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Randomized double-blind clinical trial evaluation of bone healing after third molar surgery with the use of leukocyte- and platelet-rich fibrin

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Abstract. The objective of this study was to evaluate the use of leukocyte- and platelet-rich fibrin (L-PRF) in bone healing after mandibular third molar extraction. In this prospective, double-blind, split-mouth study, 34 extractions were performed. On one side, the socket was sutured primarily (control side); on the other side, L-PRF was inserted before suturing. The patients were assessed for postoperative bone regeneration, pain and soft tissue healing. The primary outcome was bone regeneration, which was performed through tomographic evaluation in the immediate postoperative period and 3 months after the procedure. The ITK-SNAP software was used for image evaluation by the intensity of grey of each voxel. Pain was analysed using a visual analogue scale (VAS), and soft tissue healing was analysed both based on the modified healing index of Landry et al., and by comparing pre- and postoperative periodontal probing at the distal of the lower second molar. The application of L-PRF improved bone density, which was higher in test group ($p = 0.007$). There was no statistical difference related to pain or soft tissue between the groups ($p > 0.05$). There was evidence for improved bone healing in response to L-PRF. However, to better understand the effect of L-PRF more clinical trials with larger samples are necessary.

Key words: third molar surgery; platelet-rich fibrin; pain; bone healing.

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Socket healing is a coordinated sequence of biochemical, physiological, cellular and molecular responses, aiming to restore tissue integrity and functional capacity after surgery[1,2]. Over the years, surgical adjuvant, bone grafting or surgical procedures have been used to improve periodontal status, regeneration, and bone quality[3,4]. The development of biomaterials capable of reducing side effects and accelerating healing process remain challenging to clinicians and prompt researches[5].

Leukocyte- and platelet-rich fibrin (L-PRF) is a second-generation platelet concentrate developed by Choukroun et al.[6]. This autologous biomaterial consists of a strong fibrin matrix with a complex three-dimensional (3D) architecture. It is produced through the immediate centrifugation, after blood collection, and without the addition of anticoagulant[7–10].

L-PRF is a rich source of cytokines and growth factors, such as transforming growth factor β, platelet-derived growth factor, vascular endothelial growth factor, and has important properties for healing such as angiogenesis, immune control and wound protection[11]. The slow release of these biochemical components have synergetic effects on the healing process[10].

The effects of L-PRF have already been assessed in vitro, suggesting enhancement in osteoblasts, fibroblasts and keratinocytes proliferation. L-PRF was able to induce and stimulate proliferation in all cell types, promoting intense differentiation of osteoblasts, in all culture conditions. Dohan et al.[12] suggested that growth factors and the fibrin matrix are responsible for these biological events.

In contrast to in vitro studies, evidences of L-PRF effects on bone healing in clinical trials and systematic reviews showed controversial results. In some studies L-PRF shows no positive effect on bone healing after extraction of mandibular third molars; while in others it shows evidence of increasing bone regeneration[13–22].

The aim of this study was to determine whether the use of L-PRF improves bone healing, pain and soft tissue healing after mandibular third molar extractions.

Material and methods

A prospective double-blind randomized split-mouth study, between September and November 2016 in 20 patients (12 women and eight men) requiring bilateral lower third molar extraction was performed. A single surgeon operated on all of the patients. This study began after the approval of the institutional review board and in accordance with Declaration of Helsinki, and was previously registered on the clinicaltrial.gov database (NCT02890680). All patients provided informed consent before surgery.

Inclusion criteria were as follows: (1) patients between 16 and 29 years of age; (2) class I patients according to the American Society of Anesthesiology (ASA); (3) need for bilateral third molar extraction; (4) bilateral similarity between third molar position according to Pell and Gregory classification; (5) coagulogram showing platelet values within normal range (150,000–400,000 p/mm^3). Exclusion criteria were: (1) patients with pericoronitis in the lower third molar region; (2) periodontal disease at the time of operation; (3) absence of lower second molar; (4) allergy to any of the drugs used during postoperative therapy; (5) patients who smoke.

One surgeon was responsible for the surgery, blinded to which side was the control or the test group, and a second operator was responsible for the insertion of L-PRF in the socket and wound closure. To blind the patients regarding the side in which L-PRF was inserted, they received dark glasses and the operator manipulated both sockets in the same manner simulating insertion of L-PRF on both sides.

The decision regarding which socket to insert the L-PRF into was made using the random number table method. The randomization data were kept unknown by a third investigator until the end of the study, ensuring the concealment of the allocation sequence at the time the participants were recruited.

