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Adjuvant aqueous ozone in the treatment of bisphosphonate induced necrosis of the jaws: report of two cases and long-term follow-up

M. A. BROZOSKI¹, C. A. LEMOS², M. DA GRAÇA NACLÉRIO-HOMEM³, M. C. Z. DEBONI³

Bisphosphonate induced necrosis of the jaws (BONJ) does not have a unique protocol of treatment and many therapeutic approaches have been arising in oral medicine with debatable results. A male and a female attended the University Oral Surgery Clinic presenting oral bone lesions induced by intravenous and oral bisphosphonates respectively as complications of dental extraction. Treatment included daily mouthwashes and weekly intra oral irrigations with 4 mg/L of aqueous-ozone, antibiotic therapy and sequential superficial debridement for sequestrectomies. Long-standing follow-ups showed complete mucosa covering of exposed bone area and resolution of purulent secretion. Antibacterial and antifungal properties of aqueous ozone may have played important roles in the treatment. The outcome measured intra oral examination and panoramic radiographs of the affected bone. The application of aqueous ozone daily mouthwashes and weekly professional irrigation were safe; free from adverse effects, easily of handling and worked as an important adjuvant therapeutic strategy for the treatment of BONJ.

KEY WORDS: Disphosphonates - Osteonecrosis - Ozone.

Since 1960, bisphosphonates have been used for the management of bone diseases such as osteoporosis, bone metastases, multiple myeloma and Paget's disease, cancer's bone metastases and malignancies

related to hypercalcemia. This drug delays the onset of skeletal complication related to metastases, decreases pain, reduces the incidence of hypercalcemia and improves quality of life.^{1, 2} Bisphosphonates acts on osteoclasts, inhibiting chemotaxis, cutting osteoclast lifespan, slowing their activity and inducing apoptosis. Its main goal is to decrease bone resorption.^{2, 3}

One important side effect of bisphosphonates is the induced necrosis of the jaw (BONJ) more often associated with long-term bisphosphonates intravenous administration than with oral use.³ Adverse effects related to oral bisphosphonates with manifestations in soft and bone tissue of the oral cavity seem to be more frequent than the small number of published cases pointed out. BONJ affects the mandible twice as often as maxilla.¹

Current literature presents several forms of treatment, but it lacks a standard protocol. BONJ management depends on its evolution and clinical stage. Oral surgery

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has been demonstrated to aggravate bone exposure. Caution surgery procedures to remove bone sequestrum associated with antibiotic therapy and oral antiseptic rinses have been frequently recommended.¹⁻⁴ Hyperbaric oxygen therapy for management of BONJ is debatable.^{4,5} Alternative proposals employing ozone delivered in oil suspension applications have been reported in the treatment of avascular necrosis of the jaw.⁵

Two cases of bisphosphonate associated osteonecrosis are reported: one in maxilla and another in mandible with three-year and one-year follow-up respectively. Both were successfully treated using adjuvant daily antiseptic aqueous ozone solution irrigation and subsequent debridement. Currently literature is also discussed.

Case series

Case 1.—A 68-year-old man was referred to Oral Surgery Clinic of the University of São Paulo

with chief complain of halitosis, local pain and bone exposure in left maxilla with evolution of one year. Medical history accounts that in 2004 he developed prostate cancer and underwent forty-five sessions of radiotherapy. In 2006, bone metastasis was diagnosed. Twelve more radiotherapy sessions were received with concomitant monthly intravenous applications of twenty-one doses of 4 mg zoledronic acid (Zometa®). During bisphosphonate therapy the first left upper molar was extracted for oral implants rehabilitation (Figure 1A). However, the region did not heal properly. Zoledronic acid was interrupted then. Systemic medication was changed to luteinizing hormone-releasing hormone (Zoladex®) which reduces serum concentration of testosterone in men. Patient reported that in another oral surgery service he underwent a 21-day-treatment of oral 1 g amoxicillin daily and oral antibacterial mouth washing with 0.12% digluconate of chlorhexidine three times a day without success. Intraoral examination showed an exposed bone in the maxilla first left molar region surrounded by a friable erythematous mucosa (Figure 1A). The Panoramic radiograph did not show any image which could suggest bone sequestrum or pathologic areas (Figure 1B). Hematological laboratory test was within normal limits. The morning fasting

