Conjecturas

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Use of platelet- and leukocyte-rich fibrin (l-prf) in bisphosphonate-related osteonecrosis of the jaw (bronj) in rats - split-mouth study

Uso da fibrina rica em plaquetas e leucócitos (l-prf) na osteonecrose dos maxilares associada ao uso de bisfosfonatos (onmab) em ratos: estudo de boca dividida

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ABSTRACT

This study aimed to clinically evaluate the effect of platelet- and leukocyte-rich fibrin (L-PRF) membranes in preventing bisphosphonate-related osteonecrosis of the jaw (BRONJ) in rats. In this study, twelve Wistar rats (six males and six females) were used. A split-mouth study was performed; the right-side was used as treatment, with treatment of platelet- and leukocyte-rich fibrin membranes (L-PRF group, LPRFG), and the left-side received no intervention as control (control group, CG). The rats received intravenous Zolendronate (Zol) (80 ug/kg/week) injections during nine weeks to induce the BRONJ. The surgical extractions were divided into two stages: in the eighth week of Zol injections, the first lower molars on both sides were removed followed by bone decorticalization. In the ninth week of Zol injections, extractions of the second lower molars were performed on both sides, followed by bone decorticalization. L-PRF membranes were made of 1 ml of blood by cardiac puncture. The following clinical variables were analyzed: presence of bone exposure, inflammation (edema, erythema), suppuration, bony sequestrum and epithelialization of the alveoli. In addition, the mesiodistal (MD) and buccolingual (BL) dimensions of bone exposure were obtained using a millimeter probe. Statistical analysis was performed using Fisher's exact test, with a significance level of 0.05. There were no significant differences between the sides regarding the presence of bone exposure, inflammation, suppuration, bony sequestrum and epithelialization of the alveoli ($p > 0.05$). However, lower bone exposure was observed in the MD ($p = 0.002$) and BL ($p = 0.03$) dimensions in the LPRFG. Thus, the use of L-PRF membrane decreased bone exposure contributing to the alveoli healing of BRONJ in rats.

Keywords: Osteonecrosis; bisphosphonates; platelet- and leukocyte-rich fibrin; L-PRF.

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RESUMO

O objetivo deste estudo foi avaliar clinicamente o efeito do uso de membranas de fibrina rica em plaquetas e leucócitos (L-PRF) na prevenção da osteonecrose dos maxilares associada ao uso de bisfosfonatos (ONMAB) em ratos. Neste trabalho foram utilizados doze ratos Wistar (seis machos e seis fêmeas). Foi realizado um estudo de boca dividida: o lado direito foi utilizado como tratamento, com inserção de membranas de fibrina rica em plaquetas e leucócitos (grupo L-PRF, GLPRF), e o lado esquerdo não recebeu intervenção para controle (grupo controle, GC). Os ratos receberam aplicação endovenosa de Zolendronato (Zol) (80 ug/kg/semana) durante nova semanas para induzir a ONMAB. As extrações dentárias foram divididas em duas etapas: 1) na oitava semana de aplicação do Zol foi realizada a exodontia dos primeiros molares inferiores em ambos os lados, associada à descorticalização óssea. Na nona semana de aplicação do Zol foram realizadas as exodontias dos segundos molares inferiores, em ambos os lados, seguidas de descorticalização óssea. Para confecção das membranas de L-PRF retirou-se 1 ml de sangue através de punção cardíaca. As seguintes variáveis clínicas foram observadas: presença de exposição óssea, inflamação (edema, eritema), supuração, sequestro ósseo e epitelização dos alvéolos. Além disso, o tamanho da exposição óssea mésio-distal (MD) e vestíbulo-lingual (VL) foi obtida com o auxílio de uma sonda milimetrada. A análise estatística foi realizada usando o teste exato de Fisher, com nível de significância de 0,05. Não houve diferenças significativas entre os lados no que se refere à presença de exposição óssea, inflamação, supuração, sequestro ósseo e epitelização dos alvéolos ($p > 0,05$). No entanto, observou-se menor exposição óssea nos sentidos MD ($p = 0,002$) e VL ($p= 0,03$) no GLPRF. Assim, pode-se concluir que o uso da membrana de L-PRF diminuiu a exposição óssea contribuindo para o reparo de alvéolos em ONMAB.

