CRANIOFACIAL RESEARCH CONNECTION JOURNAL

LEUKOCYTE AND PLATELET-RICH FIBRIN USES IN THIRD MOLAR SURGERY

Literature Review

Novais Ferreira, C.
Algayer,E.
Mioso, F.
Thereza-Bussolaro, C.

Dentistry Department,
UNIFASIPE, School of Dentistry,
Sinop-MT, Brasil

Novais Ferreira C, Algayer EC, Mioso FV, Thereza-Bussolaro C. Leukocyte and platelet-rich fibrina uses in third molar surgery. Craniofacial Research Connection Journal. 2022;2(52-61) DOI: 10.6084/m9.figshare.19565995

Submitted: 08/12/2021
Reviewed: 10/12/2021
Accepted: 08/02/2022

ABSTRACT: The evolution of dentistry has an increasing need for the creation of new materials that facilitate postoperative adversities, such as pain and edema experienced by patients. The leukocyte and platelet-rich fibrin membrane (L-PRF) is an example of platelet concentrates that presents a preparation process from a patient's own blood sample, which is subjected to a specific centrifugation procedure, which results in a fibrin membrane, rich in leukocytes and growth factors. L-PRF has been used with the promise of improving tissue healing and reducing the inflammatory process after third molar extractions. Based on this utility, this study aimed to review the literature on the use of L-PRF in the post-extraction alveolus and seek an answer to the research question: What are the effects and how leukocyte and platelet-rich fibrin membrane (L -PRF) has been used in post-extraction alveolus? Studies in Pubmed, Cochrane and Google Scholar were searched. Based on the 4 studies included, the use of L-PRF after third molar extractions significantly reduces the risk of alveolar osteitis, and has a positive effect on pain, trismus and edema. And also L-PRF when combined with HA (hyaluronic acid), can be used to minimize post-operative edema after mandibular third molar surgery.

KEYWORDS: Healing. Extraction. L-PRF. Third Molars.

INTRODUÇÃO

Dentistry has shown great development in recent decades, with the improvement of techniques and the inclusion of new technologies. Platelet concentrates are part of the arsenal of new techniques that mark the evolution not only of dentistry, but also of the medical field. Among the various platelet concentrates, Platelet Rich Fibrin (PRF) is one of the most used in surgical procedures and has multiple applications in the area of oral and maxillofacial surgery.[1]

PRF is a platelet concentrate developed by Choukroun, in France, originated through the manufacture of inappropriate preparation intended for autologous use. His proposal is to promote better and faster healing in the repair of surgical injuries. The original objective was to develop a treatment where platelet concentrates could be placed in the lesions, using our body's natural effectiveness to obtain the healing process in a competent way.[1]

The main purpose of a dental surgical treatment is the maintenance of health, in addition to well-being and functionality.[1] The extraction of third molars is one of the most common procedures in the area of oral surgery and may be associated with some complications and adverse effects, such as alveolar osteitis, trismus and infection.[2] Thus, the impact of the use of PRF and its derivatives has been investigated in third molar surgeries[2,3] in order to assess its effect on adverse effects.

Leukocyte and Platelet Rich-Fibrin (L-PRF), originating from PRF, incorporates leukocytes, platelets, leukocyte cytokines and growth factors into an autologous fibrin matrix[1,2] has been associated with improvement in pain, edema and occurrence of osteitis alveolar ridge after third molar extractions[4] Due to its gelatinous consistency, it favors the stability of the clot and the grafting material.[5] In parallel with this established clinical ease of use and handling, the composition of L-PRF by-products provides it with attractive biochemical properties, hemostatic, angiogenic, osteogenic, anti-inflammatory, antimicrobial and pain inhibitors in wound healing.[6-9]

Alveolus recovery is a sequence of biochemical, physiological, cellular processes and molecular responses intended to remodel tissue and functional capacity after surgery. The progress of biomaterials capable of decreasing side effects and speeding up the healing process remains a challenge for dental surgeons and leads to research. This autologous biomaterial consists of a strong fibrin matrix with a complex three-dimensional constitution. It is provided by immediate centrifugation, after blood collection, and without the addition of anticoagulant.[10]

Thus, the use of L-PRF has been proposed with the expectation of better tissue healing and less postoperative inflammation and complications after third molar extractions[1,8,11] however, in addition to requiring specific equipment and a certain time of preparation, negligible effect on soft tissue healing after removal of impacted lower third molars, has been reported.[1]

The aim of this study was to review the literature on the use of L-PRF in the post-extraction socket and seek an answer to the research question: What are the effects and how does leukocyte and platelet-rich fibrin (L-PRF) has being used in post extraction socket?

