

Use of Lactoferrin + Tetracycline as Wound Protection and Healing In Cases of Medication-Related Osteonecrosis of the Jaws

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Received Date: 19 April, 2021; **Accepted Date:** 23 April, 2021; **Published Date:** 30 April, 2021

Abstract

Purpose: This paper aims to discuss the protection of the surgical wound in treating Medication-Related Osteonecrosis of the Jaws (MRONJ).

Patients and Methods: A literature review was carried out to seek alternatives for protective materials for wounds from MRONJ. Articles that talk about surgical treatment without the use of covering material were excluded. Two cases were reported exemplifying the use of lactoferrin + tetracycline that can be used in these situations.

Results: Covering paste exercised an essential protective factor, both mechanical and biological, against wounds from MRONJ. It is a very useful maneuver to treat infections in cases of MRONJ.

Conclusions: Lactoferrin + tetracycline paste are efficient as wound protection and infection treatment associated with MRONJ.

Keywords: Bisphosphonate-Associated Osteonecrosis of the Jaw; Lactoferrin; Tetracycline

Introduction

Medication-related osteonecrosis of the jaws (MRONJ) is a pathology where there is a tissue death of the bone due to a decrease in blood supply. It can have multiple etiologies such as trauma, coagulation disorders, tumors, chemotherapy, and radiotherapy. Nowadays, the most discussed cause in the literature is drug osteonecrosis. Some drugs used mainly to treat osteoporosis or some neoplasms such as zoledronate and denosumab are included in this list.

These drugs, bisphosphonates or antiresorptive, alter bone homeostasis with significant interference in osteoclasts. Patients taking any of these medications are at risk of decreasing the blood supply to the jawbones, leading to necrosis, which is often challenging to treat.

The first reports of osteonecrosis of the jaws of medicinal origin date back to 1977, but it was only in 2003 [1], that the literature began to speak more consistently and give due attention to this pathology.

Several treatments are proposed, from expectant, clinical to surgical, more aggressive treatments. Some protocols were created to define the best treatment depending on the degree to which osteonecrosis is found, but there is still no consensus for all cases.

An item treated in the literature with superficiality covers surgical wounds, regardless of the type of treatment chosen. This article aims to discuss precisely this critical step in obtaining an excellent result in the treatment of MRONJ.

Case report

Case 1

Female patient, 63 years old, smoker, denies alcoholism. She underwent osteoporosis treatment based on bisphosphonate for 10 years, having suspended it by medical orders about three years ago. She has been using simvastatin for more than 10 years. Toothless upper tooth, nine maxillary implants were installed for prosthetic rehabilitation about two years ago. In the surgery for the installation of the left-most posterior implant, the bone found in the installation area did not present adequate consistency, as in the other perforations, and although the perforation was performed, the implant was not installed.

About a year after the implant installation and prosthetic rehabilitation, the patient presented

fenestration in the bottom region of the upper left vestibular deepening, very close to where the perforation occurred without installing the implant. She was submitted to decontamination with chlorhexidine and suturing of the region, but the region's soft tissue was again tearing and a new fenestration appeared. Radiographic examination revealed a small area suggestive of osteonecrosis (Figure 1) with some purulent collection drainage one week later first decontamination. The patient was submitted to a new local cleaning and decontamination plus insertion of a paste made of tetracycline 500mg and lactoferrin (blue[®]m, Netherlands) in 1:1 proportion surgery. Only with one consultation, five days later, the patient was free of infection and pain. In more ten days, she was submitted to a total sequestrectomy, about 12mm large (Figure 2) with the use of manual instruments plus placement of the PRF membrane (2,000 RPM cycle at 3 minutes) over the lesion and suture (Figure 3). In 10 days she had total repair of the region's soft tissue. She has been under control for over a year, with no recurrence of the injury.