Palavras-chave: Osteonecrose; bisfosfonatos; fibrina rica em plaquetas e leucócitos; L-PRF.

INTRODUCTION

Bisphosphonates are a group of drugs that have potent bone antiresorptive action and are widely used in the treatment of osteoporosis, metabolic bone disease associated with neoplasms, such as malignant hypercalcemia, multiple myeloma, Paget's disease and bone metastases (BRIERLY et al., 2019) These medications tend to accumulate in areas with high osteoclastic activity (bone resorption and remodeling), hence the high susceptibility of the jaws (VILELA-CARVALHO et al., 2018). Regardless of the via of administration (oral or injectable), there is a high deposition of the drug in the jaws, leading to impaired post-trauma repair. Another important factor for the occurrence in the jaws is the presence of thin mucosa, susceptible to trauma, and presence of oral biofilm (HOKUGO et al., 2019).

Bisphosphonate-Related Osteonecrosis of the Jaw (BRONJ) is a pathology widely discussed in the medical field. It is characterized the presence of non-scarring and necrotic

exposed bone in the jaws or fistula for a minimum period of eight weeks in patients with a previous or current history of use of antiresorptive drugs, and who have not been submitted to head and neck radiotherapy (RUGGIERO et al., 2014; TENORE et al., 2020). Some local risk factors are described for the occurrence of BRONJ, such as periodontal disease, caries, periapical lesions, trauma caused by ill-fitting dentures and poor oral hygiene. However, tooth extractions seem to be one of the main predisposing factors (RUSILAS, BALČIŪNAITĖ, and ŽILINSKAS, 2020).

Studies on the use of platelet- and leukocyte-rich fibrin membranes (L-PRF) have been increasing, due to their composition, which adds growth factors (epidermal, transforming β, vascular endothelial, pro-coagulant, cytokines and antimicrobials) to the surgical site (HEYMOVSKI et al., 2021; STROPARO et al., 2021). On a daily basis, it is commonly used for maxillary sinus augmentation, bone grafting combined with biomaterials, treatment of oroantral communication and orofacial harmonization. These indications are due to the composition that accelerates the healing processes (Nicolatou-GALITIS et al., 2019). Some articles already use L-PRF as a possible treatment for osteonecrosis of the jaws, and should be used in along with surgical treatment (ABDULLAH, 2016; MIRON and CHOUKROUN, 2018).

Several therapies for BRONJ have been suggested in the literature, including antibiotic therapy, alveolar curettage, and extensive bone resection surgeries (EGUCHI et al 2017). However, to date, there is no treatment described as fully effective. Thus, efforts have been made to identify substances or procedures that can favor the repair process and minimize the occurrence of BRONJ after invasive surgical procedures (exodontia) (ABDULLAH, 2016; MIRON and CHOUKROUN, 2018).

Given that the L-PRF membrane accelerate bone and soft tissue healing (HEYMOVSKI et al., 2021), we hypothesized that the L-PRF could aid in bone healing after tooth extractions, preventing BRONJ. Thus, the aim of this research was to clinically evaluate the effect of L-PRF membranes in preventing BRONJ after tooth extractions in rats.

MATERIAL AND METHODS

Ethical aspects

This study was approved by the Animals Ethics Committee of Positivo University (CEUA protocol number: 503). The study followed the ARRIVE guidelines (KILKENNY et.al, 2010).

Study Design

In this study, twelve female (n = 6) and male (n = 6) Wistar rats (ages 12 months, weighing approximately 500 g) were used. A split-mouth study was performed; the right-side was used as treatment, with treatment of platelet- and leukocyte-rich fibrin membranes (L-PRF group, LPRFG), and the left-side received no intervention as control (control group, CG). All animals received intravenous Zolendronate (Zol) (Novartis, Curitiba, Brazil; 80 ug/kg/week) injections via caudal vein during nine consecutive weeks to induce the BRONJ.

