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# Teeth extraction protocol in high-risk medication related osteonecrosis of the jaw patients

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**Abstract :**

Tooth extraction in patients treated with intravenous bisphosphonates (BPs) for oncologic indications is a well known trigger factor for Medication-related Osteonecrosis of the Jaw (MRONJ) developpement

A clinical prospective study is conducted to acess the efficency of a teeth extraction protocol in preventing MRONJ in high risk patients.

Patients and Methods : A clinical study was conducted in the Unit of Oral Medicine, Oral Pathology of the university Hospital Farhat Hached, Sousse, Tunisia. A total of 11 patients treated with intravenous BPs for cancer bone metastasis and multiple myeloma, requiring dental extractions of nontreatable teeth, were included in this study.

Results : We performed 14 extractions in 11 patients treated with intravenous bisphosphonates, mainly zoledronate. Two patients had signs of MRONJ following tooth extractions.

Conclusion : The proposed preventive protocol seems to reduce the risk of BRONJ after extraction in a group of patients treated with intravenous bisphosphonates, however other factors may be involved especially : site of the extraction and the bisphosphonate' cumulative dose.

Dental screening before initiating any type of ONJ-related medications can significantly decrease the MRONJ risk . Those high risk patients should also be informed about the benefits of prophylactic dental care, they should undergo dental screening through a clinical and radiographic assessment to eliminate ongoing acute infections and prevent possible future occurrences.

**Introduction :**

Medication-related osteonecrosis of the jaw (MRONJ) is a serious complication that affects the life quality of patients undergoing intravenous bisphosphonates and produces significant morbidity [1,2,3].

It is defined as an intraoral exposed bone with or without signs of infection that persists for a minimum period of 8 weeks, occuring in patients who are under current or previous treatment with BPs or other anti-resorbing drugs, without a history of the head and neck radiotherapy [4,5].

The aim of this study was to acess the efficacy of a teeth extraction protocol in preventing Medication-related Osteonecrosis of the Jaw (MRONJ) in high risk patient.

**Patients and Methods :**

A total of 11 patients treated with intravenous BPs and requiring extraction of nonsalvageable teeth were referred to the Unit of Oral Medicine, Oral Pathology of the university Hospital Farhat Hached, Sousse, Tunisia, from 2018 to 2020, were included. All Of the patients were treated with intravenous BPs for metastatic breast cancer and multiple myeloma. All the patients were informed about individual risk of MRONJ occurrence after dental extraction and were given the option to undergo the extraction via the atraumatic technique.

The inclusion criteria were : Patients undergoing or with a history of administration of intravenous bisphosphonates (zaledronic acid 4 mg) for metastatic breast cancer and multiple myeloma with at least 6 injections administered at the time of tooth extraction.

The non inclusion criteria were : Patients with a history of head and neck radiotherapy, patients who have received oral bihosphonates or intravenous bisphosphonates for osteoporosis, patients with coagulation disorders or patients on medications that affect blood clotting (anticoagulant or platelet inhibitors)

Teeth extraction protocol :

when no conservative dental treatment would have been reliable , tooth extraction was performed by oral sugery residents respecting the following protocol :

-Peri-operative dental scaling and polishing and antimicrobial rinsing with chlorhexidine mouthwash 0.12- 0.2%.

-Two days before the tooth extraction, the patients started to take 1 g of amoxicillin 2 to 3 times per day in combination with metronidazole (500 mg, 2 times per day) and this was continued till the mucosal healing, approximately for two weeks. In case of allergy to penicillin, erythromycin (600 mg, 3 times per day), clindamycin (600 mg, 3 times per day) or ciprofloxacin (500 mg, 2 times per day) were prescribed.

-Before starting the tooth extraction procedure, a blood sample of the patient was collected in sterile tubes, anticoagulent free. The sample was centrifuged at 3000 rpm for 10 minutes to get an autologous platelet rich fibrin (PRF) clot.

-After intra-oral local anesthesia via tissue infiltration (2% mepivacaine mg/ml + 1:100,000 adrenalin), the tooth removal was performed with the least traumatic extraction technique and preferably one tooth at a time or a sextant by-sextant approach. If obvious sharp socket wall margins or inter-radicular bone are observed following the procedure, these should be reduced selectively without lifting the periosteum from the bone.

-The extraction socket was irrigated with betadine and physiological serum, and well curetted to remove all granulation and infected tissues

-An autologous platelet-rich fibrin (PRF) clot was placed in the extraction socket which allows obtaining a hermetic closure of the post-extractive surgical site without the need of mucoperiosteal flaps or periosteal releasing incisions.

-Post-operative chlorhexidine mouthwash was also be used for 10 days.

