



Efficacy of fibrin-rich platelets and leukocytes (L-PRF) in tissue repair in surgical oral procedures in patients using zoledronic acid—case–control study

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Abstract

Introduction Medication-related osteonecrosis of the jaws (MRONJ) is a complication that develops in patients who use or have used antiresorptive or antiangiogenic medications for the treatment of bone metabolic disease and bone metastases. Clinically, MRONJ is characterized by the appearance of an inflammation in soft tissues and exposure of necrotic bone tissue in mandible or maxilla, for a period of 8 weeks, in patients with no history of head and neck radiotherapy that were being or are being treated with antiresorptive and/or antiangiogenic agents. The fibrin-rich platelets and leukocytes (L-PRF) membrane has been used as an alternative for MRONJ prevention. The aim of this study was to evaluate the use of L-PRF in prevention and treatment of bone necrosis.

Material and Methods The patients included had MRONJ diagnosis confirmed after clinical and radiographic examination and patients whose only therapeutic option was dental extraction.

Results Twenty patients were included in the study and were divided in three groups. Two patients were removed from the study due to previous history of pentoxifylline and tocopherol use. The result of surgical treatment was successful in 57% in group 1 (control/MRONJ prevention), 100% in group 2 (MRONJ prevention), and 80% in group 3 (MRONJ treatment).

Conclusion L-PRF is an autologous biomaterial that allows the release of growth factors for a prolonged time, resulting in a better healing, reducing the risk contamination, edema, and postoperative pain, being a great ally in the prevention and treatment of MRONJ because it returns to these patients, mainly quality of life, reducing pain, and recurrent infections commonly seen in the processes of bone necrosis of the jaws.

Keywords Bisphosphonate-associated osteonecrosis of the jaw · Platelet-rich fibrin · Treatment outcome

Introduction

Bisphosphonates (BPs) are the most used antiresorptive medication in the management of cancer-related conditions, such as the prevention of bone metastatic malignancies, and

are also used for the treatment and prevention of osteoporosis [1]. In 2003, the first case of osteonecrosis of the jaws as an adverse effect of these medications was reported in cancer patients [2].

Over the years, other classes of non-BP drugs (antiresorptive or antiangiogenic medications) have been related to clinical features of bone exposure in the jaw [3]. Based on that, in 2014 the Association of Oral and Maxillofacial Surgeons (AAOMS) renamed the complication as “medication-related osteonecrosis of the jaw” (MRONJ) [4].

BPs act for years (by adhesion to the bone mineral and remain until the bone site in which it is found is reabsorbed) after the first therapeutics doses decreasing local vascular support and regulating bone metabolism, thereby reducing the action of osteoclasts and decreasing angiogenesis affecting bone remodeling and deposition of physiological bone

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matrix [5]. Therefore, an interruption or discontinuation of bisphosphonate medication (drug holidays) does not lead to the desired therapeutic effect [7].

One of the most discussed and controversial aspects of this complication are the risk factors, which are most commonly associated with bisphosphonates therapy, such as invasive dental treatment, concomitant illness, and harmful habits. These risk factors can be classified into three groups: (1) risk factors related to the medication (type of medication, dose, frequency, and treatment duration), (2) risk factors associated with dental disease and/or dental procedures (dental extraction, denture placement, implant placement, local infection or bone/tissue trauma) and periodontal procedures (periosteum damage), and (3) other risk factors (age, gender, type of oncological disease, tobacco and alcohol use, and corticosteroids) [8].

The clinical diagnosis of MRONJ follows three mandatory conditions: presence of bone exposure area or persistent intra- or extra-oral fistula for 8 weeks or more in patients without history of radiation therapy who were or are being treated with antiresorptive and/or antiangiogenic agents [4].

MRONJ can be challenging to treat and can cause significant pain and reduced quality of life [9]. Many studies have established that preventive oral care methods combined with effective oral health practices are associated with a lower rate of MRONJ [10]. When it comes to treatment, there is no definitive standard care and the most effective treatment is still controversial. Treatment options are classified into conservative, surgical, and adjuvant non-surgical therapies, and they can be used in combinations [11]. AAOMS describes that the first choice of treatment is a conservative approach including local debridement and disinfection with antimicrobial rinses and/or systemic antibiotic therapy, and when conservative treatment fails, surgical therapy through bone debridement, sequestrectomy, or resection is recommended [4]. Nowadays several publications have reported that in all stages of the necrosis, surgical treatment is more effective than conservative therapy, proving the success of early-stage surgical therapy [12].

