

Osteonecrosis of the Jaw in Patients undergoing Long-Term Treatment with Bisphosphonates: Incidence and Associated Characteristics

Silvana Noemi Picardo* and Eduardo Alberto Rey

Universidad de Buenos Aires CABA, Buenos Aires, Argentina

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*For Correspondence

Silvana Noemi Picardo, Universidad de Buenos Aires CABA, Buenos Aires, Argentina, Tel: +541165666424.

E-mail: silvana_picardo@hotmail.com

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ABSTRACT

Introduction: Bisphosphonates (BPs) provide a well-known, favorable therapeutic action on the bony tissue of patients receiving these drugs.

Aim: The aim of this study is to link long-term treatment with nitrogenous bisphosphonates to ONJBPs (osteonecrosis of the jaw caused by bisphosphonates), the most frequently encountered side effect in jaws. In 2007 the AAOMS defined the concept of ONJBP as "an exposed necrotic bone area in the mouth present for over eight weeks in patients who have undergone long-term treatment with bisphosphonates and who have not received radiation therapy to the head and neck." Subsequently in 2009 the AAOMS defined 4 clinical stages (0 to 3) of ONJBPs.

Subjects and methods: Between January 2007 and December 2013 25,538 patients were referred to the Department of Maxillo-facial Surgery and Traumatology II of the School of Dentistry, University of Buenos Aires Argentina. All these patients underwent surgical dental treatment and the 1097 patients found to have healing dyscrasias were subsequently divided into three groups. All 1097 patients included in this study underwent semiological systemic clinical, dental, biochemical, histopathological studies as well as densitometry and X-ray imaging.

Results: Of the 25,538 patients evaluated, 0.33% were found to have ONJBP. Of the 1097 patients with healing dyscrasias, the incidence of ONJBP was 7.75%. Among the 270 patients who took BPs the incidence of ONJBPs was 31.5%. Clinical studies in Group 1 patients revealed mainly stage 1 and 2 disease. There were no significant differences in CTX levels for either of the two groups evaluated.

Conclusion: The results of the present study suggest a significant incidence of ONJBPs, especially when only individuals treated with BPs are included for the calculations. It is also clear that interaction among healthcare professionals is essential, since ONJBPs prevention is better than its treatment.

INTRODUCTION

Classification of the jaws and skull is similar to that of other bones in the body, but due to various homeostatic stimuli (ectodermal structures, teeth, mesodermal structures: muscles, eyeball, etc.), the biomechanical response is different ^[1,2]. BPs are anticatabolic drugs, mainly zoledronate, pamidronate, alendronate, ibandronate, risendronate (ZOL, PAM, ALE, IBA, RIS), used to reduce bone remodelling, preventing the loss of bone mass and thus reducing the risk of vertebral, non-vertebral and hip fractures by increasing bone mineral density ^[3].

Treatment with amino BPs might also prevent bone metastases. In vitro, BPs reduce cell migration, proliferation, and adhesion and also inhibit the activity of cytotoxic T lymphocytes ^[4].

In 2007 the AAOMS defined Osteonecrosis of the Jaw associated to the long-term treatment with (ONJBPs) as: "exposed necrotic bone area in the mouth lasting for over eight weeks, in the presence of long-term treatment with bisphosphonates and

absence of radiation therapy to the head and neck". This pathology is on the rise due to the use of more powerful BPs which remain longer in the bony microenvironment. In 2009 4 stages (0–3) of ONJBPs were defined based on clinical and radiological aspects of the osteonecrotic lesion [4]. A potentially logical theory explaining the development of osteonecrosis involves the suspension of angiogenesis, as BPs would inhibit the angiogenic growth factor (VEGF). But above all, ONJBPs are known to be chemical osteomyelites and from this it follows that treatment management is clinical conservative and not resection of the maxillary bone sequestrations [5]. Histologically, bone biopsy samples obtained from patients with ONJBPs show signs of osteomyelitis: cell detritus, bacterial colonies and inflammatory infiltrates. The presence of thinner than normal, necrotic sclerotic trabeculae is revealed, exhibiting a compartmentalized mosaic-like structure. This fact reflects an aspect similar to a bone with pagetoid features, unable to receive nutrients and with obvious signs of remodelling [6].