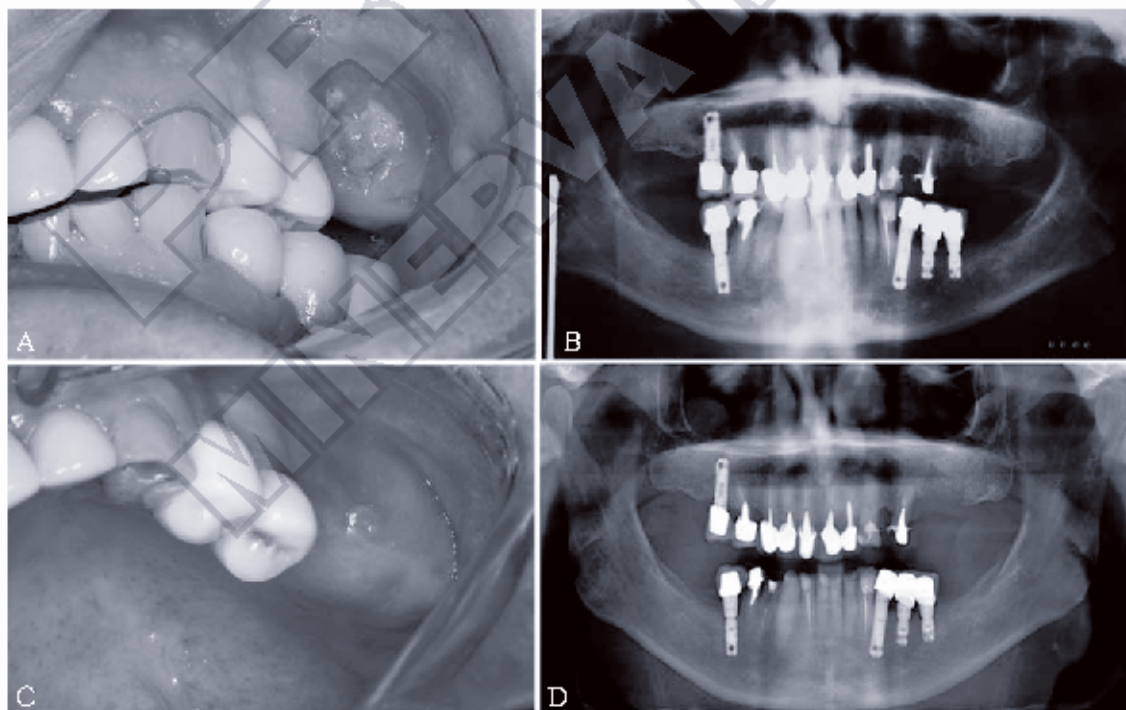


Figure 1.—Case 1 (A) Bone exposure in the maxilla first left molar region surrounded by a friable erythematous mucosa (B); panoramic radiograph image showing a slight bone defect; C) Clinical aspect after three-year of treatment shows normal mucosa; D) Panoramic radiograph image showing bone defect but any bone sequestrum.

serum C-terminal telopeptide (CTX) result was 135 pg/mL. A clinical diagnosis of stage-II bisphosphonate-associated osteonecrosis of maxilla was established. Treatment started with professional weekly irrigation with 200 mL of 4 mg/L of aqueous ozone solution on bone exposed region. The patient was instructed to use 15 mL of 0.12% digluconate of chlorhexidine twice a day and mouthwashes intercalary with 100 mL 4 mg/L of aqueous ozone solution domestic lesion irrigation three times a day. After one month, it was possible to observe that surrounded gingival tissue started to overgrow the exposed bone. The mucosa erythema had diminished and complaint of halitosis had ceased. After six more months of irrigation procedures, small fragments of bone were detached. Superficial debridement conjugated to abundant aqueous ozone solution (4 mg/L) rinsing was performed and bone sequestrum was removed. The fragments of bone underwent histological examination and confirmed necrotic bone diagnosis. After 14 days, we could notice an improvement on the mucosa coverage with little necrotic bone exposition. The patient maintained the domestic antiseptic irrigations. Another superficial bone debridement was achieved after one month. At this time CTX result was 210

pg/mL. After one year, the mucosa was completely recovered. A three-year-follow-up shows that the mucosa is still covering the region (Figure 1C) and panoramic radiograph did not show any bone sequestrum (Figure 1D).

