The role of fibrin rich platelets and leukocytes (L-PRF) in the medication-related osteonecrosis of the jaw: report of premaxilla necrosis

Abstract:

Bisphosphonates (BPs), antiresorptive and antiangiogenic drugs are used to prevent metastatic bone cancers in prostate cancer, breast cancer and multiple myeloma and to treat osteoporosis and Paget’s disease. Recently, in 2003 the first case of osteonecrosis of the jaws was induced, hitherto by bisphosphonates, but a few years later it was shown that other medications were also responsible for the development of this type of necrosis. Thus, in 2014 there was a change in the name for medication-related osteonecrosis of the jaws (MRONJ). Since then, the treatment for this type of necrosis is quite controversial in the world literature, and there is still no protocol for established treatment, be it clinical or surgical. The objective of this work is to demonstrate the efficacy of platelet and leukocyte-rich fibrin membranes (L-PRF) after curettage of necrotic bone tissue in the management of drug-related jaw osteonecrosis, since they have innumerable biological benefits such as large amount of growth factors and cytokines, hemostatic capacity, angiogenesis capacity, and has been shown to accelerate and improve results in hard and soft tissue wound healing. The patient presented MRONJ and have been treated with surgical necrotic bone debridement, placement of L-PRF in the affected site and primary closure. Patient were followed up clinically and radiographically until total mucosal coverage of the necrotic bone was achieved.

Keywords: Platelet-Rich Fibrin; Multiple Myeloma, Diphosphonates, Osteonecrosis, Maxilla.
INTRODUCTION

Medication-related osteonecrosis of the Jaw (MRONJ) is a severe adverse drug reaction, consisting of progressive bone destruction in the maxillofacial region of patients being a side effects of the antiresorptive and antiangiogenic therapies. Was first reported in 2003 after intravenous administration of zoledronate and pamidronate in patients with multiple myeloma and metastatic breast cancer.

The major cause of MRONJ occurs is related to tooth extraction. However, in most cases it is not clear if the tooth extraction causes development of MRONJ. Nowadays, it is proven that periodontitis and mucosal lesions such as pressure marks, smoking, and corticoids also represent risk factors.

The clinical manifestations of MRONJ has been classified by AAOMS since 2009 and has been modified in 2014. To be considered to have MRONJ the patients must present the following clinical characteristics: Current or previous treatment with antiresorptive or antiangiogenic agents; Exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for longer than 8 weeks and no history of radiation therapy to the jaws or obvious metastatic disease.

The complex topic of management of this condition will depend on stage of the necrosis and patient’s symptoms. There are no definitive guidelines as to how we should approach management of MRONJ. What we know is that non-surgical therapy is employed in mild disease or symptoms (prevention infection and symptom control). Surgical therapy on the other hand, is reserved for larger, more painful, progressive and infected areas of necrosis and where conservative management has failed.

Because of this, new alternative therapies has emerged, such as the use of laser therapy, hyperbaric oxygen, ozone therapy and platelet concentrates, being this last technique one of the newest and promising treatments for the management of MRONJ. The Fibrin rich Platelets and Leukocytes (L-PRF) is a second-generation of autologous growth factors, which encourages healing and is proposed to be associated with effective and early organization of bone substance and bone volume percentage. Moreover, L-PRF is a platelet concentrate with leukocytes in dense fibrin matrix, which can be conveniently prepared from autogenous non anti-coagulated blood when centrifuged.

CASE REPORT

64-year-old male patient was referred to Department of Oral and Maxillofacial Surgery of the Erasto Gaertner Hospital with complaints of bone exposure in the premaxilla which arose after tooth extraction (Figure 1). Medical history showed that patient uses intravenous Zoledronic Acid (Zometa®) once a month due multiple myeloma since February 2017 and had teeth extractions five months before referring to our service. Computed Tomography (CT) examination revealed a poorly defined hypodensity area in the pre-maxilla region (Figure 2). With the help of anamnesis, clinical and CT examinations, MRONJ diagnosis was made which caused by the treatment of multiple myeloma with...
Zoledronic acid. As a medical treatment, mouthwash (0.12% Chlorhexidine Gluconate) with a combination of Pentoxifylline and Tocopherol. Oral Clindamycin started as soon as the diagnosis was made advised for at least two weeks.