SUBJECTS AND METHODS

The subjects of the study were those patients referred by treating dentists and physicians to the Department of Maxillofacial Surgery and Traumatology II of the School of Dentistry, University of Buenos Aires. Patient participation was totally free of charge, voluntary and confidential. All the subjects signed an informed consent in the presence of a witness not linked to the Educational Department prior to their admission in the study.

Inclusion Criteria

Patients who underwent surgical-dental treatment and developed bone healing dyscrasia processes. Compliance with the principles of the Declaration of Helsinki was observed.

Exclusion Criteria

Patients who did not sign the informed consent; patients who had received radiation therapy to the head and/or neck or who presented systemic pathology that modified the normal physiology of bone tissue.

All the patients underwent dental surgery and were divided into: Group I patients treated with BPs with ONJ (n=85); Group II, patients treated with BPs without ONJ who exhibited anomalous healing, which remitted spontaneously (n=185); Group III: Patients not treated with BPs who exhibited anomalous healing, which remitted spontaneously (n=827).

All the patients included in the present study underwent systemic clinical studies (clinical signs assessed: exposed bone, inflammation, osteomyelitis, mucosal changes, tissue damage, sequestrations, facial redness, edema, halitosis, xerostomia, sialorrhoea, bruxism. neural signs and symptoms assessed: paresthesia, anesthesia, analgesia, neuralgia. Assessed clinical symptoms: hemorrhage, suppuration, mucosal fistula, cutaneous fistula, trismus, sinusitis, bucco-nasal communication, bucco-sinus communication, prosthesis disadaptation, fracture, dental movement, rizolysis, dental avulsion, adenopathy, fever, feverishness, hyperthermia, faintness, dysgeusia, ageusia, dysphagia, vomiting, pain, headaches, loss of appetite. Stomatologic lesions assessed: blisters, pustules, erythema, tumour, necrosis, ulcer, pseudomembrane fistula. Clinical dental examination: DMFT, O`Heary, Silness Loe, Moments of sugar, and bleeding index; imaging studies: periapical x-ray, panoramic x-ray, CAT.

Patients treated with BPs additionally underwent biochemical studies. Common practices: CBC, erythrocytation rate, uremia, uricemia, cholesterolemia, glycemia, complete blood clotting studies, and specific tests for bone and phospho-calcium metabolism including: calcemia, phosphatemia, calciuria, phosphaturia, creatininemia, creatininuria, bone resorption marker: serum CTX; ELISA (Nordic Bioscience); bone formation marker: FAO; colorimetric wheat-germ lectin precipitation assay, 25-hydroxy vitamin D assay (25 HOD): Diasorin (RIA) systemized at the Medical Osteopathy Service of Hospital de Clínicas José de San Martín School of Medicine, University of Buenos Aires; densitometry of the femoral neck and lumbar vertebrae L1–L4. According to the base pathology, an interconsultation with the treating physician was also requested. The biopsies were performed on patients with ONJBPs. Other patients with ONJBPs had histologic studies performed on bone samples remitted by spontaneous exfoliation of these at the FOUBA Pathologic Anatomy Service. Palliative pharmacologic therapy was prescribed in the presence of acute systemic signs and symptoms awaiting spontaneous sequestrectomy; according to the assessed clinical case the prescription consisted of antibiotics: Amoxicillin 500 mg+clavulanic acid 125 mg, Metronidazole 500 mg, Ciprofloxacin 500 mg; antiseptics: Chlorhexidine 0.12%, Povidone Iodine 10%, Rifamycine 0.05%; and painkillers: Ibuprofen 400 mg, Paracetamol 500 mg [7]. Post-surgical controls were performed at 1, 2, 4, 8, and 10 weeks and at any other time deemed necessary [8].

STATISTICAL ANALYSIS

Results were expressed either as the mean \pm standard deviation (SD) or as the mean and percentiles 25% 95%, according to the distribution of variables. The normality of these was assessed through the SHAPIRO-WILK TEST and variance homogeneity through the LEVENE TEST. Data with normal distribution were analysed using variance analysis (ANOVA) while asymmetrically distributed data were analysed using the KRUSKAL-WALLIS TEST for non-parametric data. The multiple comparison tests were applied in the difference among the various groups to determine among which groups there were significant differences. Statistical analyses were performed using the SPSS 19.0 program for Windows (SPSS, Inc. Chicago, IL). P value under 0.05 ($p < 0.05$) was considered significant.