METHODS

The present study deals with a literature review consisting mainly of scientific articles, researched in national and international online scientific databases: Google Scholar and PubMed. A search on the search platforms was carried out on April 26, 2021, with no date or language limitation. The search terms were: PUBMED ((("platelet rich fibrin"[All Fields])) OR ("plasma rich growth factors"[All Fields])) OR ("leukocyte rich plasma"[All Fields] OR "leukocyte rich platelet"[All Fields] OR "leukocyte rich platelet rich"[All Fields] OR "leukocyte rich platelet rich plasma"[All Fields])) AND ((((("oral surgery"[All Fields]) OR ("dental surgery "[All Fields])) OR (dentist)) OR ("buccal surgery"[All Fields])) AND (clinicaltrial[Filter] OR randomized

controlled trial[Filter]). Google Scholar used the exact phrase “Leukocyte and platelet rich fibrin”, “surgery” both in the “titles”, without including patents and/or citations. Manual search was also performed on the articles found on reference lists. Inclusion criteria: randomized controlled trials, clinical trials. Exclusion criteria: case reports, animal studies, surgeries not related to dentistry, surgeries other than minor oral.

LITERATURE REVIEW

BLOOD COMPONENTS

Blood is a connective tissue that contains a solid phase, which comprises the formed elements, and a liquid phase, which corresponds to plasma. Blood plasma consists of 10% solid elements and 90% water.[12] The solid elements of plasma are mainly proteins, fats, carbohydrates, electrolytes, organic and mineral salts, and hormones. The formed elements of blood are: red blood cells (erythrocytes), white blood cells (leukocytes) and platelets. Blood has the functions of transporting gases, nutrients and degradation products, transporting processed molecules, transporting regulatory molecules, regulating pH and osmosis, maintaining body temperature, protecting against foreign substances and clot formation.[12]

The vast majority of the proteins that make up plasma are albumin, globulins and fibrinogen. Albumin (58% of plasma proteins) is responsible for blood viscosity and osmotic pressure. α and β globulins (38%) act as transport molecules and other globulins, for example antibodies, which are involved in immune function. Fibrinogen (4%) is responsible for the formation of fibrin, which is essential for blood clotting.[13]

Leukocytes, or white blood cells, are nucleated cells produced in the bone marrow and found in the blood with a spherical shape. They are part of the body's immune system. They have the function of fighting and eliminating microorganisms and chemical structures that are foreign to the body through their capture or the production of antibodies, whether pathogenic or not.[12]

The inflammatory response is linked to the process of controlling and eliminating the harmful agent, being part of the innate immune system, so called for its ability to provoke a non-specific response against the causative agent. Inflammation is triggered by inflammatory stimuli and regulated by chemical mediators, cytokines.[14]

Cytokines are proteins that modulate the function of other cells or the cells that generated them. They are produced by several cells, but mainly by activated lymphocytes and macrophages, being important to induce and regulate the inflammatory and immune response.[13]

The number of inflammatory mediators involved in the inflammatory process is very significant. The three main leukocyte cytokines are: Interleukin 1-β (IL-1β), Interleukin 6 (IL-6) and Tumor Necrosis Factor-α (TNF-α). It is observed that during an inflammatory episode, the peaks of cytokine secretion are synchronized in space and time. In fact, these three molecules together constitute a fundamental link in inflammation.[14]

IL-1β is produced by macrophages, neutrophils, endothelial cells, fibroblasts, keratinocytes and Langerhans cells. It is an inflammation control gauge. Its main function is the stimulation of T Helper lymphocytes. In combination with TNF-α, IL-1 β may be involved in osteolysis, where it activates osteoclasts and inhibits bone formation.[14]

IL-6 is produced by mononuclear phagocytes, vascular endothelium cells, fibroblasts and other cells in response to microorganisms and other cytokines, especially IL-1 and TNF-α. It has action both on the innate and adaptive immune system, having as main biological functions the synthesis of proteins in the acute phase of inflammation by the hepatocytes, inducing the production of neutrophils and the growth of B lymphocytes that differentiate into antibody producers, the plasma cells.[14]

TNF-α can be produced by activated macrophages, lymphocytes or monocytes. The main stimulus for its production is the presence of lipopolysaccharides that make up the membrane of gram negative bacteria. After being produced and released, TNF-α will bind to specific receptors called TNF receptors (TNF-R) I and II, so that it can produce its biological effect. TNF receptors (mainly TNF-RII) can trigger apoptosis (programmed cell death). However, the mechanism that will determine which effect will be dominant is not yet fully understood.

