Use of platelet- and leukocyte-rich fibrin (L-PRF) as an alternative for tissue regeneration in sinus lift surgery

Uso de fibrina rica em plaquetas e leucócitos (L-PRF) como alternativa para a regeneração tecidual em cirurgias de elevação do seio maxilar

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Abstract
This study aimed to understand how fibrin rich in platelets and leukocytes acts as an alternative for tissue regeneration in surgeries for maxillary sinus elevation. This integrative review was developed in six steps, where the guiding question was formulated according to the PICO strategy. Thus, a total of 142 publications were searched and a total of 23 articles were selected for this review after applying the inclusion and exclusion criteria. Platelet- and leukocyte-rich fibrin (L-PRF) has been increasingly investigated as a potential bioactive substance for more effective bone regeneration, not only because it is considered an easily obtained autogenous material, but also due to its high concentration of fibrin, platelets and leukocytes, assisting in the process of angiogenesis, thanks to its growth factors, which contributes to bone formation when associated with grafts, as it multiplies fibroblasts and osteoblasts. Furthermore, for the surgical method, the use of L-PRF decreases the dispersion of the graft particles used, helping to condense more mineral and consequently resulting in a smaller volume introduced into the maxillary sinus, thus minimizing the time to obtain vertical bone height. However, since the preparation is properly autologous, the amount of L-PRF acquired is insufficient, causing a disadvantage in its use. In this sense, we realize the importance of L-PRF
in maxillary sinus elevation surgery, as it is a simple, cheap and the most accessible technique for the production of autologous fibrin membrane or platelet concentrate.

**Keywords:** Platelet-rich fibrin; Maxillary sinus; Bone regeneration.

**Resumen**

Este estudio tuvo como objetivo comprender cómo la fibrina rica en plaquetas y leucocitos actúa como alternativa para la regeneración tecidual en cirugías de elevación del seio maxilar. Tal revisión integrativa fue desarrollada en seis etapas, donde la pregunta guía se formuló de acuerdo a la estrategia PIco, así, se buscaron un total de 142 publicaciones y se seleccionaron un total de 23 artículos para esta revisión tras aplicar los criterios de inclusión y exclusión. La fibrina rica en plaquetas y leucocitos (L-PRF) se ha investigado cada vez más como sustancia bioactiva para una regeneración ósea más eficaz, no sólo por ser considerado un material autógeno de fácil obtención, sino también por su alta concentración de fibrina, plaquetas y leucocitos, auxiliando en el proceso de angiogénesis, gracias a sus factores de crecimiento, lo que contribuye a la formación ósea cuando se asocia a injertos, ya que multiplica los fibroblastos y osteoblastos. Además, para el método quirúrgico, el uso de L-PRF disminuye la dispersión de las partículas de injerto utilizadas, ayudando a condensar más mineral y, consecuentemente, resultando en un menor tiempo para obtener la altura ósea vertical. Nesse sentido, percebe-se a importância do L-PRF na cirurgia de elevação do seio maxilar, por ser uma técnica simples, barata e a mais acessível para a produção de membrana de fibrina autóloga ou concentrado de plaquetas.

**Palavras-chave:** Fibrina rica em plaquetas; Seio maxilar; Regeneração óssea.

1. **Introduction**

The paranasal sinuses can be defined as cavities inside the pneumatic bones of the face distributed in pairs, located in the frontal, sphenoid, ethmoid and maxillary bones. The latter is in the body of the maxillae and is the largest of the paranasal sinuses; however, its dimensions may change depending on the age, race and sex of the individual. In addition, another factor that can change the extent of the sinus is tooth loss or trauma to the upper molar region, which can lead to progressive bone resorption and decreased residual bone height in the posterior maxilla, thus causing intense pneumatization of the maxillary sinus (Nizam et al., 2018).

Thus, to make up for the deficiency of bone structure and allow oral rehabilitation of the edentulous area, sinus augmentation surgery has become an alternative with great predictability and good clinical results, in which a surgical procedure is performed to increase the amount of bone in the maxilla by elevating the sinus membrane, known as Schneider's membrane. The definition of the technique to be used for maxillary sinus elevation will depend on the thickness of the remaining local alveolar bone, since the success of the implant restoration depends to a large extent on sufficient bone volume and density. Among the techniques used are the atraumatic method with osteotomes, with immediate implant installation, as...
well as the lateral access or Caldwell-Luc technique (Liu et al., 2019).

In addition to the correct surgical execution, the selection of the biomaterial for grafting is of utmost importance for the success of the procedure, so autogenous bone, considered as one of the best materials, is well used for the filling of maxillary sinus insufficiency as this material has an osteogenic, osteoconductive and osteoinductive characteristic. Thus, in order to improve techniques and maximize the adhesion of bone grafting materials for maxillary sinus augmentation, more and more adjuvant strategies have been studied and proposed, including, platelet- and leukocyte-rich fibrin (L-PRF) has been widely used in dental implant surgeries due to its ability to reduce healing time and avoid perforation of the sinus membrane, in addition to being considered the cheapest and simplest technique to perform (Kim et al., 2017; Simonpieri et al., 2011).