Postoperatively, the same drug protocol was given to all patients: they were instructed to take 8 mg of dexamethasone 1 h before the surgical procedure; 400 mg of ibuprofen every 6 h and 750 mg of acetaminhophen every 6 h both for 5 days after surgery.

Surgical procedure

A mucoperiosteal flap was the choice for the third molar extractions. The detachment was performed anteroposteriorly, avoiding extension beyond the external oblique line. Osteotomy was performed around the crown followed by tooth section with surgical drills, both accompanied by copious irrigation with saline solution. The complete cleavage of the tooth was accomplished with straight lever in the groove created by the burr, and the tooth was removed in parts when necessary.

Post-extraction the residual cavity was irrigated with sterile physiologic saline solution. After irrigation, primary closure was achieved in both groups using silk thread 3.0 suture. The test group received the L-PRF before final closure.

Preparation of L-PRF clot

L-PRF was prepared according to the technique described by Dohan et al.[7]. Blood samples were taken without anticoagulant in 10-mL tubes, which were immediately centrifuged at 2700 rpm (approximately 400 *g*) for 12 min. A fibrin clot was obtained in the middle of the tube. The platelet-poor plasma that accumulated at the top of the tubes was discarded. For each patient, two tubes were used to fill one extracted socket.

To evaluate bone healing, cone beam computed tomography (CBCT) was used to access bone density. The tomographic data were collected immediately after surgery (T1) and 3 months after the procedure (T2) with the iCAT device (ICAT NEXT GENERATION®).

Volume and density analysis were performed by semi-automatic segmentation with the aid of a medical image processing program, ITK-SNAP 3.0 (Cognitica, Philadelphia, PA, USA). The volume corresponding to the region of the lower third molar socket was determined respecting the pre-defined limits in axial, sagittal and coronal views in the smallest square area containing the whole socket. All measurements were performed by the same operator, who was also blind to the randomization of the groups. Exams were evaluated three times, at 1-week intervals, and a maximum of two CBCT exams were evaluated on the same day.

The ‘‘Segment 3D’’ tool was used, and an appropriate threshold level was adjusted. Then the reference points were selected on the cavity for semiautomatic segmentation. When the ‘‘Start segmentation’’ tool was used, the software automatically segmented the cavity starting from the reference points using the contrast differences on the grey scale images. Thus, both the 3D model and the volume in mm^3 were obtained with the software ITK-SNAP (Fig. 1).

After segmentation, the software provided grey scale intensity of each voxel in the selected region and the values of T1 and T2 in the test and control group. Then, T1 values were subtracted from T2 and the difference was used to compare test and control groups. Higher values in grey scale indicated higher bone density (Fig. 2).

Pain was evaluated in the postoperative period using a 10-cm VAS with a score of 0 meaning ‘‘no pain’’ and 10 ‘‘the most severe pain possible’’. After surgery, patients were instructed to note their postoperative pain on the scales. The evaluation of the postoperative pain was carried out at 24 h, 72 h and 7 days after the procedure.

Soft tissue evaluation was performed using two parameters: (1) periodontal probing at the distal of lower second molar; (2) soft tissue healing. The periodontal probing at the distal of lower second molar was measured before surgery and 3