This study was divided into two stages: the first stage (Phase 1) comprised the bilateral extraction of first mandibular molars to induce BRONJ; the second phase (Phase 2) included a second surgery for bilateral extraction of second mandibular molars followed by the use L-PRF membranes on the right-side.

The rats were housed, two per cage, fed normal animal chow and water ad libitum. During the experimental period, the environmental conditions of light, temperature and humidity were controlled by a digital panel in order to maintain the photoperiod of 12 h, a temperature of 18-22 °C, and a relative humidity of 65%.

Phase 1

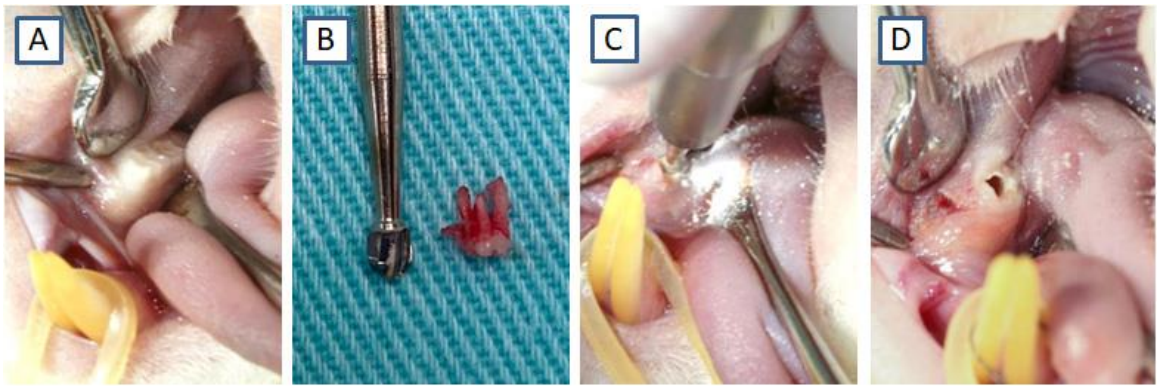
The animals were sedated with 3L/min isoflurane inhalation (Cristalia, Itapira, SP, Brazil) for approximately one minute. After sedation, the intravenous Zol (Novartis, Curitiba, PR, Brazil) injections were administered at a dose of 80 µg/kg, in the caudal vein, once a week for nine weeks.

On week 8, the animals underwent a surgical procedure to remove bilateral first mandibular molars. The procedure was done under general anesthesia using intramuscular injection of xylazine hydrochloride (12 mg/kg, Vetbrands, Paulínia, SP, Brazil), ketamine (90 mg/kg, Vetbrands, Paulínia, SP, Brazil). During the surgery, the

rats were positioned laterally and the mouth was opened with orthodontic elastics n 5/16 attached to hemostatic clamps. The tongue was retracted with 4-0 nylon suture thread (ethicon) (Figure 1A). An adapted surgical extractor was used to perform the syndesmotomy and dislocation of the teeth and a 14 cm Mayo-Hegar needle holder for the avulsion of the teeth (Figure 1B). At the time of extraction, the extraction socket was cleaned using a carbide 2 mm round bur coupled to a handpiece (Kavo, Biberach, BW, Germany) to remove any remaining root fragments. residues and promote decorticalization (Figures 1C and 1D). The use of the bur aimed at standardizing the extraction defect.

For postoperative analgesia, the rats received subcutaneous Tramadol hydrochloride 7 mg/kg (Chemical Union, Jabaquara, SP, Brazil), and oral Acetaminophen 13.3 mg/kg (Chemical Union, Jabaquara, SP, Brazil). For one week after surgery, the animals were fed with pasty food.

Figure 1 – Surgical steps and socket preparation. A) Retraction of the tongue and cheek for extraction, B) Extracted tooth next to carbide 2 mm round bur, C) Decorticalization of the alveolus, D) Final appearance of the alveolus.