Aqueous ozone solution was obtained following the method described by Bocci in 2004⁶. Briefly, an ozone generator (Ozone&Life 3.0[®]) sourced by 1L/min flow of medicinal O₂. During 10 minutes O₃ gas produced by the generator bubbled into 2L of MilliQ[™] water contained in a glass tube. Concentration of ozone diluted was checked by Indigo Blue's method (Bader and Hoigne 1981) employing Chemets Kit (Chemetrics[®], Inc- USA). Ozonated water was freshly prepared every week. The patient stored it in a glass bottle in a regular domestic refrigerator (8 °C) to preserve maximal ozone concentration.

Case 2.—A 62 year-old woman was referred to Oral Surgery Clinic of the University of São Paulo with chief complaint of halitosis, local pain and bone exposure and recurrent purulent drainage episodes in mandible alveolar bone first premolar region with evolution of one year. Intraoral examination showed an alveolar bone fistula in the

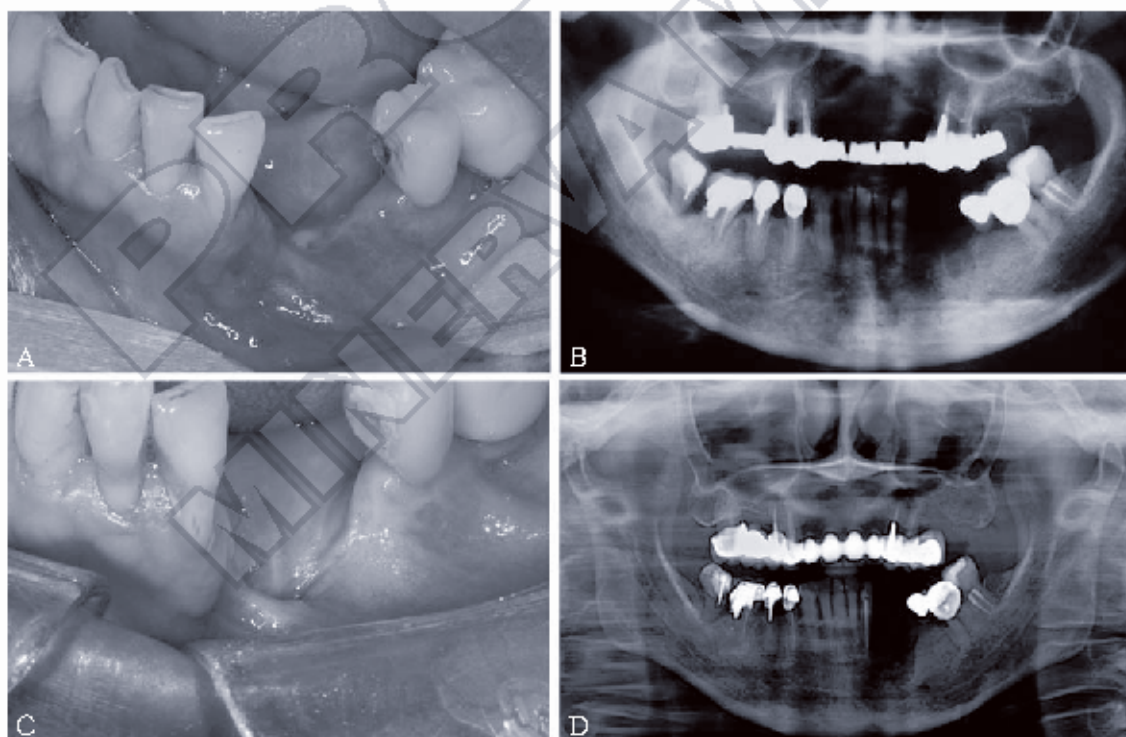


Figure 2.—Case 2 (A) alveolar bone exposure in inferior first premolar region surrounded by an erythematous mucosa and suppurative secretion; (B) panoramic radiograph exhibited bone defect; (C) eighteen-month follow-up shows that mucosa healed properly; (D) panoramic radiograph after one year showed a regional bone defect, but without sequestration.

