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Case Report

# The use of Platelet-rich Fibrin in the management of medication-related osteonecrosis of the jaw: A case series

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ABSTRACT

Medication related osteonecrosis of the jaw (MRONJ) is characterized by exposed necrotic bone in the maxillofacial region that persists for more than eight weeks in patients taking antiresorptive or antiangiogenic drugs for bone metastasis or osteoporosis. The management of such condition depends on several factors, among which the staging of MRONJ. Though, a specific gold standard treatment has not been established to date. The aim of this case series is to describe the outcome of surgical treatment of MRONJ with the adjunct of Platelet-rich Fibrin (PRF). Eleven patients under therapy with alendronate underwent surgical removal of necrotic bone and debridement, followed by placement of PRF membranes in the bone defect. The outcome of the surgical treatment was successful in all patients, in a follow-up range from 12 to 36 months. In the cases presented, the macroscopic evaluation showed excellent and fast soft tissue healing, with no recurrence of bone exposure and no signs of infections. PRF membranes were also effective for postsurgical pain control. The use of PRF may represent a valuable adjunct in the surgical management of MRONJ.



## 1. Introduction

Osteonecrosis of the jaw (ONJ) is characterized by exposed necrotic bone in the maxillofacial region that persists for more than eight weeks. Bisphosphonate (BP) related to osteonecrosis of the jaw (BRONJ) was first described by Marx in 2003, after he observed the association of these lesions with the use of bisphosphonates in patients affected by cancer or osteoporosis with no previous history of radiation therapy to the jaws [1]. Since then, the number of articles in literature describing this condition has constantly grown, and several treatment protocols have been reported.

Bisphosphonates interfere in the process of bone turnover by inhibiting the resorption of trabecular bone by osteoclasts, hence preserving bone density, and impairing angiogenesis [2]. The main indication for BPs is the reduction of the risk of metastasis in patients with cancer, especially breast and prostate cancer, and of the risk of fractures in patients with osteoporosis/osteopenia. Nonetheless, one of the consequences of impaired bone healing and turnover in the jaws, mainly following common oral surgery procedures like tooth extraction, cyst removal or implant placement, is the exposure of the bone leading to pain and even infection or fracture of the jawbone.

Over the years, other classes of non-BP drugs (mainly antiresorptive or antiangiogenic medications) have been related to clinical features of bone exposure in the jaws [3]. Since 2009 the term BRONJ was modified to medication-related osteonecrosis of the jaw (MRONJ). In the Position Paper of the American Association

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of Oral and Maxillofacial Surgeons (AAOMS) published in 2014, [4] the lesions of ONJ maintained the classification in 5 stages. The first stage is the "at risk" category, in which there is no apparent necrotic bone in asymptomatic patients who have been treated with intravenous or oral anti-resorptive or antiangiogenic therapy. The last one, the stage 3, with the exposed necrotic bone in patients with pain, infection, results in pathologic fracture, extra-oral fistula, oral antral/oral nasal communication [4].

Currently, there is not a specific gold standard treatment for MRONJ cases, nonetheless the first choice of treatment is a conservative approach including local debridement, removal of bone sequestrum and association of systemic antibiotic treatment or antiseptic solutions (e.g. chlorhexidine). Most of the cases can result in the reduction of the clinical signs and symptoms or complete healing. In recent years some therapeutic protocols have been proposed in order to enhance the healing and the predictability of the surgical treatment, such as low-level laser therapy, [5] ozone therapy, [6] hyperbaric oxygen, [7] and autologous platelet concentrates. [8] The association of the surgical treatment and autologous membranes of platelet-rich fibrin (PRF), [9] has the objective to add growth factors to the surgical site in order to accelerate bone and soft tissue healing. A focused systematic review [10] suggested that the adjunct of autologous platelet concentrates may be beneficial to treatment of ONJ, as a high proportion (91.6%) of successful cases with satisfactory healing was found in the literature. However, most studies published so far are case reports or case series based on a very low sample size, confirmed in an update of the above cited review. [11] Systematic reviews on this topic concluded that there is still insufficient evidence to prove the real benefits of the platelet concentrates to the healing of the ONJ lesions. [10–12]

The aim of this article was to describe the outcome of surgical treatment of MRONJ using PRF in a series of patients.