Thus, the main physiological effect of TNF-α is to promote the immune and inflammatory response through the recruitment of neutrophils and monocytes to the site of infection, in addition to activating them.[15]

Platelets play a key role in hemostasis and are a natural source of growth factors (FC). These factors are stored in platelet granules, with CF playing a key role in healing and healing.[13] Platelet activation is critical to initiating and supporting hemostasis due to its aggregation in damaged tissue and interactions with clotting mechanisms.[16]

Growth factors are specific polypeptides present in plasma, which regulate cell proliferation and differentiation, generating tissue regeneration. The main ones are: Transforming Growth Factor β (TGF-β) which stimulates the proliferation of undifferentiated mesenchymal cells, regulates endothelial fibroblast and osteoblast mitogenesis (increase in the population of healing cells), inhibits the proliferation of lymphocytes and macrophages, regulates the mitogenic effect of other CF, as well as regulates collagen synthesis and collagenase secretion. Basic Fibroblastic Growth Factor (bFGF) promotes growth and differentiation of chondrocytes and osteoblasts, and is also mitogenic for mesenchymal cells, chondrocytes and osteoblasts.[16]

Platelet-Derived Growth Factor (PDGF) are crucial regulators for the migration, proliferation and survival of mesenchymal cells. PDGFs, associated or not with TGF, increase tissue vascularization, promote the proliferation of fibroblasts, increase the amount of collagen, stimulate the production of granulation tissue and improve angiogenesis (endothelial mitosis in functional capillaries).[16]

Epithelial Growth Factor (EGF) stimulates endothelial chemotaxis and angiogenesis, regulates collagenase secretion, and stimulates epithelial and mesenchymal mitogenesis. Insulin-Like Growth Factor (IGF) is a positive regulator of proliferation and differentiation of most cells, including tumor cells. They form the major axis of the regulation of apoptosis death, through the induction of survival signals that protect cells from various matrix apoptotic stimuli.[16]

Vascular Endothelial Growth Factor (VEGF) is considered the main regulatory molecule of angiogenesis. It has a direct role in controlling the behavior of endothelial cells such as proliferation, migration, differentiation or survival.[17]

Hemostasis and Coagulation

Hemostasis boils down to preventing bleeding by vasoconstriction and clot formation. In hemostasis, blood flow in the vascular lumen is restricted until the lesion is repaired, so that the blood is contained within this internal space and is kept in a liquid state. The hemostatic process is very efficient and requires circulating proteins, blood cell elements and the endothelium for its accomplishment.[12]

Hemostasis is performed in three stages: transient vasoconstriction and platelet aggregation, to form a platelet plug at the site of injury (primary hemostasis); coagulation, aiming to form a fibrin mesh (secondary hemostasis) and fibrinolysis, for the removal of platelets and fibrin plug (thrombus retraction).13 The reduction in blood flow decreases blood loss in addition to allowing a more effective enzymatic reaction in the coagulation processes and platelet aggregation.[18]

In the primary phase of hemostasis, the first response to vascular injury is vasoconstriction, which results in decreased blood flow distal to the injury site. This initial phase corresponds to a transient response resulting from reflex neurogenic mechanisms (central response) and, at the site of injury, by endothelins, potent vasoconstrictors derived from endothelial cells (local response). The reduction in blood flow reduces blood loss in addition to enabling a more effective enzymatic reaction in the clotting and platelet aggregation processes.[18]

After the initial vasoconstriction, platelet thrombus formation occurs rapidly, defining the second stage of the hemostatic process. A cluster of platelets occurs that seals small breaks in blood vessels. Initially, platelets bind to exposed collagen (platelet adhesion), and this adhesion is mediated by von Willebrand factor (FvW), which is a protein produced and secreted by the endothelial cells of blood vessels.[13]

Adenosine diphosphate (ADP) and thromboxane activate other platelets, thereby causing them to release surface

receptors that bind to fibrinogen. Fibrinogen forms a bridge between the surface receptors of different platelets, forming a loose platelet thrombus (platelet aggregation).[13]

Exposed collagen and other factors present in tissues initiate the coagulation cascade, and inactive plasma proteins are converted to active enzymes (clotting factors), causing the enzyme thrombin to convert fibrinogen to fibrin, strengthening the platelet plug (clot). Fibrin is the end product of a series of enzymatic reactions involving clotting factors, non-enzymatic cofactors, calcium and membrane-derived phospholipids, mainly from platelets. The main role of fibrin in wound repair is hemostasis, but fibrin also provides a matrix for the migration of fibroblasts and endothelial cells that are involved in angiogenesis and responsible for new tissue remodeling.[12]