Autologous platelet concentrates have been used in the oral and maxillofacial field for more than 20 years, and in 2007 they were used for the first time in MRONJ [13]. The base of L-PRF is a 3-dimensional fibrin network with embedded thrombocytes, leukocytes, and stem cells, also includes a wide variety of growth factors, cytokines, and proteins [14].

The aim of this study was to evaluate the effects of L-PRF on patients suffering from MRONJ or patients in need of dental surgical procedures. The objective was to assess the prevention and the treatment of MRONJ with L-PRF-supplemented surgical therapy with the prognosis of traditional surgical therapy in terms of healing and recurrence.

Materials and methods

Ethical considerations

The procedures employed followed the ethical standards of the 1975 Declaration of Helsinki revised in 2000. The research was submitted and approved by the Ethics Committee in Research of the Erasto Gaertner Hospital and registered in the National System of Ethics in Research—SISNEP under the number 27354919.8.0000.0098.

The patients underwent surgical treatment at the Department of Oral and Maxillofacial Surgery at Erasto Gaertner Hospital, in Curitiba, 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 was conducted by calibrated local residents assisted by the principal author.

Research participants

Patients were included in the study after attending a routine consultation at the Department of Oral and Maxillofacial Surgery at the Erasto Gaertner Hospital. Inclusion criteria were diagnosis of MRONJ or need of tooth extraction in patients under oncological treatment (prostate and breast cancer or multiple myeloma) with bisphosphonates (alendronate sodium or zoledronic acid); patients able to undergo surgical treatment (ASA-1 or ASA-2); and patients able to sign an informed consent form. The diagnosis of MRONJ was confirmed in all patients after clinical examination, including history, oral, and radiographic exam (panoramic radiography and/or computed tomography).

The exclusion criteria were other types of cancer; cancer patients for prostate/breast cancer or multiple myeloma who were not in use of alendronate sodium or zoledronic acid; patients with history of radiation therapy in the head and neck area; and patients with previous history of use of pentoxifylline and tocopherol.

Patients were divided randomly (by convenience sampling) into three groups—group 1: control; group 2: prevention (patients without diagnosis of MRONJ but needed for tooth extraction); and group 3: treatment (patients with diagnosis of MRONJ in any stage).

L-PRF production

Blood samples were collected from each patient with a 21 G peripheral intravenous access (BD, Brazil), in 9-mL glass red top blood collection tubes (BD, Brazil). After collection, the blood was immediately centrifuged (DT4000, Daiki), with a force of approximately 400 g for 12 min, at 2700 rpm.

At the end of the procedure, the clot (L-PRF) was removed from the collection tubes and implanted into the operated site after the surgeon applied a light pressure on the L-PRF clot with L-PRF box (Supremo Instrumentais, Caieiras, São Paulo, Brazil), to remove the excess of serum and obtain a L-PRF membrane.

Surgical procedures

Oral antibiotic treatment with amoxicillin 500 mg and metronidazole 400 mg was initiated 7 days before surgery and continued every 8 h for 7 more days after the procedure. Oral rinse with 0.12% chlorhexidine gluconate alcohol-free was prescribed twice a day, for 1 min. All surgical procedures were performed by trained residents in the presence of a third dental surgeon, who was in charge of data collection. The following information was collected: age, gender, medications in use, duration of antiresorptive therapy, surgical site, tooth extracted, degree of mobility of the extracted tooth, the state of the tooth (decayed, broke, rooted), and postoperative follow-up (7, 15, 30, 90, 180 days).

None of the patients interrupted the use of antiresorptive medication. Local anesthesia was induced by 2% lidocaine with 1:100,000 epinephrine in 3 groups.

Group 1 (control): patients who had an indication for surgical treatment of MRONJ or when tooth extraction was the only treatment option. All patients received the same techniques and treatments already recognized in the world literature but did not receive L-PRF membranes at the surgical site.

Group 2 (prevention): patients that presented a condemned tooth in which the only treatment option was extraction.

Group 3 (MRONJ treatment): patients diagnosed with MRONJ with indication of surgical treatment.

For groups 1 and 2, patients underwent minimally invasive tooth extractions, with the least possible trauma to bone tissue and gingival mucosa. After curettage and irrigation of the surgical alveolus with 0.9% saline solution, L-PRF membranes were inserted, filling the entire surgical alveolus, and 3–0 nylon sutures were performed.

In order to access the surgical site, a mucoperiosteal flap was elevated (when necessary) and mobilized to facilitate tension-free closure. Necrotic bone was removed with rotating burs (and abundant irrigation with 0.9% saline solution to avoid heating the remaining bone) 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 or panoramic radiography findings and intra-operative appearance of the bone vitality (bleeding) at the resected area.

The amount of L-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. The suture was performed with a nylon suture (3–0 size).