## 2. Materials and methods

### 2.1. Ethical considerations

The procedures employed followed the ethical standards of the 1975 Declaration of Helsinki revised in 2000. The patients underwent surgical treatment at two private clinics, in Rio de Janeiro, Brazil, after signing a free and informed consent form, including the release of image rights and the use of their data for scientific publication. The treatment of the lesions was conducted by two calibrated dental professionals.

The study was conducted according to the Case Report Guidelines (CARE, www.care-statement.org), [13] which state that a series should present diagnostic assessment, therapeutic intervention, follow-up, and outcomes, without the need for control groups for effectiveness, focusing instead on a comprehensive description of the technique and results obtained.

### 2.2. Research participants

The inclusion of participants was based on their screening at the two private clinics from 2014 to 2017. The diagnosis of MRONJ was confirmed in all patients after clinical examination, including history, oral examinations, and radiographic examination (X-ray and/or computed tomography). [4] Inclusion criteria were: diagnosis of MRONJ and need for surgical management under local anesthesia; patients able to undergo surgical treatment (ASA-1 or ASA-2); patients able to sign an informed consent form. Based on the above criteria, 11 patients under therapy with oral alendronate for osteoporosis (without associations to treat this condition), that were diagnosed with MRONJ, were included in this interventional case series. The patients did not report previous treatment in the affected area, however, they did not know precisely when their MRONJ condition started.

### 2.3. PRF production

Blood samples were collected from each patient with a 21 G vein needle (BD, Brazil), in 10-mL glass collection tubes (BD, São Paulo, Brazil), without the addition of anticoagulants. After collection, the blood was immediately centrifuged (Intra-Spin® EBA 200, Intra-Lock System, FL, The United States of America), with a force of approximately 400 g for 12 min, at 2700 rpm. After centrifugation, the tubes were placed vertically in a rack allowing the blood to clot for no more than 15–20 minutes. At the end of the procedure, the clot (PRF) was removed from the collection tubes and implanted directly into the operated site. The surgeon applied a light pressure on the PRF clot with PRF-Box® (Intra-Lock System, FL, USA), to remove the excess of serum and obtain a PRF membrane.

### 2.4. Surgical procedures

Oral antibiotic treatment with amoxicillin and clavulanic acid was initiated the day before surgery (Clavulin BD®, 875/125 mg, GlaxoSmithKline, Rio de Janeiro, Brazil) and continued each 12 hours for nine more days. All surgical procedures were performed by two experienced professionals in the presence of a third dental surgeon, who was in charge of data collection. The following information was gathered: age, gender, medication (Anti-resorptive drug), duration of anti-resorptive therapy (time of use), location of the lesion, surgical site, MRONJ stage, number of PRF membranes, and post-operative follow-up. The patients able to undergo surgical treatment (ASA-1 or ASA-2) were observed, in our cases, controlled high blood pressure (hypertension) (seven patients) and/or diabetes (3 patients). No other comorbidities nor concomitant treatment with corticosteroids were reported.

All patients interrupted the use of anti-resorptive medication three months before surgical procedure. Local anesthesia was induced with 2% lidocaine with 1:100.000 epinephrine (two tubes for each procedure) (DFL®, Brazil). In order to access the surgical site, a mucoperiosteal flap was elevated and mobilized to facilitate tension-free closure. Necrotic bone was removed with rotating burs and the bone surface underwent surgical debridement of the necrotic bone. Any sharp edge was removed. The extent of the resection was based on the preoperative computed tomography findings and intra-operative appearance of the bone vitality (bleeding) at the resected surface.

The amount of PRF membranes used was left to the surgeon's decision and it was personalized for each case as needed, depending on the extension of the surgical bone defect (Table 1). The suture was performed with a silk suture black threads with the needle (4-0 size).