The primary platelet clot is reinforced by fibrin formation. The elastic force is increased by the cross-mesh of the fibrin polymer, mediated by factor XIIIa, which converts α 2-antiplasmin to fibrin, in addition to protecting the clot against fibrinolysis. However, fibrinolysis is a prerequisite for hemostasis. Tissue Plasminogen Activator (APT) is released by endothelial cells and converts plasminogen to plasmin, a protease. After blood vessel repair, the clot retracts and is slowly dissolved by plasmin.[12]

Tissue Repair Process

The tissue repair process has been divided into three basic stages: inflammatory, fibroblastic (proliferative) and remodeling (regenerative) which, although not respectively exclusive, participate in this sequence.19 Inflammation is all reactional episodes initiated in response to a specific aggression. The inflammatory phase begins at the moment of tissue injury and lasts from three to five days. It is divided into two stages: vascular phase and cellular phase.[14]

The fibrin threads from blood clotting that cross in wounds form a network on which fibroblasts can initiate the anticipation of ground substance and tropocollagen. Fibroblasts cause undifferentiated mesenchymal cells present at the site and in the circulation to start producing tropocollagen on the third or fourth day after tissue injury. Fibroblasts also secrete fibronectin, which helps stabilize fibrin, recognize foreign materials, acts as a chemotactic factor for fibroblasts, and also helps guide macrophages along fibrin strands for eventual fibrin phagocytosis.[19]

Collagen remodeling is activated in the formation of granulation tissue. In this phase, endothelial regression and reduction of all cellular elements, including inflammatory cells, occur. Wound maturation begins during the third week and is characterized by an increase in resistance, without an increase in the amount of collagen.[19]

Bone regeneration

Bone is a dynamic tissue that is in a constant process of resorption and remodeling, and the events that occur during these processes include several steps, with osteoblasts and osteoclasts as responsible cells.[20] Osteoblasts are derived from three sources: periosteum, endosteum and undifferentiated pluripotent mesenchymal cells. Osteoclasts, derived from monocyte precursor cells, function to resorb necrotic bone and bone that needs to be remodeled. The osteoblasts then deposit the osteoid, which, if kept completely immobile during the healing process, ends up calcifying.[21]

The differentiation and development of osteoblasts from mesenchymal cells is dependent on the release of FCs such as bone morphogenetic proteins (BMPs), IGF, PDGF and FGF. CFs are responsible for regulating important cellular processes involved in tissue repair by binding to specific receptors on the cell surface.[16]

Classification of Platelet Aggregates

In modern tissue regeneration, the evolution of platelet aggregates is considered a faster, easier and less invasive way, using autogenous products that minimize the risks of patient rejection.22 Platelet aggregates are classified in two ways, by the presence of leukocytes and by fibrin density, and can be divided into 4 groups: P-PRP (Platelet Rich Plasma Pure) which has low fibrin density and has no leukocytes, L-PRP (Platelet Rich Plasma and Leukocytes) which has leukocytes and

low fibrin density, P-PRF (Pure Fibrin Rich Plasma) which do not contain leukocytes and have high fibrin density, and L-PRF (Pure Fibrin Rich Plasma and Leukocytes) which contain leukocytes and have high fibrin density.[23,24,25]

L-PRF Technique

Described by Joseph Choukroun in 2001, PRF is derived from an autogenous preparation of concentrated, second-generation platelets, in which the product is obtained through a natural process, and does not require the incorporation of thrombin. or anticoagulants to be effective, thus eliminating the risks that bovine thrombin could cause.[22]

As this technique does not require the use of anticoagulants or bovine thrombin, it is simply centrifuged blood without any additive, the technique that resembles the natural clotting process is the simplest and with the most economical protocol.[26] The preparation of L-PRF requires a suitable centrifuge and a collection kit that includes: a 24 gauge butterfly syringe, and 10 ml test tubes for blood collection.[27]

The PRF protocol is simple: a blood sample is obtained without anticoagulant in 10ml tubes that are centrifuged at 2700 to 3000 rpm (approximately 400g) for 10 minutes.[1] In view of this, three layers are obtained: erythrocytes, PRF clot (contained most platelets and leukocytes) and PPP (Platelet Low Plasma). The upper layer of the tube (PPP) is removed and collected in an intermediate fraction, two millimeters below the division between this layer and the erythrocytes, thus having L-PRF. The success of this technique depends on the period of time between the collection of blood and its transfer to the centrifuge, as the blood without the addition of anticoagulants begins to clot immediately with the simple contact with the walls of the tube.[27]