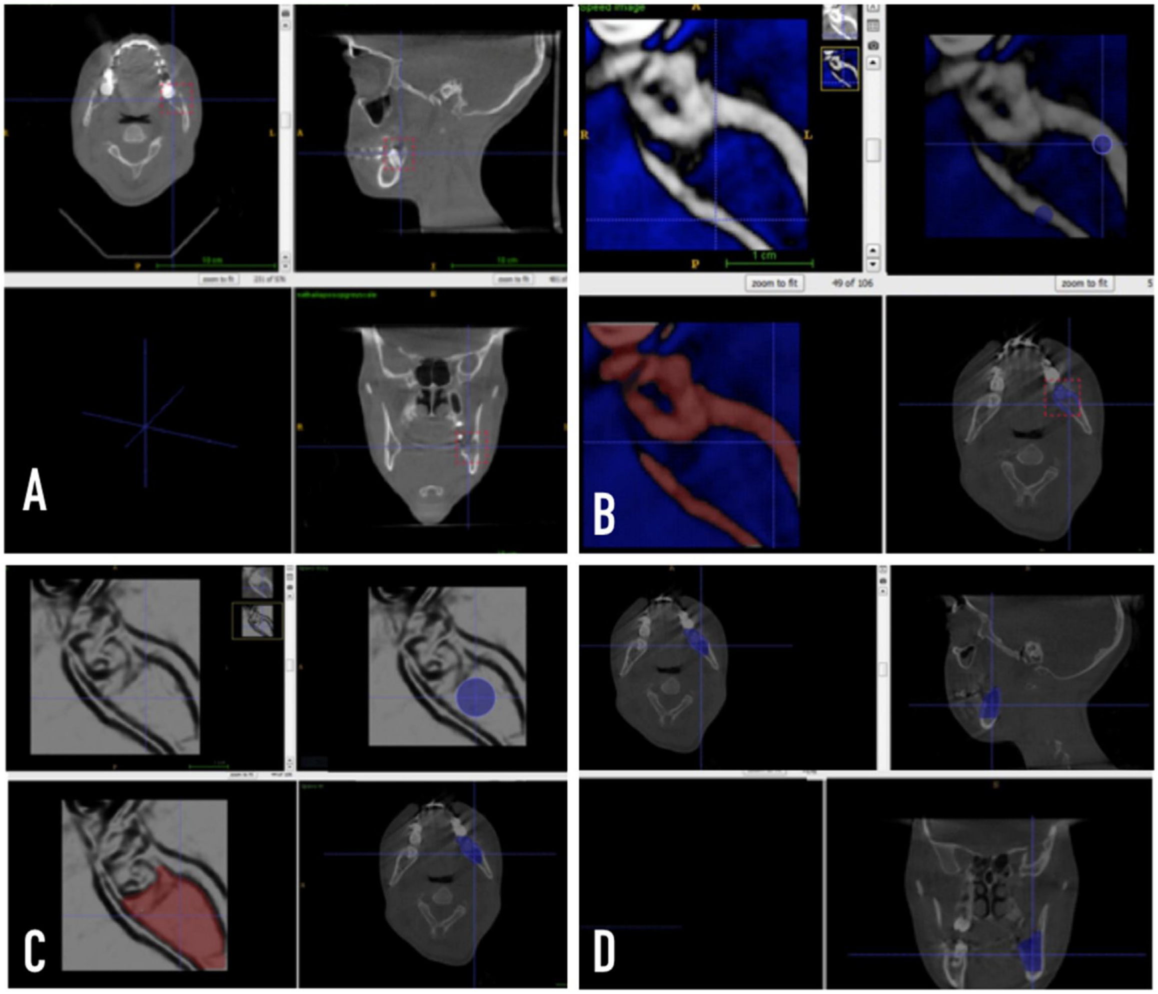

Fig. 1. (A) In ITK-SNAP software, region of interest was determined in the smaller square in all three planes of views containing the whole socket. (B)The reference points were selected first in the cortical bone (C) then in medullar bone (D). Volumes in mm^3 were obtained in the software.

months after surgical procedure using a periodontal probe in the gingival sulcus until resistance to penetration was found.

The soft tissue healing was assessed based on modified healing index of Landry et al.[23]. The index intended to assess and grade colour of tissue, epithelialization of wound margins, presence of bleeding on palpation, and granulation (Table 1).

For each of the parameters mentioned above, except for tissue bleeding, a comparative analysis of control and test groups was performed and a score from 1 to 5, where 1 represented poor healing and 5 excellent tissue healing were given. The bleeding parameter was classified as 0, when there was no bleeding and −1 when there was bleeding.

Results

Twenty patients were selected to participate in the study, three patients did not return at the proposed time for tomographic exam. Seventeen patients (seven females and 10 males) were analyzed. These patients ranged in age from 16 to 29 years old (mean 21.8 years old).

Reproducibility of pre- and postoperative measurements of bone density were tested by the intra-class correlation coefficient. The method described by Weir was used to analyze the reliability of the measurements[24]. The variable showed excellent reliability (>0.980).

The Levene test indicated that the sample was homocedastic and then *t*-test was performed for independent samples with continuous variable. The mean value of increased bone density in the L-PRF side after 3 months (954.100 ± 500.768) was significantly higher as compared to the control side (522.514 ± 352.281), $p = 0.007$ (Table 2).

Before applying statistical tests to evaluate pain, Shapiro–Wilk normality and Levene were performed; the sample was homocedastic ($p > 0.05$). The parametric analysis was accomplished using *t*-test with $p > 0.05$. Although the use of L-PRF results in reduced pain, there was no significant statistical difference between the means (Table 3).

For soft tissue and probing evaluation, Mann–Whitney test was applied and the *p*-value was not significant ($p > 0.05$), which suggests that the insertion of L-PRF into the socket after extraction does not influence soft tissue healing.