A pasty liquid diet was prescribed for 2 weeks, analgesics (ibuprofen 600 mg every 12 h and paracetamol 750 mg every 8 h) for 3–5 days after surgery. The suture was removed within 15 days and the patients received regular clinical and radiographic follow-up until 6 months after surgery.

The outcomes considered a success were well-healed soft tissue at the treated site and disappearance of any symptoms. The occurrence of postsurgical complications, such as infection or persistent painful symptoms, and bone exposure recurrence was considered as unsuccessful.

Results

Clinical evaluation

Twenty patients were included in the study. The mean age of the participants was 61.9 years (range 41–91 years); 8 (40%) were male. The mandible was the site most frequently involved (55%). The patients' features and the data collected from all participants are presented in Table 1.

All patients took intravenously zoledronic acid every month. The mean duration of medication therapy before MRONJ occurrence was 10.2 months (range 8–36 months). The outcome of the surgical treatment was successful in 57% in group 1, 100% in group 2, and 80% in group 3. The mean follow-up was 6 months. The clinical evaluation showed excellent soft tissue healing from first follow-up, without bone exposure and signs of infections in the groups 2 and 3. In group 1, the healing process was slow with a variety of complications (post-op pain and suture dehiscence with inflammation and infection), including bone re-exposure. In groups 2 and 3, total soft tissue closure was achieved by 4 weeks. In group 1, the healing process took 8–12 weeks, when achieved. Local pain was not reported by patients within the first week post-surgery and no postoperative complications occurred throughout the follow-up period in the groups who received the L-PRF membranes.

To assess success, we considered complete closure of bone exposure without recurrence during the entire follow-up period. We also consider success when there was suture dehiscence in the mediate postoperative period with posterior epithelization. In addition, the absence of local inflammatory/infectious processes and pain were taken into account.

For group 2, we observed a fast healing process with formation of granulation tissue within the first 7 days after surgery and an even faster healing after the removal of the

Table 1 Data collected from all groups

	Patients	Age (years)	Sex	Underlying disease	Location of lesion/tooth extraction	Outcomes
Group 1	#1	57	Female	Breast cancer	Mandible	No MRONJ
	#2	56	Male	Multiple myeloma	Maxilla	No MRONJ
	#3	77	Male	Prostate cancer	Mandible	No MRONJ
	#4	66	Female	Breast cancer	Mandible	MRONJ development
	#5	41	Female	Breast cancer	Maxilla	No MRONJ
	#6	49	Female	Breast cancer	Mandible	MRONJ development
	#7	70	Female	Breast cancer	Mandible	No MRONJ
Group 2	#1	70	Male	Multiple myeloma	Maxilla	No MRONJ
	#2	73	Male	Prostate cancer	Maxilla	No MRONJ
	#3	41	Female	Breast cancer	Mandible	No MRONJ
	#4	56	Male	Multiple myeloma	Mandible	No MRONJ
	#5	62	Female	Breast cancer	Mandible	No MRONJ
	#6	51	Female	Breast cancer	Maxilla	No MRONJ
	#7	57	Female	Breast cancer	Maxilla	No MRONJ
	#8	57	Female	Breast cancer	Mandible	No MRONJ
Group 3	#1	68	Male	Multiple myeloma	Maxilla	MRONJ recurrence
	#2	66	Male	Multiple myeloma	Maxilla	Healing
	#3	91	Male	Prostate cancer	Mandible	Healing
	#4	73	Female	Breast cancer	Mandible	Healing
	#5	57	Female	Breast cancer	Maxilla	Healing

sutures on the 15th day after the procedure. We also noticed a lower rate of postoperative pain and edema when compared to the control group.

In group 3, patients already had some stage of bone necrosis, in addition to pain complaints and presence of local suppuration. None of these patients had an extra-oral fistula. The tissue repair and healing process in this group was slower, taking up to 12 weeks for complete healing when there was no recurrence of bone exposure as it was shown in some cases. Pain complaints and postoperative edema were not reported by the evaluated patients. Full recovery occurred in more than 50% of patients in this group.

Discussion

The direct clinical effect of use L-PRF in the surgical treatment of MRONJ is an early epithelization of the surgical sites [15]. In our study, we evaluated that the best results were seen in group 2, where patients did not present bone necrosis, when compared to group 3. Group 3, although showed a slow healing process, full recovery was considered high. This can be explained by the fact that the research took place within a specialized service of oral and maxillofacial surgery, in a cancer hospital that has broad experience in treating this kind of complication associated to cancer therapy.