Use of L-PRF in alveoli after third molar extraction

Third molar extraction is a procedure constantly performed in the clinical routine of the dental surgeon. Pain, swelling and trismus are commonly experienced by patients postoperatively.28 L-PRF is used to improve tissue healing and to reduce the postoperative inflammatory process and complications after third molar extractions.[2]

Its use proposes a positive effect on angiogenesis, immunity and wound healing, due to the high amount of leukocytes and macrophages present. These leukocytes and macrophages are responsible for fighting infections and releasing growth factors responsible for tissue and bone support.[2]

The surgical procedure may be associated with possible postoperative side effects that include pain, trismus, swelling, infection, and dry sockets. Fibrins rich in platelets and leukocytes came to complement tissue regeneration, transforming a more effective and qualified healing. Analogous to natural curing, slow polymerization during L-PRF preparation forms a fibrin mesh that enhances cell migration and proliferation. Starting a reservoir of platelets, leukocytes, cytokines and immune cells, L-PRF has been reported to allow the slow release of cytokines that play a critical role in angiogenesis and tissue healing.[2]

RESULTS

14 articles were found in Pubmed, 10 in Google Scholar and 2 in Cochrane after applying the inclusion and exclusion criteria, 4 studies4,10,29,30 were selected for complete analysis, 210,30 from Pubmed, 129 from Google Scholar and 14 from Cochrane.

Daugela et al (2018) bring a randomized clinical study, where thirty-four patients were randomized and underwent extraction of bilateral impacted mandibular third molars. After extraction, one well received L-PRF randomly and the other well served as a regular blood clot control. Postoperatively, the soft tissue healing index, pain according to the visual analogue scale, facial swelling with horizontal and vertical guidance, and the incidence of alveolar osteitis were evaluated 1, 3, 7, and 14 days after surgery. and the L-PRF treated sites resulted in improved soft tissue healing index (P = 0.001) and lower pain scores (P = 0.001) in the first postoperative week. Significant reduction in facial edema was recorded on the first (P = 0.035) and third (P = 0.023) postoperative days in L-PRF sites versus controls, with the

non-significant difference ceasing on day 7 (P = 0.224). None of the L-PRF sites and four control sites were affected by alveolar osteitis (P = 0.001).[4]

Ritto et al (2019) conducted a randomized double-blind study where thirty-four extractions were performed. On one side, the socket was sutured without the L-PRF (control side); on the other side, L-PRF was inserted before suturing. As a result, the application of L-PRF improved bone density, which was higher in the test group (p = 0.007). There was no statistical difference regarding pain or soft tissue between groups (p>0.05). There was evidence of improvement in bone healing in response to L-PRF.[10]

L-PRF was also associated with other materials, as in the study by Afat et al (2018)[30], in which L-PRF was combined with hyaluronic acid. We performed a double-blind randomized trial evaluating the effects of leukocyte- and platelet-rich fibrin (L-PRF) alone and combined with a hyaluronic acid (HA) sponge on pain, swelling, and trismus after mandibular third molar surgery. A total of 60 patients were involved, they were divided into 3 groups: L-PRF group, L-PRF+ HA group (L-PRF combined with HA) and control group (nothing was applied). The evaluation of postoperative edema was made by the limitations of the distances from tragus to pogonion (TPO), tragus to labial commissure (TCO) and mandibular angle to lateral corner (ACA) were measured with a flexible ruler and pointed preoperatively. These 3 measurements were repeated on postoperative days 2 and 7, and the differences between these values. All three measures of edema (TPO, OCT and ACA) showed significant changes between groups. The mean increase in TPO on day 2 was considerably greater in the control group than in the L-PRF-plus-HA group (P = 0.001), and the mean increase on day 7 in the control group was significantly greater than in the L-group. PRF (P = 0.003) and L-PRF - plus - HA group (P = 0.007). The mean increase in OCT on day 2 was significantly greater in the control group than in the L-PRF-plus-HA group (P = 0.001). Mean increases in ACA on days 2 and 7 were substantially greater in the control group than in the L-PRF group (P = 0.011 and P = 0.002, relatively) and L PRF – plus – HA group (P = 0.001 and P = 0.006 , respectively). There was no relevant difference between groups in trismus measures or VAS pain scores. Analgesic intake on the day of surgery in the L-PRF-plus-HA group was considerably lower. The results concluded that L-PRF associated with HA can be used as an effective anti-inflammatory agent after third molar surgery and minimized postoperative swelling after mandibular third molar surgery.[30]