A soft diet was prescribed for two weeks, and topic 0.2% chlorhexidine (Perioxidin®, Lacer, Brazil) was used for two weeks after the surgical procedure. The patients were strictly followed until soft tissue closed and any symptom disappeared, and then they were scheduled for follow-up control visits.

The outcomes were the success of the surgical treatment (hard and soft tissue healing at the treated site, disappearance of any symptoms) and the occurrence of postsurgical complications.

## 3. Results

### 3.1. Clinical evaluation

The mean age of the 11 patients included in the case series was 67.7 ± 14.6 (standard deviation) years (range 38–84 years); nine

**Table 1**
Data collected from the case series participants.

| Patients | Age (years) | Sex | Medication | Time of use (months) | MRONJ stage | Location of lesion | PRF membranes | Follow-up (months) |
|---|---|---|---|---|---|---|---|---|
| #1 | 68 | F | Alendronate | 69 | 2 | 12–22 | 8 | 36 |
| #2 | 71 | F | Alendronate | 84 | 2 | 25.26 | 6 | 30 |
| #3 | 77 | F | Alendronate | 48 | 2 | 26 | 8 | 32 |
| #4 | 38 | F | Alendronate | 36 | 2 | 34 | 6 | 24 |
| #5 | 84 | F | Alendronate | 60 | 2 | 43.44 | 6 | 20 |
| #6 | 77 | F | Alendronate | 36 | 2 | 43–48 | 12 | 36 |
| #7 | 82 | M | Alendronate | 72 | 2 | 34.35 | 6 | 16 |
| #8 | 59 | F | Alendronate | 60 | 2 | 36.37 | 10 | 18 |
| #9 | 51 | F | Alendronate | 60 | 2 | 45.46 | 6 | 20 |
| #10 | 80 | M | Alendronate | 60 | 2 | 26 | 4 | 14 |
| #11 | 58 | F | Alendronate | 48 | 2 | 46,47 | 6 | 12 |

were female. The mandible was the site most frequently involved (seven cases). The patients' features and the data collected from all participants are presented in Table 1, in chronological order of treatment.

MRONJ was triggered after a surgical procedure for dental implant placement in the mandible. In the maxilla, two cases were also triggered by the same procedure, and one was caused by multiple dental extractions (#1).

Nine of the patients orally took one 70 mg tablet of alendronate sodium per week. Only two patients (#4 and #9) took 10 mg per day. The mean duration of medication therapy before MRONJ occurrence was 57.6 ± 14.7 months (range 36–84 months). The outcome of the surgical treatment was successful in all patients (100%). The mean follow-up was 23.5 ± 8.7 months (range 12–36 months). The clinical evaluation showed excellent soft tissue healing at any follow-up, without bone exposure and signs of infections. In all cases complete soft tissue closure was achieved by 2 weeks. Local pain disappeared within the first week post-surgery in all patients and was not reported any more throughout the study. No complications occurred throughout the follow-up period

We demonstrated one case to exemplify the surgical procedure in figures one to seven. Patient #6 presented with a mandibular MRONJ lesion localized in region 43 to 48 (Fig.1).Removal of the lesion was performed, until conspicuous bleeding in the area (Fig. 2). The surgical site required the implantation of 12 PRF membranes to complete the bone defect filling (Fig. 3) before suturing. The clinical aspect after ten days of surgery showed the beginning of the healing process with partial closure of the soft tissues (Fig. 4). After one year it was possible to observe the total coverage of the area with soft tissue and the healthy appearance of tissues surrounding the surgical site (Fig.5). After three years the soft tissues maintained an excellent aspect (Fig. 6), and there was radiographic evidence of bone healing at the defect site (Fig. 7 X-ray at 3 years). Throughout the observation period the patient remained without pain and other symptoms and no recurrence of MRONJ was reported.