A systematic review published recently found that application of PRF for the treatment of MRONJ with complete recovery was found in 92.8% [16]. Other authors also show that the healing results are very similar and positive with rates of complete resolution exceeding 75% in all studies [17–21].

Our study had some limitations. First, we had a limited sample that was affected by SARS-COV-2 pandemic that reduced the face-to-face appointments, with longer periods between appointments. This led to a reduce number of patients included in the study, and to a concern about early diagnosis and prevention of this complication. Also, not all patients were able to perform the radiographs at the desired frequency; however, we understand that in successful cases, mucosal healing is related to the condition of healthy and non-necrotic bone. On the other hand, sample randomization and standardization were important to minimize research bias.

All patients included in the sample presented MRONJ-risk associated intravenous use of Zoledronic Acid® as well poor teeth condition and although recommendation is to avoid oral surgical procedures, sometimes it is the only option for some cases. Patients with a history of pentoxifyline and tocopherol use were excluded from the study so that the result would not be interfered with by other drugs already used in the control and treatment of MRONJ. Thus, this study demonstrated that adjuvant treatments such as

L-PRF can be very useful to prevent and treat medication-related osteonecrosis of the jaws.

MRONJ is a well-recognized complication of drug therapies for bone metabolic disease or cancer. Antiresorptive drugs, such as bisphosphonates and denosumab, are used in low and high doses, and a recent literature review identified a range of other medications classified as tyrosine kinase inhibitors, monoclonal antibodies, mammalian target of rapamycin inhibitors, radiopharmaceuticals, selective estrogen receptor modulators, and immunosuppressants that have been implicated in MRONJ in addition to the drugs already mentioned [22]. Many studies have investigated the mechanism of MRONJ development and various therapeutic methods have been proposed but still poorly understood [23, 24].

Radiographically, osteonecrosis caused by different types of antiresorptive drugs are very similar, but the panoramic radiography (PR), computed tomography (CT), and magnetic resonance imaging (MRI) are considered important examinations in the general evaluation of the lesions, the latter two being important in assessing the limits of disease. Also, MRI as well as bone scintigraphy (BS) may be useful in detecting subclinical osteonecrosis when the bone is not exposed. However, BS has no specificity and low resolution [25].

Surgical treatment is considered to be the most standard treatment of MRONJ, although some differences exist in the treatment approach depending on the stage [26]. Complete removal of the necrotic bone, until bone appears healthy in terms of structure with perioperative antibiotic treatment, infection control, and smoothing of the sharp bone edges before tension-free sutures are generally considered the most appropriate approach for successful recovery [27].

In order to improve wound healing and reduce the rate of recurrence, local therapeutic measures are becoming increasingly popular based on surgical debridement combined with local application of platelet-rich blood products such as platelet-rich fibrin and leukocytes (L-PRF) [7].

Platelet concentrate refers to an autologous concentration of human platelets obtained by centrifuging blood. It results in a high concentration of several protein growth factors secreted actively by platelets [28]. L-PRF has been used for regenerative procedures in various fields of medicine, including dentistry and reconstructive surgery in order to deliver high concentrations of autologous growth factors directly to wounds [29]. Not only acts as a three-dimensional fibrin scaffold but also contains numerous autologous cells, such as platelets, macrophages, and neutrophils. Growth factors released by platelets include platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), transforming growth factor β (TGF- β), insulin-like growth factor-1 (IGF-1), vascular endothelial growth factor (VEGF), and epidermal growth factor (EGF) [30] and seem to persist

for at least 14 days due a slowly and naturally polymerizes during centrifugation [31].

The lack of epithelization exposes the bone to the oral microbial population, which can result in recurrent and persistent infections.³⁰ Thus, L-PRF contains numerous immune cells, which may inhibit infectious. Recently studies shown that membranes obtained by horizontal centrifugation may exert greater antibacterial effects [32].

Conclusion

L-PRF is cheap, safe, autologous, and easy to prepare treatment option for MRONJ and may reduce the risk of delayed recovery in tooth extracted patients undergoing intravenous bisphosphonate therapy. Moreover, L-PRF may be useful in preventing and treat MRONJ in patients receiving intravenous bisphosphonates. Further clinical trials are needed to establish whether the use of L-PRF could significantly reduce the incidence of MRONJ in oncological and non-oncological patients after oral surgery procedures and improve healing and quality of life in patients requiring oral surgical treatment.

Declarations

Ethics approval The research was submitted and approved by the Ethics Committee in Research of the Erasto Gaertner Hospital and registered in the National System of Ethics in Research—SISNEP under the number 27354919.8.0000.0098.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent for publication All participants have consented to the submission of the case report to the journal.

Conflict of interest The authors declare no competing interests.

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