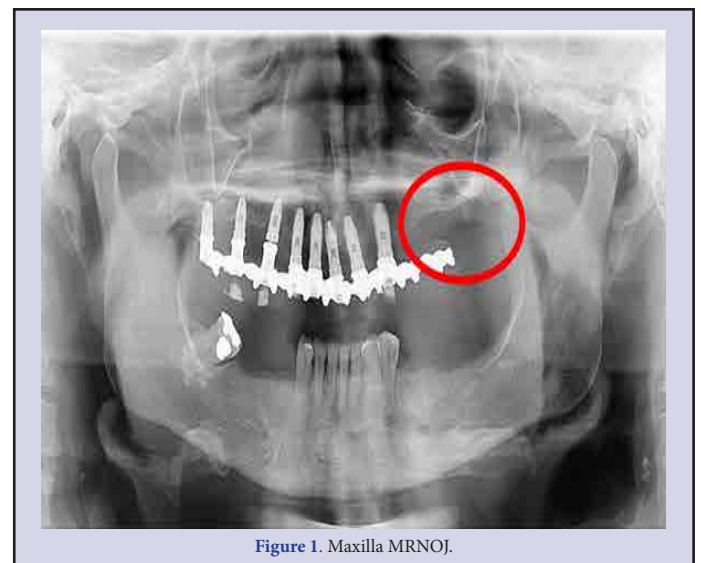


Figure 1. Maxilla MRONJ.



Figure 2. Bone fragment of 12 mm.



Figure 3. PRF membrane.

Case 2

Female patient, 75 years old, denies smoking and drinking, used bisphosphonate for 10 years to treat breast cancer. She was in consultation with a prosthodontist, and during the removal of a fixed maxillary prosthesis, tooth 15 was accidentally extracted, along with the prosthesis, due to the extreme mobility. The socket was sutured and treated as a conventional extraction. The patient returned after a few days complaining of osteitis and underwent a curettage + suture procedure. She developed suppurative infection in the region, and antibiotic therapy was introduced. After more unsuccessful attempts at local treatment of the socket, the patient was referred to a maxillofacial surgeon.

A tomographic examination was performed where osteolytic lesions could be seen in the right maxillary region (Figures 4 and 5), which, together with the anamnesis, was suggestive of MRONJ. She had local suppuration including drainage to the maxillary sinus.

The patient underwent surgical cleaning of the region under local anesthesia plus topical medication based on paste containing tetracycline 500mg + lactoferrin (blue^m, Netherlands) in the proportion 1:1. Patient returned once a week, and the medication was changed. After total control of purulent secretion and pain, in three sessions, with tetracycline/lactoferrin paste substitutions, it was decided to perform the region's sequestrectomy.

About five months after the start of local treatment (Figure 6), the patient underwent sequestrectomy employing piezosurgery, with abundant irrigation. The region was covered with two membranes of Fibrin rich in Platelets (PRF) (3000 RPM cycle at 14 minutes) and flap using cheek fat + resorbable collagen membrane (Collatape[®], Zimmer Biomet Dental, Switzerland). The suture was performed using a split-flap and simple sutures. The surgery was performed under local anesthesia + sedation using a 15mg midazolam tablet, one hour before surgery.

Postoperatively, the patient was instructed to use blue^m oral gel under the wound. Three days after surgical cleaning, she started treatment using oxygen therapy through a hyperbaric chamber; 20 sessions every two days.

More than four months after the operation, the patient has no clinical recurrence of the lesion. On tomographic examination, the lesion heals completely, without fenestration to the maxillary sinus (Figure 7).



Figure 4. Initial CT of the maxillary injury.



Figure 5. CT scans where the lesion can be seen.

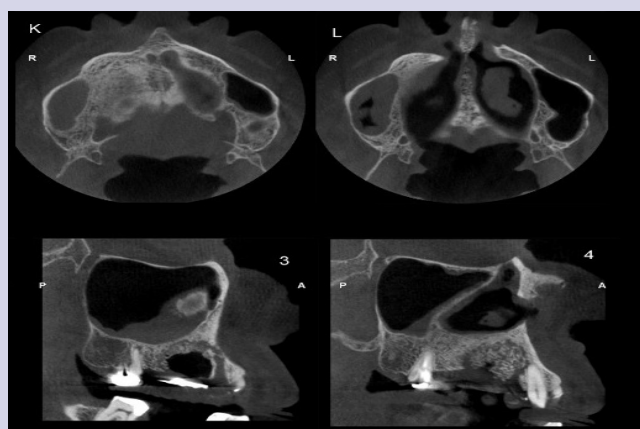


Figure 6. CT showing maxillary MRONJ five months after the start of treatment.