RESULTS

Between January 2007 and December 2013 25,538 individuals (mean age: 55 ± 12 years) referred to our department for dental surgery were evaluated. A total of 1097 (663 female and 434 male, mean age 55.8 ± 12.3 years) presented bone healing dyscrasias; 270 (253 female and 17 male, mean age 62.4 ± 6.7 took BPs). Group I: 85 patients (78 female and 7 male, mean age 67.2 ± 9.1) Group II: 185 patients (175 female, 10 male, mean age 57.7 ± 12.0); Group III: 827 (410 female, 417 male, mean age 42.7 ± 18.0).

The incidence of ONJBPs among the 25,538 individuals assessed was 0.33% (69.69% osteoporotic, 30.31% oncologic). Of the 1097 patients who suffered healing dyscrasias the incidence was 7.75% (82.2% osteoporotic and 13.8% oncologic). Of the 270 patients who were taking BPs, the incidence was 31.5% (70.63% osteoporotic and 29.37% oncologic). ONJBP stages were as follows: stage 0: 6%; stage 1: 24.7%; stage 2: 36.4%; stage 3: 32.9%.

From the dental standpoint, patients from Groups I, II, and III presented cariogenic and periodontal risk: DMFT>13, 9; O'leary>20%; sugar moments>4; bleeding index: 1.

The evaluation of clinical signs and symptoms revealed cariogenic and periodontal risk in 84% of patients in Group III, followed by 8.2% in Group I and 7.8% in Group II; it was reversible in Groups I and II.

The etiology of the healing dyscrasias was dental extraction in 76.9% of the cases, followed by dental implants in 18.75% and root canal treatment in 1.65%. With regard to anatomic location, 62.3% of the dyscrasias were found in the lower jaw, 29.4% in the upper jaw and 8.3% in both jaws; this evaluation took into account the 3 groups.

An osteoporotic base pathology was revealed in 63.9% of the patients from Group II, 22.5% from Group I, and 13.6% from Group III. Of the oncologic patients in the study, 53.2% were Group I, 31.7% Group II, and 15.1% Group III (all untreated patients) (Table 1).

Table 1. Distribution of the oncologic base patients. Pathology in Groups I, II and III measured in n=x with respect to MM (Multiple Myeloma), Breast CA (carcinoma), Prostate CA, and Ovarian CA.

	MM	BREAST CA	PROSTATE CA	OVARIAN CA
GROUP I	n: 8	n: 13	n: 3	n: 1
GROUP II	n: 3	n: 5	n: 6	n: 1
GROUP III	n: 0	n: 2	n: 5	n: 0

In the evaluation of the 270 patients undergoing treatment with BPs, treatment duration of the osteoporotic patients in Group I was 20–240 months and 6–168 months in the cancer patients; in Group II treatment duration was 4–304 months in osteoporotic patients and 6–132 months in cancer patients. In Group I, 65.9% consumed a sole BP and 34.1% took 2 consecutive BPs. In Group II 89.3% consumed a sole BP and 10.7% took 2 BPs. Coincidentally both in Groups I and II the incidence of ALE in osteoporotic patients and ZOL in cancer patients as the sole BP was significant, as was the consecutive association of ALE+IBA. The biochemical evaluation with regard to phospho-calcium metabolism did not reveal significant differences in calcemia or phosphotemia levels in Groups I and II. CTX levels were significantly higher in males than in females in both assessed groups (p<0.037); however, these levels did not present significant differences between Group I: 256 pg/ml and Group II: 252 pg/ml grouped in values >142 pg/ml. Likewise, there were no significant differences in CTX levels among osteoporotic and cancer patients for either of the two groups studied (Figure 1).