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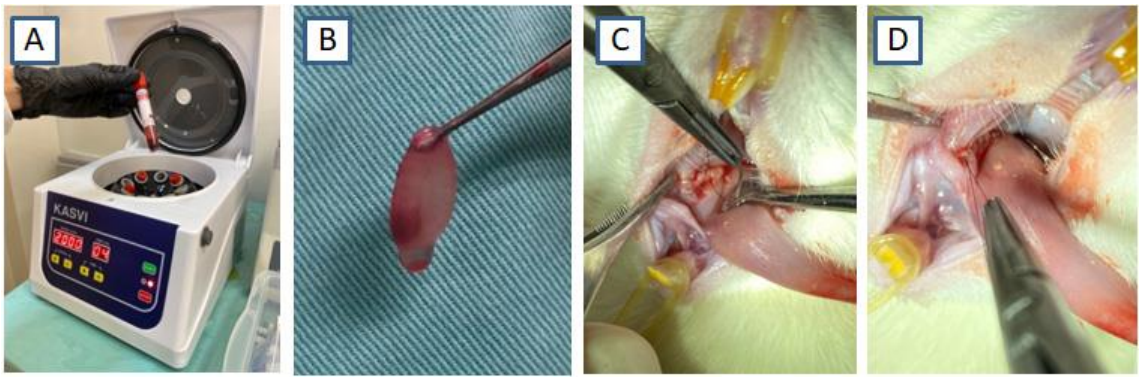
Phase 2

On week 9, the animals underwent a second surgical intervention for extraction of bilateral second mandibular molars, following the same methodology of the first surgical intervention. Immediately after extractions and decorticalization, the alveoli of the right molars were covered by a L-PRF membrane. The L-PRF membrane was made of 1 ml of blood collected by cardiac puncture. Subsequently, the blood was placed in a test tube

without anticoagulant and centrifuged at 2000 rpm for four minutes (Figure 2A). Then, the L-PRF membrane was properly formed (Figure 2B) and placed over the alveoli. In order to keep the L-PRF membrane inside the alveolus (Figure 2C), an X suture was performed with 6-0 nylon thread (Ethicon, São José dos Campos, SP, Brazil) with a ½ 1-inch needle 5cm (Figure 2D). The alveoli on the left side did not receive any additional treatment. All animals were medicated for pain control.

Figure 2 – Fabrication and application of the L-PRF membrane. A) Collected blood inserted into the centrifuge, B) PRF membrane, C) Insertion of the PRF membrane into the socket, D) Suturing the PRF membrane into the socket.



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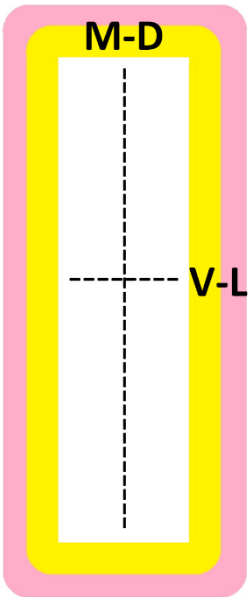
Euthanasia

The animals were euthanized six weeks after the procedure by inhalation of 3% isoflurane for approximately ten minutes until the complete absence of vital signs. For each animal, the incidence and severity of BRONJ was characterized by analysis of intraoral photographs and clinical assessment performed at the time of euthanasia. The following clinical parameters were evaluated for each extraction site: presence of bone exposure, inflammation, suppuration, bony sequestrum and epithelialization of the alveoli. Bone exposure was considered when bare bone of the maxilla (upper jaw) or mandible (lower jaw) was observed. Inflammation was considered present if there were signs of edema and/or erythema. Suppuration was considered if there was visible intraoral or extraoral pus drainage prior to dissection. Bony sequestrum is a necrotic bone fragment that separates from vitalized bone. Epithelialization corresponds to a neo-formed tissue

in the healing process. The mesiodistal (MD) and buccolingual (BL) dimensions of bone exposure were obtained using a millimeter probe (PCPUNC156) (Hu-Friedy, Rio de Janeiro, RJ, Brazil) (Figure 3).

