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Case Report

Clinical Protocol for Patients with a History of use of Bisphosphonates

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Abstract

Bisphosphonates are a group medications that have been used for the last decades for the treatment of conditions that are characterized by bone loss or destruction, cancer, menopause and non-malignant bone diseases, which is why it is very important to make a broad and correct medical history to avoid the possible complications in the healing phase of dental surgical treatments. When treating a patient with a history of this drug we should know the pharmacokinetics and pharmacodynamics to be able to plan the pre, trans and postoperative treatment of patients mainly subject to dental extractions, which is why currently this type of patients can be classified according to the results of the laboratory test of the C-Telopeptide protein. Once the patient's risk has been determined according to the results of this test, an effective and safe treatment plan can be started for the patient in which the necessary precautions are taken to not develop a mandibular or maxillary osteonecrosis. We present a case of a patient with a history of bisphosphonates where the treatment is done according to the current guidelines for treating this type of patients.

Keywords: *Bisphosphonates; C-Telopeptide; Osteonecrosis; Osteoporosis; Extraction; Cancer*

Introduction

Bisphosphonates are drugs used to prevent the loss of bone mass, care for malignant bone diseases involving bone (multiple myeloma, hypercalcemia), bone metastases from cancer (prostate, breast, lung and kidney) and non-malignant bone diseases (Osteoporosis, Piaget's disease) [1-3].

They are commonly administered to patients suffering from osteoporosis, which is the most common metabolic bone disease in humans [6] where the bones become more fragile, weak and prone to fracture [7].

Bisphosphonates are synthetic analogue chemicals to pyrophosphate, accumulate in areas of bone formation making them more resistant to bone destruction by osteoclasts and regulating the transformation of osteoblasts to osteoclasts [1,4]. They also promote osteoclastic apoptosis and have anti-tumor action reducing angiogenesis [1,4,5], are not metabolized and this causes that high concentrations in the bone are maintained for a long period inactivating the osteoclasts [9].

These medications have many benefits but also have adverse effects on the oral cavity such as Mandibular Osteonecrosis (ONJ), which causes bone death of the affected or treated area [4], frequently caused after treatments involving mandibular or maxillary bone manipulation such as tooth extractions, implant placement, periodontal surgeries or maxillofacial surgeries.

Generally bisphosphonates are administered orally in osteoporosis and bone deficiencies (Daily or weekly), but when there is a malignant disease it is administered intravenously (Annually or monthly and are 30 or 40 times more potent than oral). The most used are Etidronate, Risendronate, Alendronate, Tiludronate, Ibandronate, and Zoledronic acid [1,8].

It is extremely important to detect the use of these medications in the clinical history. If the patient is going to start a treatment with bisphosphonates, an oral conditioning should be carried out, but trying to avoid treatments involving bone. If an invasive treatment involving bone is necessary, it is very important to work in an interdisciplinary way with a maxillofacial surgeon. diagnosed and planned efficiently [7].

The main adverse effect of the use of these drugs is osteonecrosis of the jaw or maxilla (ONJ) reported for the first time in 2003 by Marx and Ruggiero [9], osteonecrosis is bone death caused by lack of blood supply, which normally occurs in the shoulder, hip and jaw [7]. According to a study carried out by Woo., *et al.* [8] in which 386 cases were reviewed, it was demonstrated that osteonecrosis is more frequent in the lower jaw (65%) than in the maxilla (26%), but can simultaneously affect the maxilla and mandible (9%). Approximately one third of cases are pain-free and are more common in women [1]. There are extraoral risk factors of ONJ such as corticosteroid therapy, obesity and diabetes, tobacco and alcohol consumption drugs, older people, low levels of hemoglobin, and renal dialysis [10]. The most common intraoral predisposing conditions are poor oral hygiene, periodontitis, tooth decay, dental abscesses, failed root canals and bone exostosis [9].

The clinical definition according to AAOMS (American Association of Oral Maxillofacial Surgeons) of the ONM is "A condition of exposed necrotic bone in the jaw or maxilla that persists for more than 8 weeks in a patient who is taking or has taken a bisphosphonate and has not has a history of therapeutic radiation in the jaws" [10]. The most common clinical presentation is bone exposed with pain, although it may be asymptomatic for months until there is infection or trauma, this progresses until there is some bone sequestration. Radiographically, initial enlargement of the periodontal ligament and sclerosis of the lamina dura is observed, with time, mottled bone areas and formation of bone sequestration [9].