mandible first premolar region surrounded by an erythematous mucosa (Figure 2A). Medical history accounts osteoporosis diagnosis established in 2003. The patient reported that from 2003 until 2007 she was medicated with D-Vitamin and Calcium (Calciferol®) and 70mg-sodium alendronate (Alendil-Ca®) once a week and 160mg-ketoprofen lisinate (Artrosil®) for artrosis for six months. From 2007 to 2009, she took 35 mg-calcium residronate (Actonel®) once a week. After that, alendronate medication was suspended; D-vitamin and calcium were maintained. In 2010, she had an inferior first premolar extracted and the alveolus did not heal properly. Panoramic radiograph exhibited bone defect (Figure 2B) and incisional biopsy confirmed devitalized bone sequestration. A bisphosphonate-induced osteonecrosis diagnosis was recognized. The patient underwent weekly 4 mg/L ozonated water and 0.12% chlorhexidine digluconate irrigations and 600 mg/day for a 7-day regimen. The patient maintained lesion rinsing with 200 mL of the aqueous ozone three times a day for three months. Later, the symptoms reduced; the necrotic bone exposition was still present, but oral mucosa had no sign of infection. Cautious and superficial debridement and bone sequestrectomy were performed under antibiotic coverage (600 mg - Clindamycin 1 hour before surgery). Debridements were repeated twice in four months. The patient maintained domestic aqueous ozone rinsing three times a day, with 4 mg/L-ozonated water and 0.12%-chlorhexidine digluconate between surgical procedures appointments. Six months later, the last debridement, bone exposure was completely recovered. One year and a half follow-up shows that mucosa healed properly (Figure 2C). Panoramic radiograph showed a regional bone defect, but without sequestration (Figure 2D).

Discussion

The exact mechanism of BONJ is not clear. The most accepted hypothesis is based on an association between bone suppressive turnover by bisphosphonates and the unique condition of oral cavity. Mandible and maxilla have a thin recovering mucosa which can be easily injured exposing bone to oral contaminated environment.^{4, 7} Since this drug can affect the balance of osteoclast, osteoblast, and osteocyte the normal healing and remodeling processes and the normal physiologic response of bone is impaired. Furthermore, it has been suggested that bisphosphonates

inhibit angiogenesis during wound repair.⁷

Nevertheless, literature includes only a small number of cases of maxillary osteonecrosis following oral surgery in patients taking bisphosphonates who were properly treated and healed. Mandible necrosis induced by oral bisphosphonates is rarely reported. Adverse drug reactions related to oral bisphosphonates are not limited to alendronate and may also be induced by etidronate and risedronate. The number of cases that are associated with alendronate have been rising over the last few years.^{3, 7}

The main goal of the treatment of patients who are at risk or have already developed BONJ is to preserve the quality of life. Pain and infection control as well as prevention of new areas of bone exposition should be focused.^{7, 8} The severity of BONJ has been categorized by Ruggiero *et al.*⁷ and revised by AAOMS⁸. It was based on bone exposure and associated pain or infection. Stage II diagnosis of BONJ was considered in the two cases here reported. They were characterized by exposed bone with associated pain, with regional soft tissue inflammation and local infection.

The control of local infection was achieved by means of a conservative approach with antibiotics and ozonated water mouth rinsing. Both patients underwent some kind of antibiotics and antiseptic mouth wash protocol for a time. Certainly, when those procedures became systematic and supervised, improved outcomes came out. The adherence of patients to the long-term treatment was critical to the achievement of the good results.

Despite the lack of evidences or strategies ensuring successful outcomes for the severity of the disease, many authors⁹⁻¹¹ propose the use of mouth rinses with chlorhexidine during all stages. Irrigations and mouth washing employing oxidants like peroxide solutions were also recommended.¹¹

In both cases, there was the necessity of two or more superficial sequestrectomies. Soft tissue coverage by a mucoperiosteal flap was equally assured. Surgery in

those conditions is still a matter of debate. Success after surgery procedures achieves cure rates of approximately 59% to 92%.¹² The choice involving a conservative treatment or a surgical procedure is a decisive issue and must be made on an individual basis. In addition, risk factors like the concomitant use of corticosteroids, chemotherapeutic agents or immunosuppressant should be also regarded.^{10, 11} Surgical debridement is recommended by some authors^{7, 9, 12} just when bone sequestrum, sharp and irregular edges of the exposed bone are presented. Sometimes, there is the necessity of repeating surgery until mucosa is properly covered. It seems that lesions in maxilla require more often and earlier repeated surgeries.¹²

The reported cases showed a completely recovery of the mucosa over the area of bone exposure, and relief of pain, halitosis and infection recurrent signs in both patients. For many authors, the success of the treatment did not mean completely recovery of the area, but improvement in patient's quality of life.^{8, 11} Bisphosphonates have a high bone affinity. Even if patient discontinues the use of medication, the drug can remain in bone tissue for up to 10 years.¹⁰ Regarding this fact, "drug holiday" is questionable for wound repair. In Case 1 report, the oncologist interrupted zoledronic acid, but probably this was not the key factor for the improvement in healing. The frequent irrigation with aqueous ozone solution and the superficial debridement seemed to have played an important role in the evolution of the wound repair.