Figure 3 – Dimensioning of bone exposure/necrosis using the necrotic-looking margins of the cavity as a reference. Vertical line: mesiodistal measurement. Horizontal line: buccolingual measurement.



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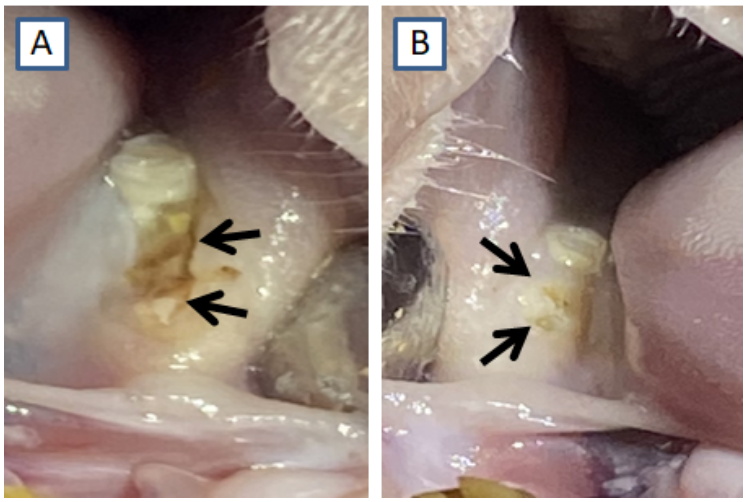
Statistical analysis

The results were submitted to descriptive and inferential analysis, using the Statistical Package for Social Science program (SPSS, version 27.0; SPSS Inc., Chicago, IL, United States), with a confidence interval of 95%. The chi-square test or Fisher's exact test was used to analyze the dependence between two nominal variables. The values obtained were submitted to a normality test (Shapiro-Wilk), and the non-parametric variables were described as median, minimum and maximum. For comparison between groups, the Mann-Whitney test was used.

RESULTS

During the preparation for the second surgical intervention, two animals died because they did not resist the cardiac puncture. Among the ten remaining animals, one of them did not receive the membrane, because the collected blood amount was not enough to make the membrane. Thus, the study was composed of a total of nine animals that presented an adequate trans and postoperative period, with the appropriate surgical technique and placement of the L-PRF membrane. The analysis was performed by clinical comparison between the side that did not receive treatment (GC) (Figure 4A), and the one who received treatment (GLPRF) (Figure 4B).

Figure 4 – Comparative results between control and test groups. A) Local aspect of the control group (CG). B) Local aspect of the test group with application of the L-PRF membrane (LPRFG).



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The comparison of clinical parameters between the sides is shown in Table 1. No significant differences were observed between CG and LPRFG ($p > 0.05$).

Table 1 - Percentage values of presence or absence of clinical parameters evaluated in the animals' hemimandibles, divided into L-PRF membrane group (LPRFG) and control group (CG).

Clinical parameters	Type	Measure	LPRFG	CG
Bone exposure	Present	n (%)	7 (77.8)	9 (100)
	Absent		2 (22.2)	0 (0)
Inflammation	Present	n (%)	0 (0)	7 (77.8)
	Absent		9 (100)	2 (22.2)
Suppuration	Present	n (%)	9 (100)	7 (77.8)
	Absent		0 (0)	2 (22.2)
Bony sequestrum	Present	n (%)	4 (44.4)	7 (77.8)
	Absent		5 (55.6)	2 (22.2)
Epithelialization (total or partial)	Present	n (%)	7 (77.8)	7 (77.8)
	Absent		2 (22.2)	2 (22.2)

Fisher's exact test, $p > 0.05$.

Source: Authors, 2022

Regarding the MD and BL bone exposure measurements in mm, it was possible to observe that the LPRFG had a smaller dimension in both dimensions compared to CG ($p < 0.05$) (Table 2).

Table 2- Comparison of bone exposure measurements (mm) between groups.