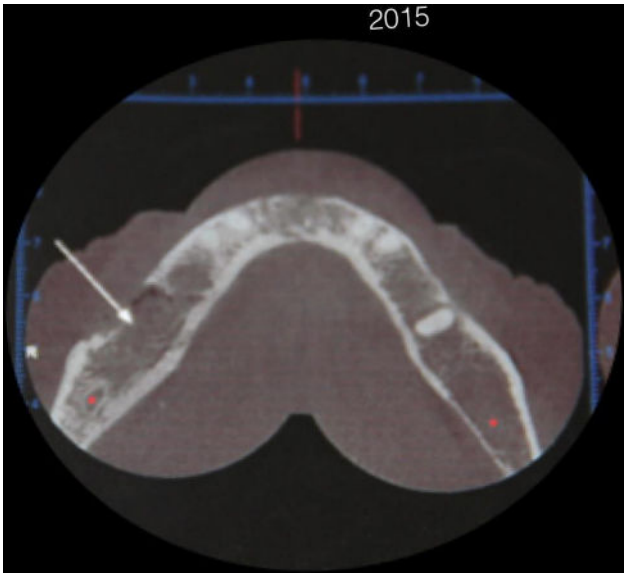


**Fig. 1.** The axial section in computed tomography of the patient No. 6. identifying a lesion of MRONJ (arrow).

## 4. Discussion

The association between the use of alendronate and osteonecrosis of the jaw has been reported a long time ago. [2,14] In the present study all patients had been taking alendronate since at least three years. It is known that the duration of antiresorptive drug exposure is a relevant factor for the occurrence of ONJ, that the surgeon should consider before the surgical procedure. A staging of grade two according to the AAOMS position paper [4] was diagnosed in all patients, because pain and erythema were present around the exposed and necrotic bone lesion, while no purulent drainage was observed. Even though a drug holiday of three months was recommended to all patients, it has a low role in bone turnover. In fact, residual action of alendronate cannot be excluded, due to the long half-life of bisphosphonates in the bone tissue. [15] However, a drug holiday may be beneficial to