Da Silva et al (2021)[29] in a double-blind randomized clinical trial looked at the effects of leukocyte platelet-rich fibrin (L-PRF) on soft tissue healing and the connection with the local concentration of growth factors (GF) and cytokines in the dental socket of lower third molars. Forty mandibular third molars (20 participants) were included in this study. After tooth extractions, randomized sides had alveolar filling with L-PRF on one side and a natural blood clot on the other side. Pain was examined for seven days and soft tissue healing (Landry index) for 14 days post-extraction. Swabs were collected from the surgical sites for evaluation of growth factors and cytokines by flow luminometry. Participants reported less postoperative pain on the L-PRF-grafted sides, who also had increased tissue healing scores (p<0.05).[29]

DISCUSSION

This literature review analyzes the use of Fibrin Rich in Platelets and Leukocytes (L-PRF) in post-extraction socket as a means of promoting better healing, as well as its efficiency in the postoperative control of pain, edema, trismus and alveolitis in articles and research carried out previously.

L-PRF is the result of an autogenous preparation of concentrated platelets, second generation, in which the product is obtained through a natural process, and which does not require the incorporation of thrombin or anticoagulants to be effective, thus eliminating the risks that bovine thrombin could entail.[2]

The advantages for clinical use in daily practice are based on the ability to effect L-PRF has on angiogenesis, immunity and wound healing. This is due to the fact that many leukocytes and macrophages are also present, they are responsible for fighting infections and releasing growth factors responsible for tissue and bone

support.[2] Due to this capacity, it is understood the benefit of using this biomaterial in post extraction alveoli.[28]

Daugela et al (2018)[4], show that the relief of postoperative pain and edema are essential for reducing discomfort and improving the patient's condition after impacted mandibular third molar surgery, which allows for a lower demand for post-operative emergency. and increased patient comfort during the postoperative period.[4]

Ritto et al (2019)[10] says that another important feature of L-PRF is the ability to improve the bone healing process. The growth factors present in L-PRF are responsible for regulating important cellular processes involved in tissue repair by binding to specific receptors on the cell surface.[10]

Afat et al (2018)[30] suggest that instead of using HA in gel or spray form, it is preferable to use a solid HA sponge, which biodegrades slowly and releases only biocompatible HA chains, such as an L-PRF membrane, ensures that effective amounts of HA remain in the socket during the first week of healing.[30]

Da Silva et al (2021) [29] show that use of L-PRF improves the soft tissue healing process and decreases postoperative pain after third molar extractions, which correlates with an increase in the local concentration of growth factors , such as PDGF and FGFb.[29]

Two systematic reviews[2-3] evaluated the effects of PRF, not L-PRF, showing results that are sometimes controversial[2] and sometimes similar[3] to those observed in our review, which included only studies4,[10,30,29] using L-PRF. In the systematic review by Al-Hamed et al (2017)[2] researchers verified five randomized controlled trials and one controlled clinical trial of 335 extractions (168 with PRF and 167 controls) in 183 participants. Qualitative and meta-analysis results did not show any relevant advances in bone healing with PRF-treated sockets compared to naturally healing sockets. Within the limitations of the available evidence, PRF does not appear to have a beneficial role in bone healing after extraction of lower third molars.[2]

In the systematic review by Canellas et al (2017)[3] researchers analyzed reports of 485 extractions (243 trials, 242 controls) in 280 patients, the results showed a reduction in pain, swelling and alveolar osteitis in the first week after surgery when the PRF was used. However, quantitative analysis was possible only in relation to alveolar osteitis.[3]

Canellas et al (2017) concluded that the use of PRF in mandibular third molar surgery is an alternative method to decrease postoperative pain and swelling and its application in the post-extraction socket may reduce the risk of developing alveolar osteitis after surgery. mandibular third molar surgery.[3]

An update of systematic reviews evaluating the use of PRF, Zhu et al (2020)[31] included 19 studies and 17 studies were eligible for meta-analysis. The study aimed to estimate the effect of PRF on the postoperative outcomes of alveolar osteitis, pain, trismus, soft tissue healing, and edema after mandibular third molar surgery. The results of this study showed that PRF can be applied to reduce the incidence of alveolar osteitis as well as postoperative pain. Furthermore, the use of PRF can also improve soft tissue healing. During the third molar surgery procedure, surgical trauma cannot be totally avoided. The release of certain biological mediators is stimulated by trauma, leading to postoperative complications such as pain and swelling.[31]

FINAL CONSIDERATIONS

In conclusion, within the limits of this study and based on the results shown, it is possible to conclude that the application of L-PRF in the post-extraction socket can reduce the risk of developing alveolar osteitis after mandibular third molar surgery. L-PRF has shown potential in improving soft tissue healing and can be considered optional in view of postoperative side effects that include pain, trismus, edema, infection and dry sockets. L-PRF when combined with HA (hyaluronic acid), can be used to minimize postoperative swelling after mandibular third molar surgery. However, these are promising treatments that need further clinical studies.