It has been seen that the prevalence of ONJ related to oral bisphosphonate intake is low (between 0.01% and 0.06%), while the incidence of ONJ in patients with malignancies receiving intravenous bisphosphonates is higher (3% to 6%) [13]. Also according to most authors, between 50% and 60% of all cases of ONJ occur after dental extraction or prolonged use of methamphetamines [20] and drugs.

Usually in the ONM lesions, atypical bacteria of the normal oral flora have been found in control subjects [21]. In addition, histopathological reports of ONM lesions have found active colonies of Actinomyces and inflammatory cells on exposed bone surfaces [22,23].

The clinical precautions we need to consider when treating patients who are receiving bisphosphonate therapy should try to avoid treatments that involve bone manipulation and periosteal detachment, non-restorable teeth should be removed from the crown and endodontic treatment in the remaining roots, implants should be avoided, and only when there is no other treatment option should extraction be done or procedures involving bone [9].

In treatment procedures where the only option is to modify or remove bone, according to the opinion of the experts and observational studies, the clinical protocol includes using a 0.12% gluconate chlorhexidine rinse one week before the surgical event and one week after [9]. If the patient's systemic condition allows it, the bisphosphonates must be removed 3 months before the event and she restarts taking the bisphosphonates 3 months after the surgical event, also a broad spectrum antibiotic should be ingested 7 days before and 7 days after the surgical event.

Recently a new test has been used to help determine a risk of ONJ in patients treated with bisphosphonates where we observe the quantity of a biochemical marker of bone remodeling "C-terminal Telopeptide of Type 1 Collagen" (CTX), since a correlation was found due to the fact that CTX levels begin to decrease when bisphosphonates are started to be ingested [17], according to Kunchur and colleagues [15] studies show that after 6 weeks of bisphosphonate use the amount of CTX decreases by 60%, it was also shown that when taking bisphosphonates for 6 months the CTX values increased from a mean of 72.9 pg/ml to a mean of 228 pg/ml [16].

Because of this a laboratory test is performed to observe the levels of CTX in the body. Once the test is performed and with the results obtained according to Marx and colleagues [16], the patient is classified as low, moderate or high risk depending on their CTX levels (See Table 1).

C-Telopeptide Protein Values (pg/ml)	Risk
< 100	High
100 -150	Moderate
> 150	Low

Table 1: *CTX Values and Risk.*

There are authors who do not agree with the recommendations of Marx and colleagues. In fact, the working group of ASBMR (American Society for Bone and Mineral Research) [16], published a document that clarified that serum CTX values could not be taken as a gold standard to know if an ONM would present itself or not [18].

The trans-operative care that must be taken into account are: perform the treatment in the least invasive way, an incision with ideal characteristics, avoid excessive removal of periosteum, avoid the use of surgical motors for bone removal due to the excessive heat they produce, removal of affected teeth efficiently and perform a good suture technique if needed. The Post-operative care is to continue with antibiotic therapy, gluconate chlorhexidine rinses, clinical and radiographic monitoring weekly, monthly and every four months.

In case of mandibular or maxillary osteonecrosis, the treatment goals of this problem should include patient education, pain control, secondary infection control, prevention of extension of lesions and development of new areas of pain. necrosis. There is currently an identification of stages of the lesion (Table 2) [10] that guides the treatment options [9].

Stages of Mandibular or Maxillary Osteonecrosis	Treatment
Stage 0 (At risk) - No bone or pain-free exposure	Conservative treatment of periodontal symptoms, with broad spectrum antibiotics, topical antiseptics and analgesics.
Stage 1 - Exposed bone, painless and without infection	Surgical intervention is not indicated, but strict oral hygiene, broad-spectrum antimicrobial treatment, antiseptic rinses and, if necessary, analgesics.
Stage 2 - Exposed bone with infection and pain	Antibiotic therapy, strict oral hygiene, antimicrobial rinses. The antibiotics of choice are penicillins and metronidazole, clindamycin and erythromycin for those allergic to penicillins. Surgical treatment can be established by eliminating necrotic tissue and surgical washes.
Stage 3 - Pathological fracture, large amount of necrotic bone, no response to antibiotics	Debridement of the infected area is performed, surgical resection in conjunction with antibiotic therapy, if there are bone sequestrations they must be removed without exposing healthy bone.

Table 2: *Treatment according to ONJ actual stage.*

Clinical Case

We present a female patient with 64 years of age, ASA II classification for hypertension, hypothyroidism, osteoarthritis and history of treatment with oral bisphosphonates (Risendronate of 35 mg every 7 days) for 3 years due to osteoporosis. The admission protocol to the faculty is carried out, which consists of a clinical history, panoramic radiography (Figure 1), periapical radiographs, intra and extraoral photographs taken, study models and completion of an integral treatment plan.