The first report on the use of L-PRF was in 2001, in France, by the physician Joseph Choukroun, who classified it as a concentration of leukocyte and platelet fibrin, this technique belongs to the second generation of platelet aggregates, which was studied and developed to facilitate the obtaining and use of this biomaterial, its terminology, previously called PRF, was changed, with the inclusion of the "L", due to its higher content of leukocytes. L-PRF has been increasingly investigated as a potential bioactive substance for more effective bone regeneration, not only because it is considered an autogenous material that is readily available, but also due to its high concentration of fibrin, platelets, and leukocytes, aiding in the process of angiogenesis, as well as fibroblast and osteoblast multiplication (Choukroun et al., 2006; Zhang et al., 2012).

In view of this, the present study aims to understand the use of L-PRF as an alternative for tissue regeneration in sinus lift surgeries.

2. Methodology

The study is an integrative literature review, developed in six stages, namely: a) development of the research question; b) definition of the databases and inclusion criteria used; c) definition of the information to be extracted from the selected studies; d) evaluation of the included studies; e) interpretation of the results; f) presentation of the synthesis of knowledge (Whittemore & Knafl, 2005).

The research question was posed according to the Population Context of Interest (PICo) strategy (Lockwood et al., 2017). Thus, the following structure was considered: P - platelet-rich fibrin (L-PRF), I - tissue regeneration from sinus lift surgery and Co - tissue regeneration. Thus, the following question was formulated: "Can the use of L-PRF be an alternative for tissue regeneration in sinus lift surgeries?".

The bibliographic searches were conducted in November 2021, using the Medical Literature Analysis and Retrivial System Online (MEDLINE) databases through PubMed, EBSCOhost and Cochrane Library. To expand on the results found, handsearching was also employed by reading the references of the selected primary studies. Two groups of independent researchers, composed of three and four members, respectively, carried out the search and selection of studies, where they standardized the steps and performed them separately, to verify possible divergences in the findings.

For the search, English descriptors indexed in Medical Subject Headings (MeSH) were selected by crossing the controlled descriptors, combined with the Boolean operator AND and their synonyms (uncontrolled descriptors), associated with the Boolean operator OR (Figure 1), which were duly adapted according to the particularities of each database used in the study.
The inclusion criteria adopted were: primary studies addressing the use of L-PRF as a tissue regeneration alternative in maxillary sinus lift surgeries, published between January 2011 and November 2021. The exclusion criteria were: editorials, theses, monographs, dissertations, gray literature, review articles, incomplete studies available electronically, duplicate articles and those that do not answer the research question.

As this was an integrative review, the research was not submitted to the Research Ethics Committee, but the authors' ideas about the publications used in the development of this study were maintained. The methodology for article selection and eligibility followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations (Page et al., 2021), as shown in Figure 2.
3. Results

A total of 71 publications were retrieved from the search, of which, after applying the inclusion and exclusion criteria, 23 articles were selected to compose this review, distributed as follows: seven (30.43%) in MEDLINE/PubMed, five (21.74%) in EBSCOhost, three (13.04%) in the Cochrane Library and eight (34.78%) by manual search.

In terms of study design, 4 (17.39%) were randomized clinical trials, 7 (30.43%) in vivo studies, 5 (21.74%) in vitro studies, 1 (4.35%) clinical trial, 2 (8.70%) prospective study, 2 (8.70%) case series, and 2 (8.70%) clinical case reports, published between 2011 and 2021, with a higher occurrence of publications in 2014 and 2015.

Table 1 shows the 23 publications selected according to the main author, year of publication, methodology, objective, and main results of the studies.
<table>
<thead>
<tr>
<th>AUTHOR/YEAR</th>
<th>METHODOLOGY</th>
<th>OBJECTIVE</th>
<th>MAIN FINDINGS</th>
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<tbody>
<tr>
<td>NIZAM, 2018</td>
<td>Randomized clinical trial</td>
<td>To evaluate the effect of leukocyte- and platelet-rich fibrin (L-PRF) in combination with deproteinized bovine bone mineral (DBBM) on bone regeneration in maxillary sinus augmentation.</td>
<td>Both techniques were effective for maxillary sinus augmentation and, after 6 months of healing, the addition of L-PRF to DBBM did not improve the amount of regenerated bone or the amount of graft integrated with the neoformed bone on histologic and histomorphometric evaluation.</td>
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<tr>
<td>OLIVEIRA, 2016</td>
<td>In vitro study</td>
<td>To investigate the amount of mineralization of a bovine bone substitute in sinus floor augmentation after healing times of 3 and 6 months.</td>
<td>Bone maturation in the sinus augmented with the bovine bone material is similar after 3 and 6 months. Therefore, implant installation at 3 months after a lateral window sinus floor augmentation approach using a bovine bone material appears to be clinically acceptable.</td>
</tr>
<tr>
<td>TANAKA, 2015</td>
<td>In vitro study</td>
<td>To evaluate the additional effects of PRF on bone regeneration in deproteinized bovine bone</td>
<td>Additional effects of PRF may be found due to higher percentages of new bone formation by the DBBM / PRF mixture than by</td>
</tr>
</tbody>
</table>
4. Discussion