Systemic antibiotics, hyperbaric oxygen, lasertherapy have also been reported with controversial results. The biological mechanism to explain the success of those therapies still remains unclear.^{4, 8, 13, 14} The antibacterial properties of those agents probably exert positive action over the healing process. We believe that the presence of oxygen in aqueous ozone solution performed antimicrobial action leading to inflammation and local infection reduction. Probably ozone molecules diluted in

water could also enhance oxygenation in necrotic tissue even though for the short periods of its applications. In the two reported cases, the erythema surrounding bone exposure had improved during the first week after aqueous ozone solution irrigation and rinsing. Literature has shown that ozone is capable of stimulating local revascularization which affects cell-growth processes involved in wound repair.^{6, 15, 16}

Local and systemic administration of ozone therapy has been empirically applied in human beings in a great variety of diseases with promising clinical results. Many authors have stated that ozone can be an alternative therapeutic agent when conventional medicine has been inefficient.^{3, 6, 15} Ozone has a broad spectrum of microbial activity in water and the present use of a 4 mg/L concentration of ozone dilution was based on previous *in vivo* and *in vitro* studies.^{16, 18} Some authors found that aqueous ozone reduces the viability of oral microorganism including Gram-positive, Gram-negative and *Candida albicans* suggesting ozonized water might be useful to control oral infections.^{18, 19} Recently, in a phase I-II study, some researchers⁵ demonstrated the use of ozone in oil suspension directly on bone necrotic surface. The preliminary results showed that the application of ozone was an effective, safe and simple option for the treatment of small BONJ lesions.⁵

The advantages of ozone in an aqueous phase are: easiness of handling, lack of mutagenicity, fast microbicidal effect, and suitability for its use as an antiseptic solution.¹⁵ Ozone in water solution, if correctly stored under refrigeration, is capable of maintaining its properties for at least 48 hours.⁶ The irrigation method proposed here could have been securely performed by the patient him/herself many times a day with no need of professional supervision. Like others authors had observed,²⁰ the clinical application of ozone diluted in water has little or no side-effects. Here, the odor of the solution and a slight blistering in the mucosa were the unique patients' complaints.

After years of clinical control, in both cases, it is certain that even though the mucosa region had overlaid bone exposure, patients must be rigorously followed up. It is difficult to ensure that the bone below the mucosa is in healthy conditions. Actually, more control studies and quality trials are undoubtedly necessary to validate ozone as an adjunctive measure for the treatment of BONJ.

Conclusions

Professionals should become aware that a primary conservative treatment, to accomplish a clinical reduction of signs and symptoms as well as early and carefully surgical procedure might be reasonable approaches in managing BONJ, mainly at early stages. Aqueous ozone as the adjuvant therapy was safe, free from adverse effects, easily of handling and probably had made the difference in the treatment of both cases.

Riassunto

Ozono liquido adiuvante nel trattamento della necrosi della mandibola da bifosfonati: segnalazione di due casi e follow-up a lungo termine

La necrosi della mandibola da bifosfonati (*Bisphosphonate induced necrosis of the jaws*, BONJ) non prevede un protocollo di trattamento unificato; pertanto, sono emersi diversi approcci terapeutici nel settore della medicina orale con risultati discutibili. Un uomo e una donna si sono presentati presso l'ambulatorio universitario di chirurgia orale con lesioni ossee mandibolari derivanti rispettivamente da bifosfonati orali ed endovenosi come complicanze dell'estrazione dentaria. Il trattamento ha incluso risciacqui quotidiani del cavo orale e irrigazioni intraorali settimanali con 4 mg/L di ozono liquido, terapia antibiotica e sbrigliamento superficiale sequenziale per le sequestrectomie. I follow-up a lungo termine hanno mostrato un completo rivestimento mucoso dell'area di osso esposto e la risoluzione della secrezione purulenta. Le caratteristiche antimicotiche e antibatteriche dell'ozono liquido potrebbero avere rivestito un ruolo importante nel trattamento. L'esito misurato includeva l'esame intraorale e le radiografie panoramiche dell'osso interessato.

L'applicazione di risciacqui quotidiani di ozono liquido e di irrigazioni settimanali professionali era sicura; tale procedura è priva di effetti indesiderati, facile da eseguire e utilizzata quale importante strategia terapeutica adiuvante per il trattamento della BONJ.

PAROLE CHIAVE: Bifosfonati - Osteonecrosi - Ozono.

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