Discussion

The aim of this study was to evaluate the influence of L-PRF on soft and hard tissue healing, using CBCT exam, after mandibular third molar extraction. Several studies have suggested that the use of L-PRF may effectively enhance soft tissue and bone healing, and reduce inflammation and postoperative pain. Although these results are promising, the methodological heterogeneity among them reveal a general lack

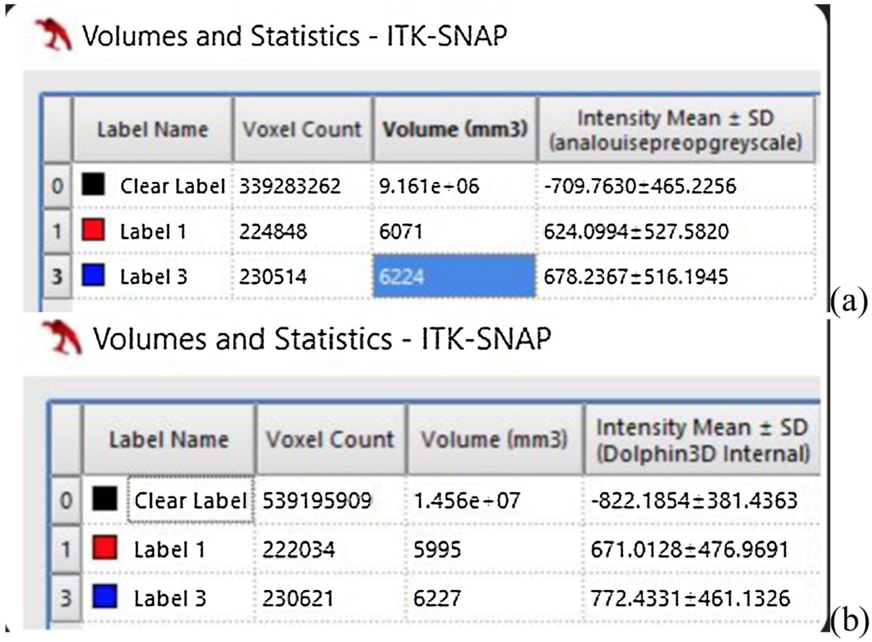

Fig. 2. Voxel count, volumetric measurement (mm^3) and mean intensity of the segmented image. (A) Pretreatment; (B) post-treatment. Red label (control group); blue label (test group).

of conclusive evidence with a need for further studies[15–22].

In the most recent systematic review that evaluated the effects of L-PRF in oral surgery procedures seven randomized clinical trials (RCTs) were included to evaluate bone healing[25]. The qualitative analysis of included RCT demonstrated that L-PRF was better in promoting bone regeneration, but due to the high methodological heterogeneity among them, it was not possible to perform a meta-analysis[16,19–21].

Two articles described the use of scintigraphy to evaluate bone healing[17,18]. However, bone scintigraphy is a nuclear scanning test used to diagnose conditions related to bone but not sensitive enough for bone mass evaluation. The use of technetium-99 (T-99) to predict the final effect of bone metabolism may lead to a high risk of bias and misleading interpretations[13,24]. Hypercaptation of T-99 by a region of the mandible is not related to bone density, as it may be increased even in resorptive processes[26].

The use of L-PRF still does not have a clear standard protocol per surgical procedure and all of the studies included in a systematic review[13] used only one L-PRF clot or membrane to fill the socket. It is well known that L-PRF has a dose-dependent effect and it is not possible to know whether one membrane would be enough to stimulate the migration of osteoblasts and endothelial cells[12].

Other systematic reviews assessing bone healing after surgery, concluded that L-PRF is able to preserve quality and density of alveolar ridge and decrease the buccal bone resorption[25,27,28]. Although some articles did not show statistically significant differences, in others L-PRF was superior to natural clot or platelet-rich plasma in promoting bone healing[16,19–21]. In accordance with the present results, Varghese et al.[20] found accelerated bone formation at the L-PRF site, evidenced by higher grey-level scores.

Grey scale was used to evaluate bone neoformation and the results were measured by the same examiner three times to validate the intraclass correlation coefficient methodology in the present study.

Table 1. Healing index.

Index	Tissue colour	Incision margin	Response to palpation	Granulation tissue
1: Very poor	>50% of gingiva red	Not epithelialized,with loss of epithelium beyond incision margin	Yes	Yes
2: Poor	>50% of gingiva red	Not epithelialized, with connective tissue exposed	Yes	Yes
3: Good	>25% and 50% of gingiva red	No connective tissue exposed	No	No
4: Very Good	>25% of gingiva red	No connective tissue exposed	No	No
5: Excellent	All tissue pink	No connective tissue exposed	No	No

Table 2. Tomographic analysis of increased bone density in test and control group.