REFERENCES

1 Choukroun J *et al*. Platelet-richfibrin (PRF): A second-generation platelet concentrate. Part IV: Clinical effects on tissue healing. Oral Surg Oral Med Oral

PatholOral Radiol Endod 2006; 101: 56-60.

2 Al-Hamed FS, Tawfik MAM, Abdelfadil E, Al-Saleh MA. Efficacy of platelet-rich fibrin after mandibular third molar extraction: a systematic review and meta-analysis. Journal of Oral and Maxillofacial Surgery, 2017; 75(6), 1124- 1135.

3 Canellas, J. V. do. S., Ritto, F. G., & Medeiros, P. J. D. Evaluation of postoperative complications after mandibular third molar surgery with the use of platelet-rich fibrin: a systematic review and meta-analysis. International Journal of Oral and Maxillofacial Surgery 2017, 46(9), 1138–1146. https://doi.org/10.1016/j.ijom.2017.04.006

4 Daugela, P, Grimuta, V, Sakavicius, D, Jonaitis, J, & Juodzbalys, G. Influence of leukocyte- and platelet-rich fibrin (L-PRF) on the outcomes of impacted mandibular third molar removal surgery: A split-mouth randomized clinical trial. Quintessence International, 2018 (Berlin, Germany : 1985), 49(5), 377– 388. https://doi.org/10.3290/j.qi.a40113

5 Toffler M, Toscano N, Holtzclaw. Osteotome-mediated sinus floor elevation using only platelet-rich fibrin: an early report on 110 patients. implant dentistry 2010, 19(5): 447-456.

6 Del Corso M, Vervelle A, Simonpieri A, Jimbo R, Inchingolo F, Sammartino G, et al. Current knowledge and perspectives for the use of platelet-rich plasma (PRP) and platelet-rich fibrin (PRF) in oral and maxillofacial surgery part 1: periodontal and dentoalveolar surgery. Curr Pharm Biotechnol. (2012) 13:1207–30. doi: 10.2174/138920112800624391.

7 Ruga E, Gallesio C, Boffano P. Platelet-rich fibrin and piezoelectric surgery: a safe technique for the prevention of periodontal complications in third molar surgery. J Craniofac Surg, 2011. 22:1951–5. doi: 10.1097/SCS.0b013e31822ea76b.

8 Choukroun J, Adda F, Schoeffler C VA. Une opportunité en paro-implantologie: Le PRF. Implantodontie. 2001;42:55–62.

9 Muñoz FT, Haidar ZS. L-PRF for use in oro-maxillo-facial surgeries: what do we know? J Oral Res. (2018) 7:88–90. doi: 10.17126/joralres.2018.012

10 Ritto FG, Pimentel T, Canellas JVS, Junger B, Cruz M, Medeiros PJ. Randomized double-blind clinical trial evaluation of bone healing after third molar surgery with the use of leukocyte- and platelet-rich fibrin. Int J Oral Maxillofac Surg 2019;48:1088–93.

11 Simonpieri A, Del Corso M, Vervelle A, Jimbo R, Inchingolo F, Sammartino G et al. Current knowledge and perspectives for the use of platelet-rich plasma (PRP) and platelet-rich fibrin (PRF) in oral and maxillofacial surgery part 2: bone graft, implant and reconstructive surgery. Curr Pharm Biotechnol. 2012;13(7):1231-56.

12 Silverthorn DU. Fisiologia Humana: uma abordagem integrada. Sangue. 5. ed. São Paulo: Artmed, 2010.

13 Guyton AC, Hall JE. Tratado de Fisiologia Médica. Física do sangue, fluxo sanguíneo e pressão. 11. ed. Rio de Janeiro: Elsevier, 2006.

14 Ehrenfest DDM. *et al*. Platelet-rich fibrin (PRF): a second-generation platelet concentrate. Part III: leucocyte activation: a new feature for platelet concentrates. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2006c, 101(3): 51-5.

15 Ehrenfest, DDM. *et al*. Do the fibrin architecture and leukocyte content influence the growth factor release of platelet concentrates? An evidence-based answer comparing a pure platelet-rich plasma (P-PRP) gel and a leukocyte- and platelet-rich fibrin (L-PRF). Current Pharmaceutical Biotechnology 2012a, 13: 1145-1152.

16 Bielecki T, Ehrenfest DMD. Platelet-rich plasma (PRP) and platelet-rich fibrin (PRF): surgical adjuvants, preparations for in situ regenerative medicine and tools for tissue engineering. Current Pharmaceutical Biotechnology 2012, 13(7): 1121-1130.