In recent years, many studies have been carried out to investigate the efficacy of using L-PRF as an auxiliary material for bone grafting in sinus augmentation surgeries. This biomaterial is able to stimulate angiogenesis thanks to its growth potential. This concept allows tailoring the optimal framework or composites for specific clinical applications.

Specific cell types are differentially distributed as a function of (cumulative) centrifugal force. This concept allows tailoring the optimal framework or composites for specific clinical applications.

In vitro study

Compare protocols for standard platelet-rich fibrin (S-PRF) (2700 rpm, 12 minutes) and advanced platelet-rich fibrin (A-PRF) (1500 rpm, 14 minutes) to establish histological cell detection and histomorphometric measurement of cell distribution.

Simultaneous sinus lift and implantation using platelet-rich fibrin as the sole graft material on bone formation in a canine sinus model.

The results of this study suggest that when platelet-rich fibrin is used as an adjunct to Bio-Oss particles for bone augmentation in the maxillary sinus, bone formation at the graft sites is significantly greater than when Tisseel is used.

Case series

To evaluate the potential use of PRF associated with deproteinized bovine bone (Bio-Oss) as grafting material in severe maxillary atrophy preimplant sinus grafts, compared to a control group in which only deproteinized bovine bone (Bio-Oss) was used as reconstruction material.

The use of PRF and piezosurgery reduced the healing time compared to the 150 days described in the literature, favoring optimal bone regeneration. At 106 days, it is already possible to achieve good primary stability of the endosseous implants, although without functional loading.

Prospective study

To evaluate PRF as a single filler material during sinus lift and simultaneous implant placement using platelet-rich fibrin (PRF) as the sole graft material.

Our preliminary result showed neither advantages nor disadvantages of the application of PRF in combination with deproteinized bovine bone mineral in breast augmentation after a healing period of 6 months.

In vitro study

To evaluate platelet-rich fibrin (PRF), mixed tricalcium phosphate (TCP) and recombinant human bone morphogenic protein-2 (rhBMP-2)-coated TCP for their potential to enhance bone regeneration in sinus lift in rabbits, as well as their inflammatory characteristics.

In the results of histological evaluation (hematoxylin-eosin staining, Masson's trichrome), experimental groups A and B showed rapid bone formation, remodeling and calcification in the second week. In addition, there was a significant difference between these experimental groups and the control group in the area of bone neoformation at the fourth, sixth and eighth weeks.

In vitro study

To examine the effect of simultaneous sinus elevation and implantation using platelet-rich fibrin as the sole graft material on bone formation in a canine sinus model.

Simultaneous sinus lift and implantation using platelet-rich fibrin as the sole grafting material is not a predictable and reproducible procedure, especially with regard to bone formation around the implants in the sinus cavity.

To compare the potentials of Bio-Oss mixed with PRF and Bio-Oss mixed with Tisseel to enhance bone regeneration in a canine sinus model.

The results of this study suggest that PRF can increase the number of marrow cells. However, PRF together with xenogeneic bone substitutes do not show a significant effect on bone regeneration.

In vivo study

To investigate the influence of platelet-rich fibrin (PRF) on angiogenesis and osteogenesis in guided bone regeneration (GBR) using xenogeneic bone in rabbit cranial defects.

Coverage of the lateral sinus window with two different absorbable membranes has been shown to result in a similar amount of vital bone formation and residual bone substitute.

In vitro study

To evaluate the effect of PRF on bone regeneration when used as a barrier membrane at the site of lateral osteotomy in sinus augmentation.

Sinus lift with simultaneous implant placement using PRF as the sole filler material can promote natural bone regeneration.

To investigate the influence of PRF on bone regeneration and simultaneous implantation with leukocyte-rich fibrin as the sole sinus filler material.

Within the confines of the present study, there was a greater reduction in probing depth, a greater gain in clinical attachment than with open flap debridement alone.

To investigate, clinically and histologically, the influence of platelet-rich fibrin (PRF) (2700 rpm, 14 minutes) to establish histological cell detection and histomorphometric measurement of cell distribution.