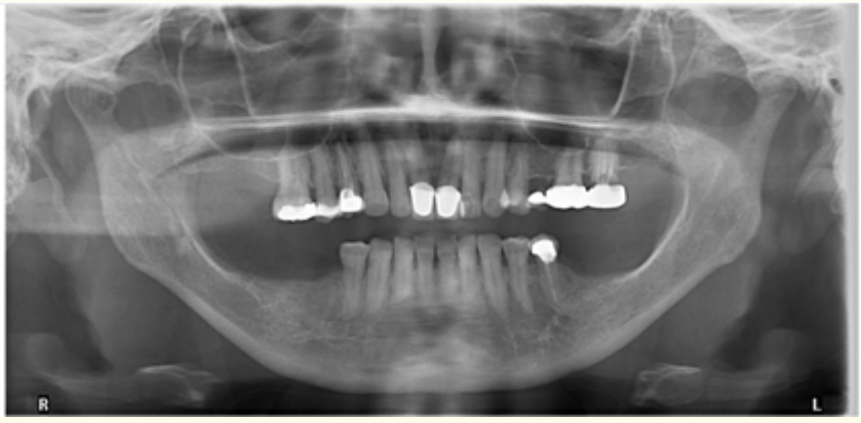

Figure 1: *Panoramic Radiography.*

The patient's current oral situation and the comprehensive treatment plan are explained to the patient. In the treatment plan, the patient was explained all the risks, precautions and care that should be taken into account due to her history of bisphosphonate intake. The necessary interconsultations were made with the Periodontics and Endodontics department, and the treatment plan included intra-alveolar extraction of tooth #27 due to coronary fracture and lack of splint effect, so the departments of Periodontics, Endodontics and Prosthodontics indicated the extraction (Figure 2). The crown and endodontic change of tooth #5 would also be performed, but when the removal of the crown was done, extensive caries was found and when the removal was finished there was no ferrule effect, so the departments of Periodontics, Endodontics and Prosthodontics suggested the extraction (Figure 3). In addition, two coronary lengthens were performed, mesial of # 16 and palatal of # 24.

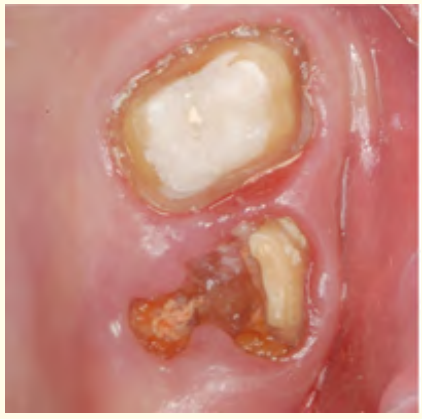

Figure 2: *Pre-Operative Situation of # 27.*

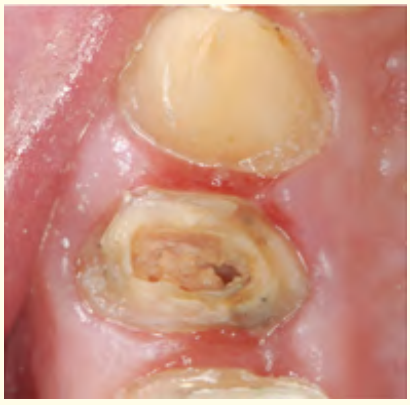

Figure 3: *Pre-Operative Situation of # 14.*

Due to this situation, interconsultation was requested with his doctor, suspending the intake 8 months before the surgical event indicated by the maxillofacial surgeon for his dental extractions. Prior to the surgical event a Hematic Biometry was requested, C-Telopeptide protein test, once the results were obtained normal levels were observed in the blood count, figures of 220 pg/ml and according to Marx and Colleagues [13]. it was determined that patient It was low risk, due to this the surgery was scheduled. As a pre-operative treatment, Clindamycin 300 mg was given every 8 hours 5 days before the event, rinses of 0.12% Chlorhexidine Gluconate for one week.

Blood pressure was taken with figures of 110/90 mmHg, anesthetized with supraperiosteal technique and palatine with 2 cartridges of articaine with 1/200,000 epinephrine. Dislocation was performed in # 14 with a straight elevator and extraction with forceps 150 (Figure 4 and 5).

