-PRF is a CF concentrate is easy to acquire, has a simple technique with one-step centrifugation and is free of biochemical manipulation (no thrombin is required due to polymerization being a completely natural process without risks of immunological reactions).) and low cost;
- L-PRF more efficient and less controversial than PRP
- It is a CF concentrate immersed in a natural fibrin network that maintains a long period of time stimulating and promoting effective tissue regeneration, angiogenesis, cell transfer and proliferation and the leukocyte presence modulating the inflammatory process in its time and intensity;
- Favors bone formation when combined with other grafting products and healing;
- Favors soft tissue healing, acting on the inflammatory process;
- Promotes healing in alveoli and gingival graft removal sites, causing lower morbidity and accelerated tissue repair;
- Poorly consistent literature results used as a replacement for soft tissue grafts;

As for the disadvantages of L-PRF are:

- Obtaining a small amount due to being an autologous material;
- The technique requires the rapid collection of blood samples that should always be collected in a glass tube and placed to centrifuge immediately after collection, any delay implies in the disposal of the material (DINIZ, 2017).

The three-dimensional structure of the fibrin gel maintains key cytokines and HR such as FGFb, VEGF, PDGF, immersed in the mesh that, added to the rigidity of the PRF matrix, directly influences angiogenesis, supporting stem and mesenchymal cells to populate this primary matrix. vigor and speed. Fibrin affinity with the various CFs is the key to rapid angiogenesis. This difference in PRF matrix configuration is what clinically differentiates the higher efficiency of L-PRF from fibrin glue and PRP (DINIZ, 2017). The expression of integrin (AVP3) by endothelial cells allows fibrin binding to fibronectin and vitronectin, and this expression is regulated by fibrin itself which does not happen in collagen (DINIZ, 2017). The cytokines controlling immune reactions are present in PRF, due to the artificially induced leukocyte induction in the tube, these cytokines give L-PRF an infinitely great protection against infections by increasing the expression of proinflammatory cytokines (IL-1b, IL6, TNF-a), anti-inflammatory (IL4), angiogenic factor (VEGF) that mobilize

immune cells to protect the wound against infectious agents (DINIZ, 2017). The mesh formed by Fibrina in L-PRF is the great asset of this biomaterial as it robustly traps Platelets that in time will release the CF and cytokines that will modulate and promote regeneration. The addition of L-PRF to dental extraction sites has the function of sustaining the required bone volume. The L-PRF film stimulates clot production, favoring the physiological healing process (DEL CORSO, TOFFLER, EHRENFEST, 2010). According to Choukroun *et al*. (2006a) and Ehrenfest *et al*. (2006) after tooth extraction the local bone structure changes rapidly and rapid bone resorption occurs. PRF-L can boost accelerated bone regeneration, faster vigorous angiogenesis and accelerate epithelialization. In addition, according to Rao *et al*. (2013) state that the costs of L-PRF film are much cheaper when compared to the costs of other recombinant CFs. Another advantage that the use of L-PRF enables is the prevention of mandibular osteitis in 90% of cases in wisdom teeth extraction (HOAGLIN. LINES, 2013). Suttapreyasri and Leepong (2013), we agree that L-PRF is a compatible biomaterial in filling post-extraction alveoli with regard to better healing and preservation.

In another study, changes in bone crest associated with healing of 21 extraction sites using L-PRF alone as a graft were quantified. Measurements of crest width and height at extraction were recorded after graft placement and after 4 months of healing. What was observed was that the grafted sites only using L-PRF exhibited rapid clinical healing, minimal flap reopening, and excellent bone density. Advantages of platelet-rich fibrin alone include shorter surgical time, elimination of techniques, better membrane-associated healing, and less resorption during healing when compared to guided bone regeneration procedures (SIMON, GUPTA, TAJBAKHSH, 2011). The study by Suttapreyasri, Leepong (2013) investigated the influence of L-PRF on early wound healing and preservation of alveolar crest shape after tooth extraction. Platelet-rich fibrin has clinically shown early healing of soft tissue orifice holes within the first 4 weeks. L-PRF entered the stable stage after the fourth week after tooth extraction, while in the control group the progression of oral contour contraction was still detected until the eighth week. In this study the preliminary result showed no better preservation of the alveolar ridge nor increased bone formation of PRF in the extraction socket, but the use of L-PRF revealed limited efficacy by accelerated soft tissue healing in the first 4 weeks.
L-PRF has the ability to accelerate physiological healing, and when associated with bone grafts accelerates the bone regeneration process, regulates inflammation and stimulates the chemotaxis immune process (CORREA, CASTILIO, 2015). L-PRF is able to support the development of three phenomena simultaneously: Angiogenesis, immune response and epithelial coverage, which are the main factors involved in the healing and tissue maturation process (CHOUKROUN *et al*., 2006a).

In the study by Hauser *et al*. (2013) investigated whether the use of L-PRF membranes for cavity filling could improve the microarchitecture and quality of alveolar bone intrinsic bone tissue after premolar extraction. Twenty-three patients requiring premolar extraction were divided into groups and in the first, simple extraction and loop filling with L-PRF were performed, in group II mucosal flap extraction and loop filling with L-PRF. and in group III control with simple extraction without filling. Post-computed tomography analysis showed better bone healing with improved microarchitecture in group I. The results support the use of a minimally traumatic procedure for tooth extraction and cavity filling with L-PRF to preserve hard tissue and minimize potential impact. reabsorption.

Conclusion

The use of platelet and leukocyte-rich fibrin (L-PRF) in alveoli after tooth extraction is well described and documented in the widely consulted literature, especially with regard to reduced bone absorption, infection, pain, local edema and wound healing. healing time and bone remodeling is a great option to be used mainly after dental extraction when rehabilitation with implant placement is intended. L-PRF presents itself as an autogenous biomaterial with great versatility, low cost, easy acquisition and wide use and infinite possibilities. It can be combined with other materials in the most diverse areas of dentistry.

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