Specific cell types are differentially distributed as a function of (cumulative) centrifugal force. This concept allows tailoring the optimal framework or composites for specific clinical applications.

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Source: Authors (2021).
factors platelet-derived growth factor (PDGF), insulin-like growth factor (IGF), vascular endothelial growth factor (VEGF), transforming growth factor beta (TGF-β) and angiogenic factor, and contributes to bone formation when associated with grafts, because it multiplies fibroblasts and osteoblasts, as well as, it has important effects of regularization of the inflammation process and stimulation of the immune process of chemotaxis, this is because plasma is an autologous graft material, able to eliminate any risk of disease proliferation Moreover, its consistent and gelatinous form favors the stability of the graft material and the clot (Tatullo et al., 2012; Nizam et al., 2018).

The time required for new bone formation is strictly related to the volume of graft used. Therefore, a large volume of grafted material in the maxillary sinus requires more time before any procedure is performed. In the in vivo study by Xuan et al. (2014), platelet-rich fibrin was found to decrease the dispersion of the graft particles used, helping to condense more mineral and consequently resulting in a smaller volume introduced into the maxillary sinus, thus minimizing the time to obtain vertical bone height.

L-PRF can be obtained by manual or automated methods, however, the most used technique is the one described by Choukroun, in which, prior to surgery, a 10 mL sample of peripheral blood is collected from the patient and 5 mL is distributed in two sterile tubes without anticoagulants, where it is centrifuged at 3000 rpm for 10 minutes at room temperature. Upon centrifugation of the sample, the coagulation cascade is activated by the contact of the blood platelets and the tube, triggering the circulation of blood thrombin, and transforming fibrinogen into fibrin. After centrifugation, three distinct layers are formed in the tube, the first consisting of platelet-poor plasma, the second of a natural fibrin clot, and the third of red blood cells (Kılıç et al., 2017; Gassling et al., 2013).

In addition, the surgical approach will be established by a thorough preoperative evaluation, conduit, the lateral access technique is considered the safest when combined with the use of autologous grafts and is considered the gold standard in sinus lift surgeries. The procedure is performed starting with an ostectomy on the buccal side of the maxilla, forming a bony window that allows visualization of Schneider’s membrane, which will be carefully detached and repositioned more posteriorly. From there, a mixture of L-PRF and the graft material chosen for the case is introduced into the sinus cavity, and finally an absorbable collagen membrane is applied to cover the entire obturated lateral window (Pichotano et al., 2018).

Because the preparation is properly autologous, the amount of L-PRF acquired is insufficient, causing a disadvantage in its use since the amount produced is poor and only a restricted volume can be used. Thus, the use of L-PRF is limited in general surgery, for example, although its potential applications are wide, requiring a practical and precise knowledge of the biomaterial used, its biology, its limits and efficiencies to improve its use in daily practice. In addition, the surgery itself may also offer complications, as a perfect elevation of the membrane, without tears or injuries, is necessary to obtain a better result (Kohal et al., 2015).

In a study by Simonpieri et al. (2011) in 20 patients requiring implants, lateral window surgeries with simultaneous implant installation were performed. L-PRF clots were used to cover the osteotomy window and protect the Schneider membrane prior to implant drilling. The maximum follow-up of the study was six years, and all patients were followed for a minimum period of two years. As a result, no implants were lost during the entire study period and vertical bone gain could be observed in all patients, demonstrating how the use of platelet-rich fibrin can promote graft site protection and aid natural bone repair.

The findings of this integrative review point to scientific evidence on the use of L-PRF as an alternative for tissue regeneration in maxillary sinus elevation surgeries, contributing directly to dentistry, especially in dental surgery. The main limitations of this study are the large number of in vitro and animal studies, which makes it difficult to sample the results in clinical routine, requiring more randomized and controlled clinical trials, as well as long-term prospective studies.
4. Conclusion

Based on the above, the importance of L-PRF in maxillary sinus elevation surgery can be perceived, since it is a simple, cheap and the most accessible technique to produce an autologous fibrin membrane or platelet concentrate. L-PRF when used as a surgical adjuvant, associated with a bone graft material in sinus lift procedures, successfully promotes vertical bone gain, accelerating bone neoformation and is also commonly used to protect Schneider's membrane during surgery, as well as accelerating local healing due to the release of growth factors. However, although there are studies exploring the efficacy of using L-PRF in sinus lift surgeries, the current evidence is limited, and many investigators still do not fully understand the effects of this biomaterial. In addition, different L-PRF preparation techniques are observed in the included studies, which may contribute to a wide range of possibilities. Therefore, based on the inconclusive results of the current literature, further studies, with larger sample size and long-term follow-up as parameters, are needed to confirm the predictability of this procedure and the standardization of the way of preparation, as well as to understand which types of grafts provide better clinical outcomes when combined with L-PRF.

References