After consultations and consents, the patient was planned to undergo general anesthesia and L-PRF application after the lesion debridement. A large mucoperiosteal flap was elevated in the exposing bone tissue area. The area of the large necrosis was excised till a firm bone surface was left (Figure 3) and the application of L-PRF obtained from patient’s blood that drewed preoperatively followed by primer wound closure (Figure 4). To prepare the L-PRF, 80mL of peripheral blood was collected from the antecubital vein into a 10 mL glass tube with no anticoagulant, and the blood samples were centrifuged at 2700rpm for 12 minutes. After centrifugation, 8 pieces of L-PRF were obtained from the middle of the tube (Figure 5). All membranes were arranged in layers covering the entire surgical bone bed (Figure 6). No suture removal was performed due to the use of absorbable suture and the Pentoxifylline and Tocopherol were not discontinued after surgical procedure. One month after the operation, it was determined that the mucosa in the area where osteonecrosis used to present was healthy but a small tissue dehiscence was observed, so follow-up period begun with monthly controls. Clinical and CT scans at the postoperative 2 years follow-up revealed healthy tissue, tissue dehiscence resolution (Figure 7 and 8) and patient’s symptoms had passed. After that, the patient maintains semi-annual follow-ups.

Figure 3. Surgical bed after curettage of necrotic bone with removal of anterior nasal spine.

Figure 4. PRF membrane after compression by using PRF box.

Figure 5. Application of fibrin rich in leukocytes and rich in platelets on the surgical bone bed.

Figure 6. Immediate post-operative after closure with use of absorbable suture.
DISCUSSION

Biphosphonates are currently the main class of medications used to treat osteoporosis and other diseases characterized by increased bone resorption. Acting through two mechanisms of action related to antiosteoclastic and antiangiogenic activity alter the mechanism of bone tissue in several levels, inhibiting reabsorption and decreasing bone turnover. Other drugs class has been utilized with similar indications than bisphosphonates, the monoclonal antibodies. Neutralizing the receptor activator of nuclear factor κB ligand (RANKL), a member of tumor necrosis factor receptor superfamily. This factor is produced by osteoblasts and activates the RANK receptor on osteoclast precursor cells and osteoclasts. The RANKL-RANK signaling pathway is essential for the differentiation, function, and survival of osteoclasts.

Nowadays the MRONJ staging is based on the Classification proposed by The American Association of Oral and Maxillofacial Surgeons (AAOMS) as showed in the Table 1 and its treatment still controversial because surgical procedures may induce disease progression and there is no a consensus regarding the best treatment.

Platelet-rich fibrin (L-PRF) for specific use in oral and maxillofacial surgery was first developed in France by Choukroun et al. L-PRF is a new generation of platelet concentrates that is not only inexpensive and autologous, but also does not require any biochemical modifications compared to other platelet concentrates. Act as a bioactive surgical additive to regulate inflammation, reduce the healing time and stimulation of chemostastic agents.

These concentrates allows the release of growth factors over a prolonged time (about 28 days), resulting in an acceleration in healing, reducing the risk of contamination, edema and postoperative pain, it helps in homeostasis, prevents tissue dehiscence and favors the remodeling and healing of both soft and hard tissues, increase tissue vascularization, overtaking one of the major factors in pathogenesis of MRONJ, the lack of vascularization. For these reasons, some researches propose applying L-PRF as a preventive measure in surgical interventions or as a treatment for cases of established MRONJ.

Dinca et al. performed removal of the bone sequestrations and curettage in the bone tissue until clear bleeding appeared from the subjacent bone. After that, bone cavities were filled out with L-PRF clots. No postoperative complications were observed and all the 10 patients were treated successfully without evidence of exposed bone.

CONCLUSION

The combined sequestrectomy and L-PRF has shown potential and good results for MRONJ healing but better communication from the prescribing physician to the dental surgeon is necessary to establish orientation and preventive treatment before initiation of the therapy with bisphosphonates or monoclonal antibodies.
Table 1. Staging and treatment strategies of BRONJ according to AAOMS4.

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<th>Staging of BRONJ</th>
<th>Treatment modalities</th>
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<td>Stage 0</td>
<td>Systemic management, including the use of pain medication and antibiotics</td>
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| Stage 1          | Antibacterial mouth rinse  
|                  | - Clinical follow-up on a quarterly basis  
|                  | - Patient education and review of indications for continued bisphosphonate therapy |
| Stage 2          | Symptomatic treatment with oral antibiotics  
|                  | - Oral antibacterial mouth rinse  
|                  | - Pain control  
|                  | - Debridement to relieve soft tissue irritation and infection control |
| Stage 3          | Antibacterial mouth rinse  
|                  | - Antibiotic therapy and pain control  
|                  | - Surgical debridement/resection for longer term palliation of infection and pain |

Furthermore the L-PRF is encouraging results and open a new path in the treatment of this pathology.

REFERENCES