-Patients were evaluated after 7 days, 2 weeks, 4weeks, 3 months, 6 months, 1 year after tooth extraction.

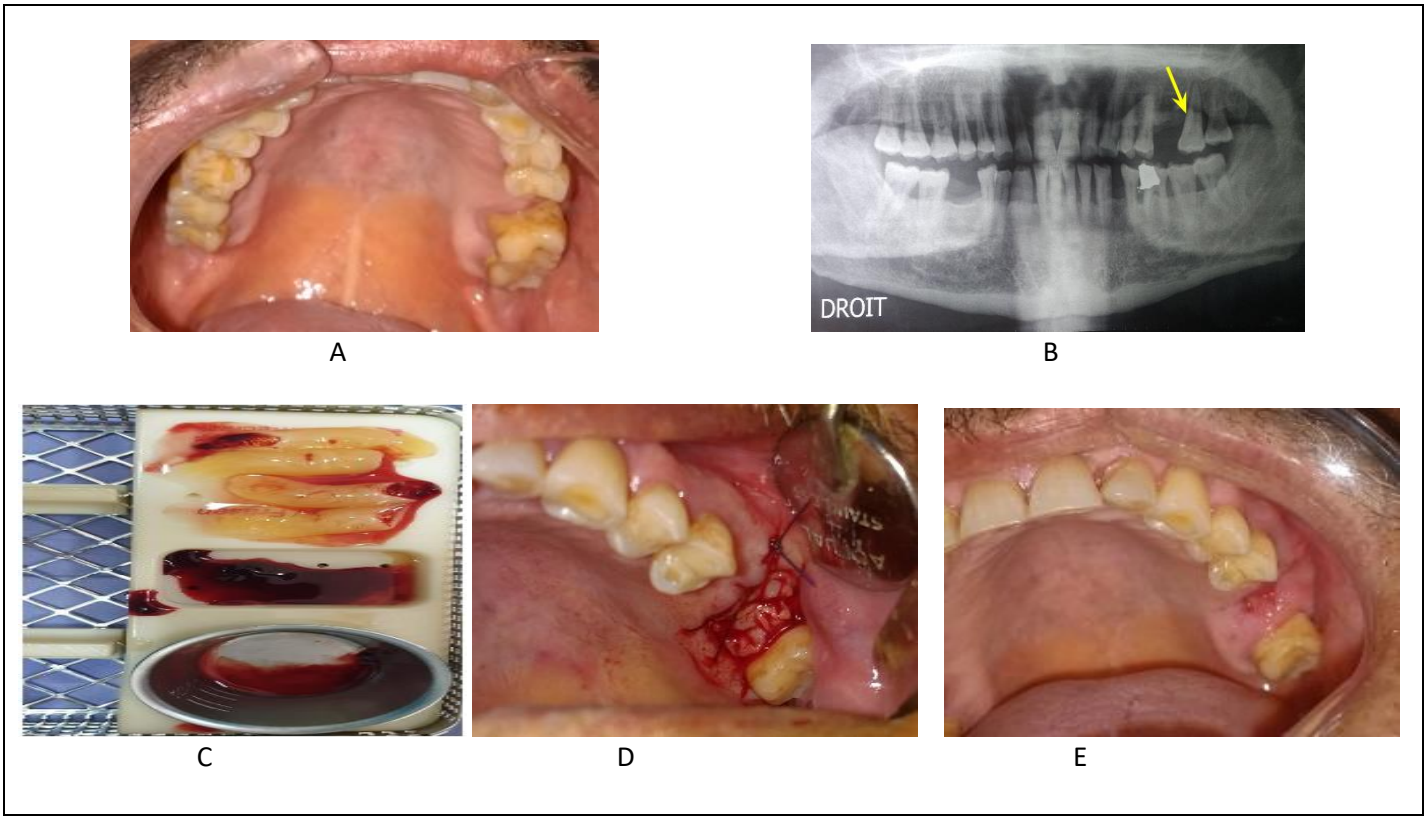


Figure 1: Teeth extraction according to the protocol in a 65 year old patient with multiple myeloma, undergoing iv bisphosphonates.

A: Initial intra-oral clinical view shows a mobility and a periodontal recession of the 27, B :panoramic radiograph, C : Platelet-rich fibrin (PRF) obtained from the patient's blood sample, D : Placement of the PRF in order to cover the post-extraction alveolar socket. The edges of the membrane were placed under the mucosal flaps and sutured to the surrounding gingiva, E : clinical view shows wound healing after 15 days.

Figure 2 : Bone exposure after extraction of the 38 in a 56 year old female patient with bone metastasis of breast cancer.