Group	*n*	Mean ± SD	SE	Levene's test	*p*
L-PRF	17	954.100 ± 500.768	121.454	0.730	0.007*
Control	17	522.514 ± 352.281	85.440		

L-PRF, leukocyte- and platelet-rich fibrin; SD, standard deviation; SE, standard error.
* $p < 0.05$, statistically significant.

Table 3. Pain evaluation: visual analogue scale.

Group	N	1st day PO (mean ± SD)	3rd day PO (mean ± SD)	7th day PO (mean ± SD)
L-PRF	17	3.00 ± 2.81	2.85 ± 2.17	1.53 ± 2.50
Control	17	3.98 ± 2.97	3.11 ± 2.61	2.11 ± 3.04
**p-value*		0,333	0,750	0,547

L-PRF, leukocyte- and platelet-rich fibrin; SD, standard deviation; PO, postoperative.
* $p < 0.05$, statistically significant.

After comparing pre- and postoperative CBCT, sockets treated with L-PRF showed higher values in grey scale than sockets in the control group. A higher value of the mean intensity of segmented image suggested better new bone formation.

In the present study, the methodology used to evaluate the socket area included CBCT images and software that was developed specifically for research[29]. ITK-SNAP generates semi-automatic segmentation of the region, using predefined anatomical limits, allowing the comparison of tomographic exams in three dimensions[30,31].

Radiographic evaluation was used for some studies[15–17] but none of them described the tools used for standardization or how they could have controlled the possible bias during image evaluation, such as error test, intra- or inter-examiner analysis or blind evaluator. Although tomographic image has limitations in relation to accurately representing small defects, digital periapical radiographs have been shown to be even less accurate[32].

The influence of L-PRF on postoperative pain was evaluated through visual analogue and numerical scales on days 1, 3 and 7. The evaluation of postoperative pain using the VAS is a reliable method for recording pain after surgical procedures. However the results should be analysed with caution because of the heterogeneity and the high risk of bias in the studies[15,33].

Kumar et al.[15] evaluated pain at first day, 1 month and at 3 months on 31 patients divided into two groups. Unlike most of the studies that evaluate pain using a 10-cm scale, Kumar et al. used a 5-cm scale. The methodology used did not consider the results between centimeters, and may have induced patients to determine an exact value for pain. Intermediate results were not considered, and a bias of interpretation may have been created.

The present study found similar results to the studies that used the split-mouth design to pain evaluation. Split mouth studies can lead to bias since it may be difficult for the patient to evaluate each surgical site independently as pain may irradiate to the opposite side. Studies that used the split-mouth design found no difference between L-PRF and control group[34–36].

Alveolar osteitis (AO) is the most common complication following wisdom tooth extraction[37]. A meta-analysis[25] evaluated 226 mandibular third molars removed from 145 patients and showed a beneficial effect of L-PRF over natural clot in reducing AO. L-PRF provides a strong fibrin matrix with a reservoir of platelets and leucocytes that support clot formation and prevent its disintegration[7,8]. However, further investigations are needed to provide more conclusive results. None of the patients in this study developed AO.

Soft-tissue healing evaluation was performed based on the Landry, Turnbell and Howley[23] method on the seventh postoperative day. There are some limitations in the present study regarding soft tissue healing: (1) the study had a small sample size; (2) the subjectivity of the index used for evaluation.

Singh et al.[33] also used the soft tissue healing index by Landry et al.[23] to evaluate soft tissue healing on postoperative days 1, 3 and 7. According to the authors, there was a statistically favourable difference for the group who received L-PRF. However, the study has a high risk of bias for not describing: (1) how the study was randomized; (2) how the surgical procedure was performed; (3) the clinical difficulty of teeth included in the study, and if osteotomy was performed in all surgeries.

Miron et al.[27] conducted a systematic review and found out that the majority of studies have demonstrated favourable results in soft tissue management and repair when L-PRF was used. Although our study did not find a difference in soft tissue healing, L-PRF seems to be beneficial. Some possible reasons for controversial results are the small sample size evaluated, the subjective analysis of soft tissue healing index, and the lack of calibration of the evaluators.

In summary, based on the results presented, it is possible to conclude that the use of L-PRF in the extraction sockets was beneficial to bone healing. Due to its good biological effects, low cost and ease of preparation, L-PRF could be considered a reliable option for treatment to stimulate cell proliferation but further studies with larger sample sizes and standardization of evaluation methods are still necessary.

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Competing interests

There are no competing interests.

Ethical approval

Ethical approval was provided by Hospital Universitário Pedro Ernesto, No. 1.591.355.

Patient consent

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