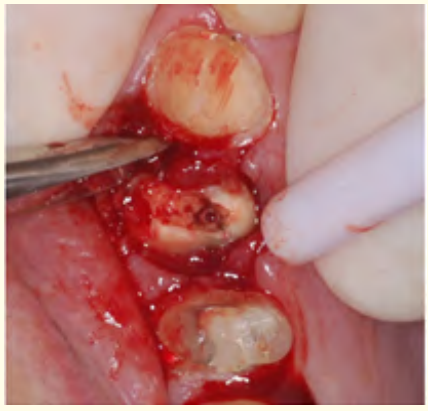

Figure 4: *Luxation with Straight Elevator of # 14.*

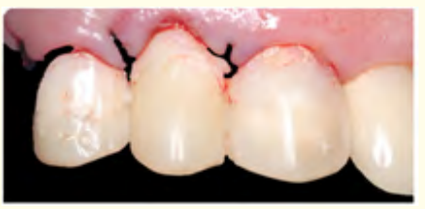

Figure 5: *Ovoid Pontic of # 14.*

For the extraction of # 27, it was decided not to perform a flap or osteotomy to try to perform the least atraumatic extraction possible and that it does not involve removal of periosteum, due to this, only odontosection was performed (Figure 6) and dislocation with straight elevator and forceps extraction 150.

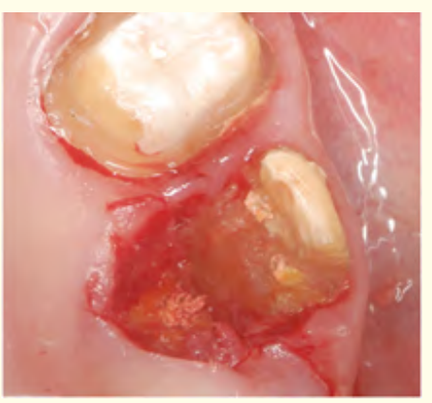

Figure 6: *Odontosection of # 27.*

For coronary lengthening, she was anesthetized with supraperiosteal technique with 2 cartridges of articaine with 1/200,000 epinephrine. Full thickness incisions are made with leaf No. 15, osteotomy of #16 and 24 is performed with diamond ball bur and irrigation (Figure 7), 4 silk sutures were placed 000 (Figure 8). Post-operative indications were given, Clindamycin 300 mg every 8 hours for one more week, Metamizole Sodium 500 mg every 8 hours for 5 days, Diclofenac 100 mg every 12 hours for 3 days, rinses of Chlorhexidine Gluconate 0.12% for two more weeks and review in a week for removal of sutures.

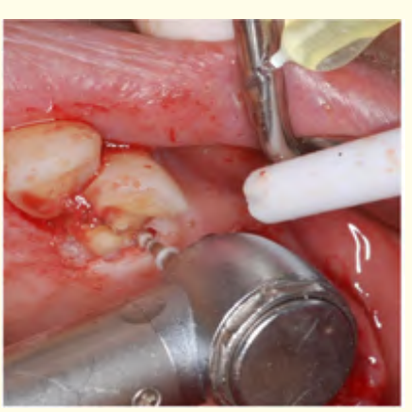

Figure 7: *Coronary lengthening of # 24.*

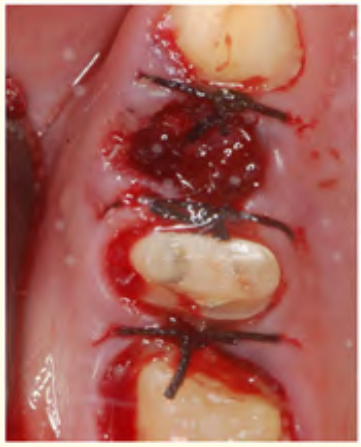

Figure 8: *Silk Sutures 000.*

In the recall appointments the evolution of the alveoli was evaluated, observing that there was no pain, suppuration and the evolution of the clot. Weekly reviews were carried out during the first month to monitor alveolus evolution, and subsequently monthly and quarterly reviews (Figures 9 to 14). While it was being evaluated, the treatment plan was continued, having a favorable evolution, without pain, without bone exposure, without suppuration and the original treatment plan was completed.