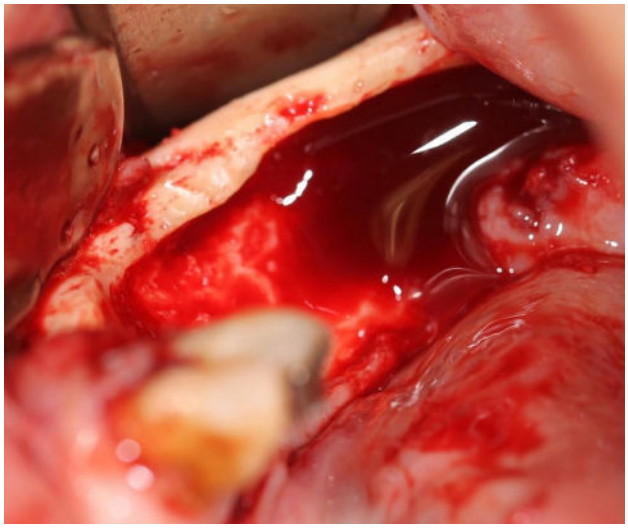

**Fig. 2.** Surgical site after removal of the lesion in the mandibular region.

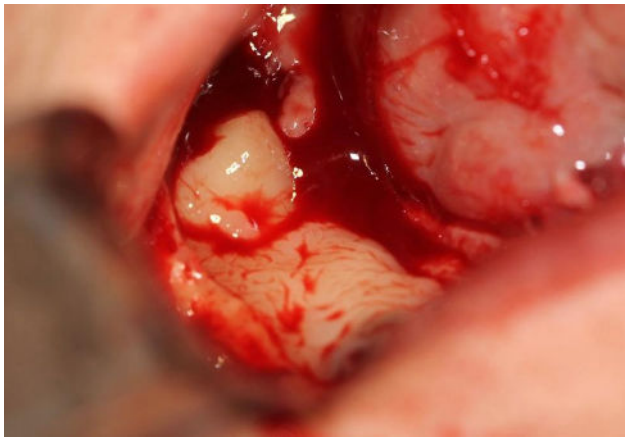

**Fig. 3.** After the implantation of the PRF membranes.

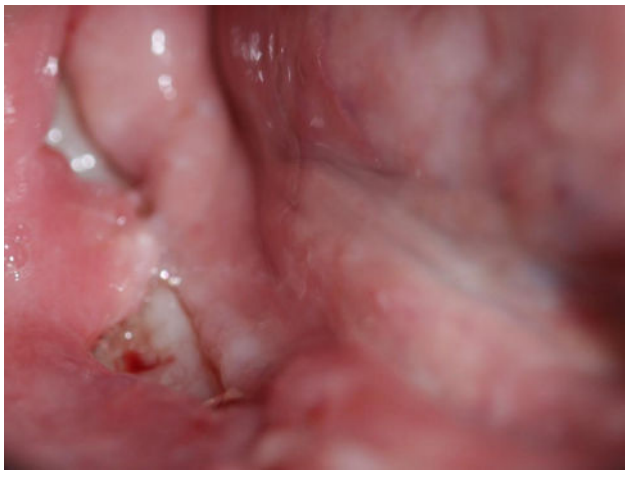

**Fig. 4.** Ten days after removal of the lesion, it is possible to observe the beginning of the healing process.

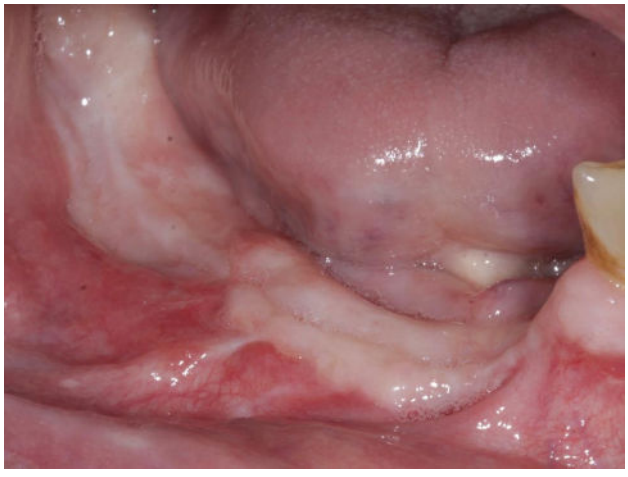

**Fig. 5.** The total coverage of the area with a healed tissue, after one year.

angiogenesis and soft tissue recovery, which, in turn, may have a positive effect on bone recovery. The use of autologous platelet concentrates as an adjunct for a better management of MRONJ was introduced to further stimulate the healing and regeneration potential of both hard and soft tissues at the lesion site. Furthermore, it is important that the treatment approach for

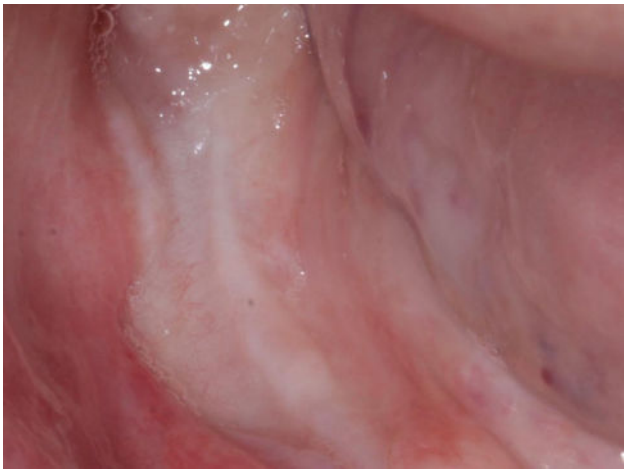

**Fig. 6.** The tissue healing after three years.

MRONJ is minimally invasive [1,4] for preserving as much as possible the health of tissues not involved by the lesion.