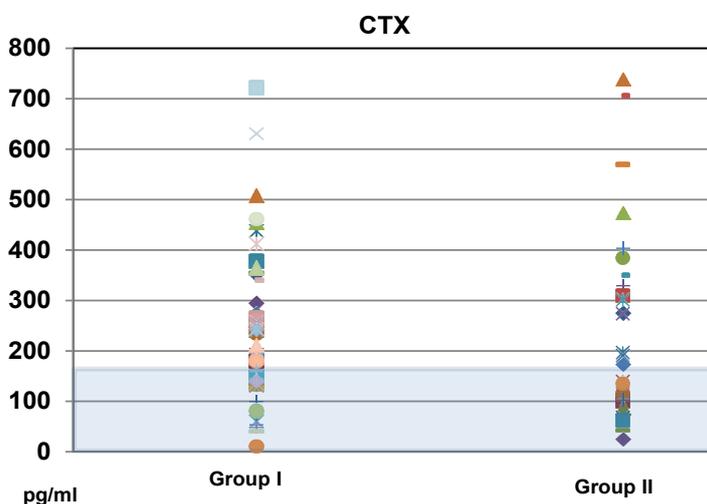


Figure 1. Distribution of CTX (pg/ml) in patients from Groups I and II resulting in values significantly higher than 142 pg/ml.

Vitamin D results (Vit D) for both Group I: 29.10 IU and Group II: 29.60 IU revealed mean values in the insufficiency range, with no significant differences between these study groups ($p < 0.05$) (Figure 2).

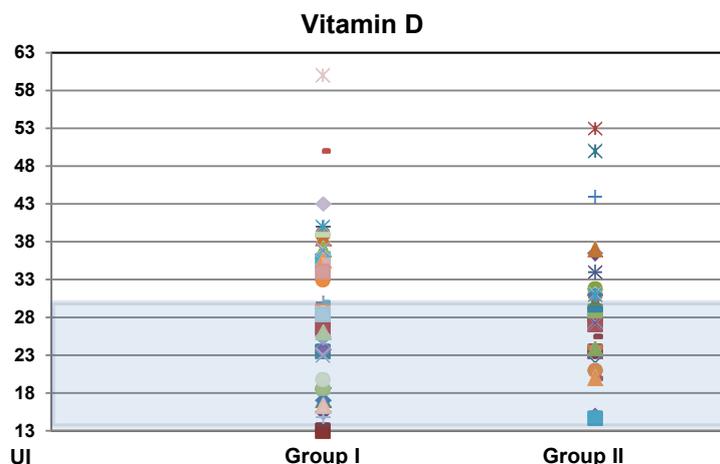


Figure 2. Distribution of VIT D (IU) in patients taking BPs, revealing insufficiency in a range of 13- 29, 10 IU in Group I and 13-29, 60 IU in Group II.

DISCUSSION

The FDA has established that BPs are safe drugs, setting forth that 93% of ONJBPs are currently associated to high-dose, long-term treatments, preferably intravenous in cancer patients. Notwithstanding this, it should be considered that there are 7% of ONJBPs due to therapeutic treatments with BPs for osteoporosis [9].

The clinical requirements for diagnosing bone necrosis involve the fulfilment of the requirements enunciated by the AAOMS in 2009 [10] and subsequent modifications, such as the one setting forth 4 disease stages [1]. With regard to the latter, the current study reveals that among the 85 patients with ONJBPs, the highest incidence was found in stage 2 disease, followed by stage 3. This result is similar to the one found in a recent study in which 254 patients with ONJBPs were evaluated [11]. On the other hand, it has been suggested that the formation of bone sequestrations may be found and, in some cases, there may not be frank bone exposure [12]. In our study, it was observed that 5 edentulous osteoporotic females with stage 0 disease presented this characteristic as a consequence of the maladjustment of their complete denture prosthetics. The clinical aspect of ONJBPs in the present study revealed the same clinical-inflammatory characteristics described in the literature: suppuration, haemorrhagic secretion, pain, inflammation, mucosal changes, sinusitis, paraesthesia, tumor (increase in volume) bucco-sinusal or bucco-nasal communication, adenopathies, feverishness, etc [10].

Retrospective studies in international publications establish a range for the incidence of ONJBPs: 27.5% incidence for oncologic treatments [11], 4.1 % incidence in osteoporotic patients [13]. Our study determined a 22.25% true incidence of ONJBPs in osteoporotic patients and 9.25% in cancer patients. These results are contrary to previous ones that suggest that the incidence is higher in cancer patients receiving high doses of BPs. With respect to the manifestation of ONJBPs according to BP treatment duration, we observed in our study a range of 20–240 months in osteoporotic patients, while the range was 6–168 months in cancer patients. The data of the current study with regard to the minimum time for the appearance of ONJBPs are lower compared to previous studies [10,12].