17 Ehrenfest DDM. *et al*. Platelet-rich fibrin (PRF): a second-generation platelet concentrate. Part II: platelet-related biologic features. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2006b, 101(3): 45-50.

18 Silverthorn DU. Fisiologia Humana. 5.ed. Porto Alegre: Artmed, 2010. TORTORA, Gerard J. Corpo Humano. Fundamentos de Anatomia e Fisiologia. 6.ed. Porto Alegre: Artmed, 2003.

19 Hupp JR, Ellis E, Tucker MR. Reparação das feridas. Cirurgia oral e maxilofacial contemporânea. Rio de Janeiro: Elsevier. 2011.

20 Araújo MG, Lindhe J. Dimensional ridge alterations following tooth extraction. An experimental study in the dog. J Clin Periodontol. 2005 Feb;32(2):212-8. doi:

10.1111/j.1600-051X.2005.00642.x. PMID: 15691354.

21 Wu CL. *et al.* Platelet-rich fibrin increases cell attachment, proliferation and collagen-related protein expression of human osteoblasts. Australian Dental Journal 2012, 57: 207–212.

22 Caruana *et al.*, From Platelet-Rich Plasma to Advanced Platelet-Rich Fibrin: Biological Achievements and Clinical Advances in Modern Surgery. Eur J Dent. 2019 May; 13(2): 280–286.

23 Ehrenfest DMD, Andia I, Zumstein MA, Zhang C-Q, Pinto NR, Bielecki T. Classification of platelet concentrates (Platelet-Rich Plasma-PRP, Platelet-Rich Fibrin-PRF) for topical and infiltrative use in orthopedic and sports medicine: current consensus, clinical implications and perspectives. Muscles, Ligaments Tendons J. 2014;4(1):3.

24 Ehrenfest DMD, Rasmusson L, Albrektsson T. Classification of platelet concentrates: from pure platelet-rich plasma (P-PRP) to leucocyte-and platelet-rich fibrin (L-PRF). Trends Biotechnol. 2009;27(3):158-67.

25 Mendoza-Azpur G, Olaechea A, Padial-Molina M, Gutiérrez-Garrido L, O'valle F, Mesa F, et al. Composite Alloplastic Biomaterial vs. Autologous Platelet-Rich Fibrin in Ridge Preservation. J Clin Med. 2019;8(2):223.

26 Ehrenfest DMD, Rasmusson L, Albrektsson T. Classification of platelet concentrates: from pure platelet-rich plasma (P-PRP) to leucocyte- and platelet-rich fibrin (L-PRF). Trends Biotechnol, v. 27, n. 3, p. 158-167, 2008.

27 Del Corso M, Toffler M, Ehrenfest DMD. Use of Autologous Leukocyte and PlateletRich Fibrin (L-PRF) Membrane in Post-Avulsion Sites: An overview of Choukroun's PRF.The Journal of Implant & Advanced Clinical Dentistry. 2010;1(9):27-35.

28 Kumar N, Prasad K, Ramanujam L, Ranganath R, Dexith J, Chauhan A. Evaluation of treatment outcome after impacted mandibular third molar surgery with the use of autologous platelet-rich fibrin: A randomized controlled clinical study. J Oral Maxillofac Surg 2015;73(6):1042–9.

29 Da Silva, M. T., de Almeida Barros Mourão, C. F., Mello-Machado, R. C., Montemezzi, P., de Lima Barbosa, R., Sartoretto, S. C., Calasans-Maia, M. D. (2021). Effects of Leukocyte-Platelet-Rich Fibrin (L–PRF) on Pain, Soft Tissue Healing, Growth Factors, and Cytokines after Third Molar Extraction: A Randomized, Split-Mouth, Double-Blinded Clinical Trial. Applied Sciences, 11(4), 1666. doi:10.3390/app11041666

30 Afat, I. M., Akdoğan, E. T., & Gönül, O. Effects of leukocyte- and platelet-rich fibrin alone and combined with hyaluronic acid on early soft tissue healing after surgical extraction of impacted mandibular third molars: a prospective clinical study. Journal of Cranio-Maxillofacial Surgery, 2018. doi:10.1016/j.jcms.2018.11.023

31 Zhu, J., Zhang, S., Yuan, X., He, T., Liu, H., Wang, J., & Xu, B. Effect of platelet-rich fibrin on the control of alveolar osteitis, pain, trismus, soft tissue healing, and swelling following mandibular third molar surgery: an updated systematic review and meta-analysis. International Journal of Oral and Maxillofacial Surgery, 2020. doi:10.1016/j.ijom.2020.08.014