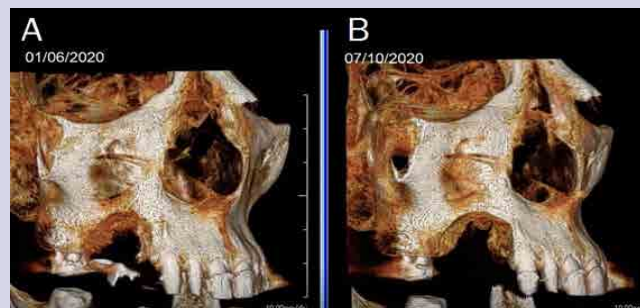


Figure 7. Comparative tomographic examination of the beginning (A) and end (B) of osteonecrosis treatment.

Discussion

MRONJ can have several etiologies, but those caused by medication, specifically bisphosphonates, are becoming very common [2], especially in patients who use them for a more extended period [3]. As it is a challenging pathology, many protocols and sequences of treatments have been created and published since the alert made in 2003 [1], and there is already a report in the literature of MRONJ due to high doses of other drugs such as simvastatin [4]. The time to start treatment is an essential factor for success because wounds that have some delay in repair generate an increase in the number of neutrophils and macrophages in the region, resulting in a chronic wound that does not heal [5].

Due to the large number of patients with MRONJ, some authors have created a care protocol related to the stage in which osteonecrosis is [6-8]. One of the most used protocols in treating more aggressive osteonecrosis includes sequestrectomy, antibiotic therapy and surgical wound management [2, 3]. Although surgical treatment is a proposal adopted by many, there is still no consensus in the literature [2]. Any way of protecting the surgical wound in an osteonecrosis region and speeding up the repair process is very welcome. Surgical wound management is the operative time with more variables in the literature, each with its advantages. Among the possibilities, bovine lactoferrin [2], Platelet Rich-Fibrin (PRF) [9], morphogenetic protein [10], teriparatide [11, 12] can be mentioned.

Bovine lactoferrin is a natural glycoprotein with a crucial anti-inflammatory activity, without adverse effects. The foam blue[®]m (blue[®]m, Netherlands) has lactoferrin as one of its ingredients. It stimulates migration and proliferation of fibroblasts and keratinocytes, which are fundamental for the reepithelization of the wound, in addition to bactericide [2], this is the only paper found that relates the use of lactoferrin in MRONJ. Lactoferrin has an essential decrease in biofilm formation [13].

Tetracycline is a broad-spectrum antibiotic that has efficacy against both Gram-positive and Gram-negative bacteria, being one of the few antibiotics that has an efficient topical action, both on the skin and in the oral region [14], being even superior to povidone-iodine gel in the total reduction of bacteria and against methicillin-resistant *Staphylococcus aureus* [15].

Association of these two drugs, lactoferrin and tetracycline, showed clinical synergy in the treatment of infection in MRONJ cases, since in addition to the migration and cell proliferation caused by lactoferrin, we have an essential bactericidal effect of both drugs. This synergy between lactoferrin and some antibiotics, specially ampicillin, oxytetracycline, streptomycin [16], and penicillin [17], was reported. No article was found in the literature reporting the paste's use containing lactoferrin + tetracycline in MRONJ treatment.

Conclusion

MRONJ is a pathology that does not have a secure treatment protocol and the clinical condition and the response to the initial treatment are the guides for a future surgical intervention. The protection of the affected area presents an essential factor in the resolution of osteonecrosis. The paste associating tetracycline + lactoferrin proved to be efficient as a covering material for the surgical wound, protecting it mechanically and accelerating the repair of the region and showing a synergistic effect.

Acknowledgments

Funding: This article was not supported by any grant.

Competing interests: The authors have no conflicts of interest to disclose.

Ethical approval: All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013.

Informed consent: Written informed consent was obtained from patient guardian included in the study to use images and records for publication.

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