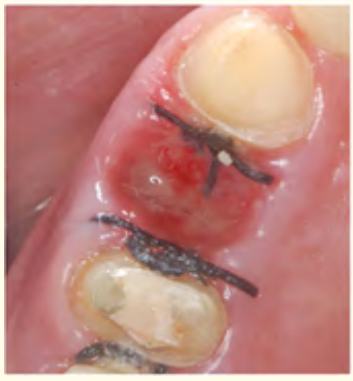

Figure 9: *# 14 area at 7 days with ovoid pontic.*

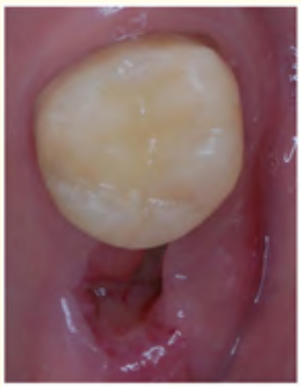

Figure 10: *Area of # 27 at 7 days.*

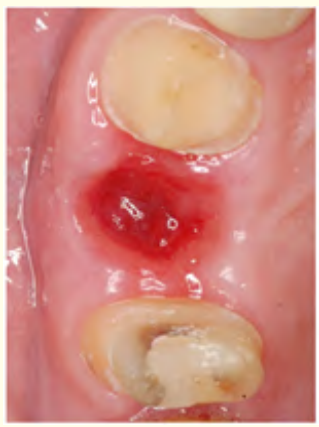

Figure 11: *# 14 area at 15 days, with ovoid pontic.*

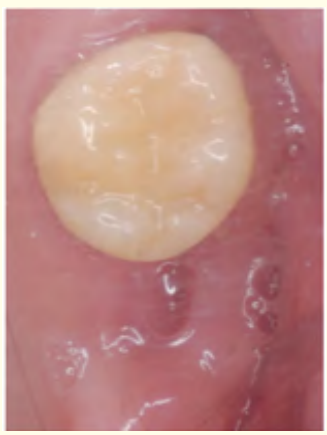

Figure 12: *Area of # 27 at 15 days.*

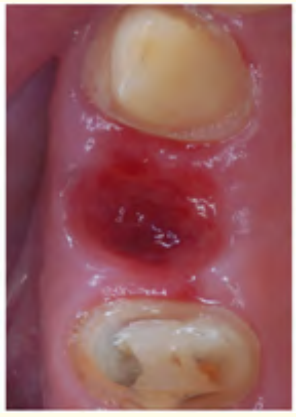

Figure 13: *Area of # 14 per month, with ovoid pontic.*

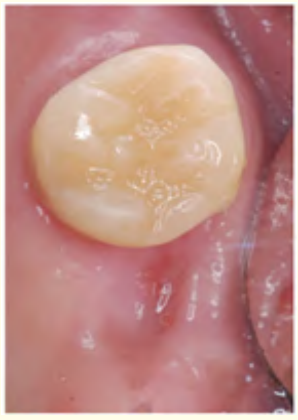

Figure 14: *Area of # 27 per month.*

Discussion

Although the information on the effects of bisphosphonate consumption is greater every day, there are still cases of osteonecrosis of the jaw (ONJ), some spontaneous cases due to periodontal disease, but others secondary to bone manipulation in dental surgical treatments or a minor trauma [19]. Although the best way to avoid osteonecrosis in these patients is not to perform extractions or surgical treatments, however, in some cases patients require the performance of these treatments due to the need to avoid a more severe infectious process or to return function and aesthetics. In our case, the realization of said surgical treatments were necessary to be able to perform an appropriate prosthetic treatment. It is important to communicate with patients once they decide to submit them to these treatments, always assess the risk against the benefit, that the patient and family members know the potential complications and treatment options in case they arise. The C-Telopeptide protein test (CTX) is a support to be able to measure the risk, however it is not definitive and it does not reduce the risk of developing the ONJ, therefore other factors, such as the systemic condition, hygiene, play an important role, habits, preoperative preparation, an adequate surgical technique always as atraumatic as possible and follow-up in order to avoid that if it were to present the ONJ, this could increase the clinical stage.

No less important is the communication with the doctor that indicates the treatment with bisphosphonates, usually when the indication is for osteoporosis there is usually no inconvenience in the suspension, but when dealing with other types of injuries, especially due to oncological treatments, the possibility should be considered. not to remove them if the treating doctor so indicates, performing alternative activities to minimize the risks. The present article has the objective of showing that even in patients who consume bisphosphonates extractions may be performed as long as we adhere to protocols in preoperative management evaluating extraoral risk factors, requesting preoperative cabinet studies such as complete blood count, C-Telopeptide test, the trans-operative surgical measures already mentioned and the follow-up until the tissues demonstrate a normal healing process.

Conclusions

Based on the existing information on protocols for treating a patient with history of bisphosphonates consumption we can conclude that we need work in conjunction with specialists and general doctors to follow a strict pre, trans and post operatory protocol every time we treat this type of patients and if you want to be more confident you can use a C-Telopeptide protein test as support to be able to measure a risk for your patient however it is not definitive and it does not reduce the risk of developing the ONJ.

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