**Resultats :**

11 patients : 8 women and 3 men, with a mean age of 65.27 ± 7.22 years (range, 53-76 years) undergoing bisphosphonates: zaledronic acid, for cancer bone metastasis: n =8, and multiple myeloma : n= 3. The mean number of injections was 9.27 (range, 1-25 injections)

A total of 14 teeth extraction were included: 9 molars (4mandibular and 5 maxillary), 4 premolars (2 mandibular and 2 maxillary), and 1 mandibular canina.

| | max | mand |
|---|---|---|
| Simple | 7 | 5 |
| surgical | 0 | 2 |

**Tableau 1 : teeth extraction distribution according to the type of extraction**

| Extraction etiology | Number of teeth |
|---|---|
| Periodontal disease | 5 |
| tooth decay | 5 |
| tooth fracture | 1 |

**Tableau 2 : teeth extraction distribution according to the etiology**

For n=9 patients, the complete re-epithelization of the wound was observed without signs of infection.

2 patients had signs of MRONJ after mandibular molar extractions : 47, 38. One patient had exposed bone one week following the teeth extraction and persisted after 2 months. The other patient had a mucosal fistula that probe to bone in the extraction site 3 months later.

**Discussion :**

Teeth extraction in patients undergoing intravenous bisphsphonates for oncologic indications has been always described as the major trigger factor for MRONJ.

In fact, there is a risk of spontaneous MRONJ occurring in any patient on bisphosphonates. Based on Australian data [6], a dental extraction can increase this risk [7].

The mechanism underlying the onset of MRONJ after tooth extraction may involve trauma to the alveolar bone during the procedure as well as complications arising during recovery [8,9,10].

The risk of developing MRONJ depends on the drug, its route of administration, dosage and the duration of exposure. More than 90% of reported cases are related to the intravenous use of zoledronic or pamidronic acid. Zoledronate, in particular, is the most agent associated with osteonecrosis of the jaw, with a risk of 1% in the first year of intake to reach 21% after 3 years from the first administration. Patients taking other types of BPs, such as alendronate per os and at lower dosage for osteoporosis, however, had a significally lower risque but not totally exempted. [7]

Other than the risk of MRONJ developped by Drug-related factors, such as the cumulative dose, duration, route of administration, added risk factors may be involved.

The local risk factors include poor oral hygiene, periodontitis, thin mucosal coverage, dentoalveolar surgery, bony tori, lower mandibular molars : Two thirds of BONJ cases have been reported in the mandible especially for mandibular molar extractions just like in our two cases.

The general risk factors include concomitant therapies [7] : corticosteroids, other immunosuppressors and chemotherapy agent, smoking, extreme of age, gender : It has been proposed that females are more at risk than males of developing MRONJ [11]. In fact, Women are prescribed bisphosphonates more commonly than men especially for breast cancer bone metastasis, thus, a higher prevalence of MRONJ in women would be expected.

As MRONJ is often refractory to treatment, prevention is fondamental by regular dental check-ups [12].

Before starting BPs, the irremediable teeth should be extracted and dental infection foci should be treated, in order to avoid the need of tooth extraction once the therapy has been started.

Before teeth extraction, endodontics should be considered as an option. In symptomatic endodontically treated teeth, endodontic retreatment should be considered. Coronectomy should also be considered for non-restorable teeth, they can be kept in the dental arch as retained roots endodontically treated. In fact, each case should be treated on its own merits.

In some cases, where the risk is very high, avoidance or delaying an extraction could be tolerable [13]. Nevertheless, the unecessary delay or avoidance of appropriate treatment can not be supported [7].

The use of PRF autologous membranes has a lot of benefits, it stimulates the healing process of post-extraction sites by promoting osteogenesis and re-epithelization and improves post-operative pain [14,15,16]. It is a very innovative alternative of traditional surgical extraction that involve mucoperiosteal flaps and periosteal releases in order to obtain a primary closure of the surgical wound.

In other studies, based on culture and sensitivity tests, the most common pathogens implicated in BRONJ are considered to be Actinomyces, Eikenella and Moraxella species. Hence, penicillin V (phenoxymethylpenicillin) 500 mg four times per day is a suitable antibacterial drug. In penicillin allergic patients, doxycycline 100 mg once daily is suitable. Metronidazole 200 mg three times per day has proven its efficiency in patients refractory to the above antibiotics. Considering the target pathogens, it should be noted that amoxycillin and clindamycin are not first line drugs for prophylaxis in this condition [7,17,18].

**Conclusion :**

Despite the methodologic limitations of our study, the proposed preventive protocol appears to reduce the risk of MRONJ after tooth extraction in a group of high risk patients treated with intravenous bisphosphonates.

The complications associated with dental extractions in those patients can be minimized by following simple yet precise rules and with cooperation of the patient. However, further attention should be taken when mandibular posterior teeth extraction is indicated as this presents a high risk local factor.

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