Unlike studies of ONJBPs patients whose base pathology is oncologic, originating mostly in patients with prostate cancer and multiple myeloma [4], in the current study a higher incidence was observed in patients with breast cancer, followed by those with multiple myeloma.

Although most published reports set that the higher incidence of ONJBPs develops from dental stimuli, mainly as a result of extractions [14], there is evidence that these may also develop spontaneously. In this regard, the histopathogenesis of ONJBPs has recently been studied [15], and it has been proposed that the antiangiogenic characteristics of BPs may produce a localized ischemia with the subsequent bone necrosis revealed in the affected area [16]. Other authors suggest that the etiopathogenesis of ONJBPs is related to the formation of pagetoid-like compartmentalized osseous sectors. The lack of nutrition to the trabecula, not in contact with the bone marrow, would diminish osseous vitality notably. Initially this would be in an aseptic manner but, by exposing the bony tissue to the septic buccal media, it would undergo secondary infection due to the pathogenicity of the micro biota [6]. Our study suggests that 72.3% of the ONJBPs originated from induced dental processes (79.6% from extractions, 18.75% from implants and 1.65% from root canal treatments); however, in 25.7% of patients treated with high concentrations of BPs for their oncologic pathology, ONJBP developed spontaneously. The location of osteonecrotic lesions demonstrated in previous studies [17] was anatomically distributed in the same order and with similar values: 62.3% in the lower jaw, 29.4% in the upper jaw, and 8.3% in both jaws. Several reports have evaluated the type of BP with respect to the development of ONJBPs;

many of these agree that ALE is the BP with the highest incidence in the development of the lesion in osteoporosis treatments [17]. Other studies show that ONJBPs often arise when ALE treatment is subsequently followed by RIS administration [4]. Coinciding with this, the results of the present study reveal that in osteoporotic patients, ONJBPs develop the most with ALE as the sole BP treatment; however, in treatments with 2 BPs, the highest incidence was observed in ALE treatment subsequently followed by IBA administration. With respect to treatments administered for oncologic pathologies, there is no doubt that ZOL is the BP which causes the highest incidence of ONJBPs; this view is shared by several reports [1,17,18].

Radiographic images typical of ONJBPs are analogous to the existence of bone sequestrations [19]. In the case of dental extractions, the post-extraction alveolus persists indefinitely [11]. The results of the present study agree that evaluation through imaging is a necessary, but not absolute, tool for the correct diagnosis of ONJBPs. It should be remembered that this pathology does not present pathognomonic radiologic features which differentiate it from various osteomyelitis involving the jaws. On the other hand, the following imaging studies have also been suggested as recommendable for the correct diagnosis of ONJBPs: Panoramic x-ray, Nuclear Magnetic Resonance (NMR), Computerized Axial Tomography (CAT), Positron Emission Tomography (PET) and Tc 99 Scintigraphy (only for cancer patients) [20]. Some authors favour the use of fluorescent tetracycline marking for the accurate visualization of the boundaries of the lesion being studied [21]. CTX is the most specific and effective marker known to date for assessing the level of bone remodelling [22]. It has been suggested that in patients on BP therapy, this assessment is useful for estimating the risk of developing ONJBPs in those patients who are scheduled to undergo an invasive dental procedure. In this regard, a risk prediction guideline for ONJBPs based on CTX levels has been developed for patients treated with BPs [23]. However, CTX levels do not on their own reflect the bone remodelling process [14] and these would not be valid for predicting the risk index of ONJBPs associated to long-term treatment with BPs [1]. In the present study, a significant decrease in CTX levels was not found in patients with ONJBPs with respect to patients under BP treatment who have not developed the pathology. This fact would determine that CTX levels are not an effective predictor of ONJBPs for the therapeutic management of patients under long-term BP treatment.