Median (min-max)		*P* value
MD - LPRFG	**MD - CG**	**0.002**
1 (1-4)	4.5 (3-6)	
BL - LPRFG	**BL - GC**	**0.030**
1 (1-2)	2 (1-3)	

Kruskal Wallis test, significance level

Source: Authors, 2022

DISCUSSION

Treatments for BRONJ include closing the bone exposure to minimize pain and infection, and also prevent progression of osteonecrosis (NICOLATOU-GALITIS 2019). However, due to the lack of studies in the literature and the world-wide increase in the prescription of drugs from the bisphosphonate group, further studies are needed to develop protocols and treatment options for these lesions. Therefore, the present study investigated the effect of L-PRF membranes in preventing BRONJ after tooth extractions.

Currently, there are major difficulties in evaluating treatment outcomes for BRONJ for two main reasons: first, the lack of definition of success when it comes to osteonecrosis regression, and second, the lack of clinical trials currently available in the literature (JACOBSON et al., 2019).

Given the difficulty of treating BRONJ, the literature focuses mainly on preventive treatment, such as plaque control, caries removal, periodontal disease control, removal of endodontic foci and adjustments/replacement of ill-fitting removable prostheses (RIBEIRO et al., 2017). In pre-existing lesion, there are some treatments that could be assign depending on the severity of the disease (stage 0, 1, 2, and 3) (RIBEIRO et al., 2017; RUGGIERO et al, 2004). Treatment with oxygen therapy in a hyperbaric chamber can stimulates the inflammatory activity, and aids the healing process (CEPONIS et al., 2016). There is also antimicrobial photodynamic therapy (low-level laser), ozone therapy, and the pentoxifylline and tocopherol (PENTO) protocol. It should be emphasized that those treatments must be individualized depending on the patient (CAMINHA et al., 2019).

According to Howie et al. (2015), the behavior and development of BRONJ in rats was similar to that in humans. For this reason, in the present study, L-PRF membrane was used as a form of prevention due to its healing properties, presence of fibrin framework with autologous cells, such as leukocytes, macrophages, neutrophils and platelets, and growth factors. (HEYMOVSKI et al., 2021; TAYSI et al., 2018). There are few reports using L-PRF for BRONJ treatment, but some studies report satisfactory results (BARBOSA et al., 2020; CANAN-DURÁN et al., 2017; PARK et al., 2017).

Our results show that the use of L-PRF membrane as a treatment subsequently to a surgical tooth extraction was efficient to reduce bone exposure of BRONJ. The group treated with LPRF had a significant decrease area of exposed bone for both MD and BL

dimensions compared to the untreated side. PARK et al. (2017) stated that the L-PRF is indicated for osteonecrosis treatment because it dissolves slowly, allowing the progressive release of cytokines and growth factors, acting as an anti-infective agent with a key role in immune regulation. Therefore, it accelerates the healing of epithelial wounds, promotes tissue vascularization and improves soft tissue regeneration.

With regards to other parameters analyzed, no associations were found for the presence/absence of bone exposure, inflammation, suppuration, bony sequestrum and epithelialization of the alveoli. However, it is important to emphasize that the sample size was restricted and could not be significant for statistical calculus. In addition, these results were obtained with six weeks of bone healing, and a longer period could present better results.

One important factor that is worth mentioning is that we only performed a clinical evaluation of the region and other types of analyzes must be included in future studies to evaluate qualitatively and quantitatively outcomes, including histologic, histomorphometry, immunohistochemistry, and X-ray microtomography parameters to fully understand the effect of using L-PRF to prevent cases of BRONJ. Furthermore, futures studies should include a larger sample of animals and increase the experimental time to evaluate the bone healing in a longer period.

It can be observed in the present study that the use of the L-PRF membrane is feasible, having a low cost and considerably reduced the bone exposure of the wound being a promising protocol for the prevention of BRONJ. However, even though it is widely used in Dentistry, more clinical researches are needed to prove the effectiveness of L-PRF as a form of prevention for BRONJ. It should be noted that this method can also be combined with other existing treatment protocols to improve clinical outcomes.

CONCLUSION

Within the limitations of the study, it can be concluded that the use of L-PRF membrane for preventing BRONJ post tooth extraction in rats decrease bone exposure contributing to the repair of necrotic alveoli.

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