Blood-derived growth factors have been used in the recent years to promote tissue healing in many oral surgery procedures. [16,17,19,20,21] The present study used PRF, which is prepared without the addition of chemicals (blood anticoagulants and platelet activators), as opposed to platelet-rich plasma or platelet-rich in growth factors [18]. PRF can be prepared in the form of membranes with physical properties that allow it to be handled and layered to cover the bone, [9] and helping the healing process of the oral mucosa. [18] This by-product from the patient's own blood has a high concentration of platelets and leukocytes that are rich in growth factors and other substances that have an important influence on wound healing, such as Platelet-derived growth factor, epidermal growth factor, transforming growth factor-beta, vascular endothelial growth factor, procoagulant factor, cytokines, and antimicrobial proteins. [22,23,24] A recent systematic review summarized the current evidence on the antimicrobial effect of platelet-rich preparations based on a number of in vitro studies and animal models of infection. [25] Such review concluded that although the specific action mechanisms of the interaction with microbial pathogens deserve further investigation, platelet-rich preparations demonstrated to have antimicrobial properties, and could therefore represent a beneficial natural tool for controlling postoperative infections at surgical site. Recent studies described antimicrobial function by induction of the peptide human beta-defensin 2 and beta-defensin 3, though it is necessary to perform more studies to prove this action. [26,27] Since microbial infection is often associated with MRONJ, either as a consequence of reduced immune defense at the diseased site or as a co-factor in the pathogenesis of such condition, [4] any means to improve the control of postoperative infection is a beneficial tool for the surgeon.

One of the strengths of this clinical report is the relatively long follow-up duration, that in 5 patients is greater than 24 months. Throughout the follow-up, patients experienced no complications and healing of soft and hard tissue was maintained over time. This excellent result of these osteoporotic patients could be due to the good systemic condition of the patients, good control of postoperative infection, the patients compliance with post-surgery protocol, and the absence of trauma in the region after the procedure. However, it should be noted that all of the patients were taking BPs orally, and not through intravenous. This important result may correlate with a good level of satisfaction and quality of life without infection and/or pain after the surgical procedure for removing the lesion.

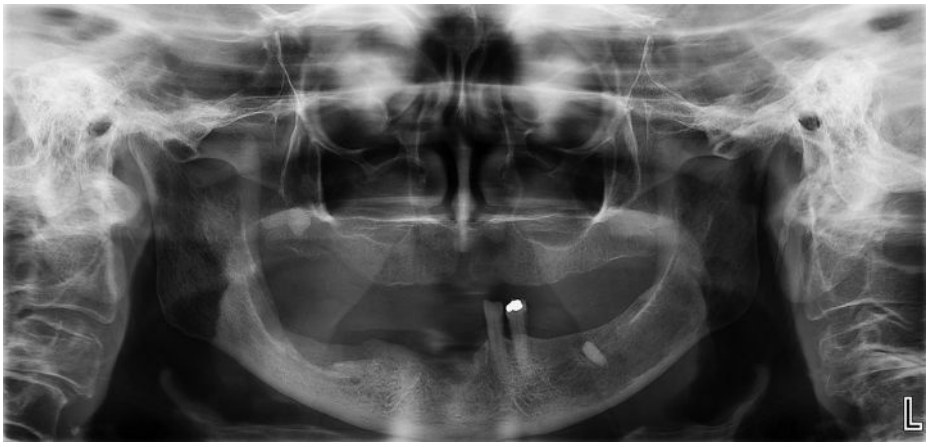

**Fig. 7.** X-ray after three years follow-up. It can be appreciated a complete healing of the bone defect.

Since there is growing evidence of the beneficial effect of platelet-rich preparation in the management of MRONJ, a clinical trial with a group treated without platelet concentrates seems challenging and unethical since there is not a gold standard treatment for MRONJ. Within the limits of this study, we propose that the adjunct of PRF in the surgical procedure could be a good alternative to treat the patient affected by MRONJ.

## 5. Conclusion

In the cases presented, the PRF membranes were effective to close the soft tissue and to remove the pain in MRONJ, being regarded as a promising alternative for MRONJ treatment. Therefore, further research such as cohort prospective studies may provide new evidence and help to elucidate the impact of PRF membranes as tools for an effective treatment for MRONJ.

### Ethical approval and Informed consent

The procedures employed followed the ethical standards of the 1975 Declaration of Helsinki revised in 2000. The participants underwent dental treatment after signing a free and informed consent form, including the authorization for the release of images for scientific publication.

### Funding

None

### Disclosure of interest

The authors declare that they have no competing interest.

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