In the present study it has been observed that in spite of long-term treatment with BPs, over 50% of the females and an even higher percentage of males with ONJBPs presented an insufficient nutritional status with respect to Vitamin D. Although this condition does not correlate with the development of ONJBP [24], it is clinically accepted that treatment with BPs would have a lesser effect or no effect on patients with Vitamin D insufficiency. There is no absolute consensus regarding the therapeutic management of ONJBPs. Some authors advise a “Drug Holiday” (therapeutic holidays from BPs) [25], while others do not agree with this recommendation [11]. However, the pharmacodynamic and pharmacokinetic characteristics of BPs extend the effect of the drug for many years after treatment discontinuation [26]. During the development of this study, prescribed treatments were continued, both in oncology and osteoporosis cases, and the assessment of patients’ evolution depended on the eventual onset of signs and symptoms.

Some authors encourage the use of the hyperbaric chamber (HBO₂) for the treatment, since it sets an own oxygen gradient [27]. In the current study, patients with ONJBPs who underwent hyperbaric chamber therapy did not have any therapeutic advantage. Other authors propose using ozone therapy or platelet-rich plasma (PRP) [28]. In our study, patients submitted to ozone therapy did not show any significant change regarding lesion morbidity. Some patients underwent PRP placement after cleansing of the necrotic floor, which provoked an increase in the volume of the ONJBPs. There is a conservative therapeutic technique for eliminating necrotic bone tissue as an alternative method to surgical resection of ONJBPs which uses low-level laser light (Er: Yag laser y LLLT, Low-level laser therapy). This procedure was not used in the present study [29].

Both the Canadian Consensus Practice Guidelines for Bisphosphonate Associated Osteonecrosis of the Jaw, set up in 2008, and the AAOMS in 2014 propose that dental implant treatments in patients receiving BPs for cancer-related causes are contraindicated; this is not the case in patients with osteoporosis (providing the possibility of developing ONJBP in the future is explicitly stated on the written consent form). In the present study, 14% of the ONJBPs originated after implant placement. The JBMR International Consensus proposes a traumatic surgical therapy, avoiding dental extractions, implant placement, or any other manoeuvre which stimulate the bony tissue in patients receiving BPs or in patients who already have ONJBPs.

ONJBP treatment in this study is conservative, administering antiseptics, painkillers and antibiotics in a palliative fashion, awaiting the spontaneous exfoliation of the bone sequestration; this situation provokes in the patient the absence of a mechanical stimulus, thus preventing expansion of the necrotic lesion volume [17]. Antibigrams to determine accurate ONJBP treatment were not applicable since the bacterial flora found at microbiologic culture corresponded in the vast majority of cases to the habitual buccal pathogen flora: *Phorphyromona gingivalis* and *Actinomyces actino-mycetemcomitans* [30].

Additionally, the “wait and see” attitude was not used in the presence of buccal septic foci involving bone tissue in clinical situations in which the sepsis became generalized and increased these infectious foci, systemically affecting the patient’s health; in these cases surgical treatments were undertaken.

CONCLUSION

In conclusion, the results of the present study suggest that the incidence of ONJBPs is significant among the 25,538

individuals assessed was 0.33% (69.69% osteoporotic, 30.31% oncologic). Of the 1097 patients who suffered healing dyscrasias the incidence was 7.75% (82.2% osteoporotic and 13.8% oncologic). Of the 270 patients who were taking BPs, the incidence was 31.5% (70.63% osteoporotic and 29.37% oncologic). ONJBP stages were as follows: stage 0: 6%; stage 1: 24.7%; stage 2: 36.4%; stage 3: 32.9%, especially if only patients treated with BPs are taken into account for its calculation. Additionally, unlike what arises from the literature, the incidence was significant in osteoporotic patients, particularly in females, possibly because of the longer duration of the BP treatment received. In the current study it was not possible to find an association between the development of ONJBPs and a frankly decreased resorption provided by the interpretation of CTX values. It should be noted development the insufficiency vitamin D was found in 61% of the patients taking BPs, this insignificance importance as, it increases the chances of developing ONJ. From the results encountered and those published in the literature, it is apparent that the interaction among healthcare professionals is essential since the prevention of ONJBPs is better than its treatment. In this regard, prior dental assessment of patients is recommendable, aimed at undertaking dental surgeries prior to beginning with long-term BP treatment.

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