

Aim of the study: The aim of the study was to report on seven cases of BRONJ treated with surgical debridement, oral antibiotics and gentamicin-collagen sponge (Collatamp EG) placed in the bone wound.

Material and methods: Seven patients with 9 sites of BRONJ stage 2 were included in the study. Perioperative oral antibiotics, surgical debridement and/or sequestrotomy and gentamicin-collagen sponge (Collatamp EG) were used. Postoperative monitoring was carried out for the next 3 months.

Results: Three weeks after the surgery, six sites of BRONJ in five patients were treated successfully. In two patients on three sites BRONJ stage 1 was observed. Three months after surgery another two sites healed fully. In one patient there was still BRONJ stage 1, however, the area of exposed bone was visibly reduced.

Conclusions: The use of surgical debridement together with oral antibiotic therapy and collagen-gentamicin sponge indicates positive results regarding the surgical treatment of BRONJ.

Key words: chemotherapy, infection in oncology, rehabilitation.

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Treatment of bisphosphonate-related osteonecrosis of the jaws – a report of seven cases

Joanna Jakiel, Mansur Rahnama, Joanna Szczerba-Gwóźdź

Oral Surgery Department, Medical University of Lublin, Poland

Introduction

Bisphosphonates (BPs) are widely used in the fields of oncology, endocrinology, and orthopaedics. Bisphosphonates are inhibitors of osteoclastic bone resorption and are therefore used in the treatment of a variety of skeletal disorders such as osteoporosis, Paget's disease, osteogenesis imperfecta, multiple myeloma, tumour-induced hypercalcaemia and bone metastases. They reduce skeletal-related events such as pathological fractures resulting from bone involvement in haematological or solid malignancies and reduce the necessity of radiotherapy or surgical treatment of the lesions [1–7]. Bisphosphonates are used in the treatment of bone metastases in the context of solid tumors such as breast cancer, prostate cancer and lung cancer [4–8].

Structurally, bisphosphonates are synthetic analogues of the naturally occurring pyrophosphates of the bone matrix [1, 4, 5, 7]. Bisphosphonate molecules are connected to hydroxyapatite crystals and internalised by osteoclasts, finally inducing osteoclast apoptosis and/or inhibiting osteoclast function [1, 3, 9]. It has been proven that bisphosphonates reduce angiogenesis by inhibition of VEGF [1, 3, 9]. Bisphosphonates have also direct anti-tumoral effects, including induction of tumour cell apoptosis, and inhibition of tumor cell adhesion and invasion, which reduces formation of metastases [1]. Bisphosphonates are not metabolised by bone, where they can remain unchanged for many years [3, 10].

Treatment with bisphosphonate drugs is associated with several complications including renal and gastrointestinal side effects, particularly oesophageal ulceration, but the most serious is that of osteonecrosis of the jaw (bisphosphonate-related osteonecrosis of the jaw – BRONJ) [1–4, 7, 11]. The pathophysiology of this disorder is not fully understood. It is believed that bisphosphonates inhibit bone resorption by inducing apoptosis of osteoclasts and/or inhibition of their activity, which impairs normal bone turnover, thereby also the site of injury, especially when exposed to biofilm of the oral cavity, rich in bacteria and fungi. Furthermore, bisphosphonates inhibit angiogenesis [3, 7, 11, 12]. Consequently, local micro damage from injury or normal mechanical loading cannot be repaired, which in turn can result in bone necrosis [3, 11]. Bisphosphonates accumulated in the bone have direct toxic effects on the oral epithelium and inhibit normal healing of soft tissues thereby favouring the persistence of bone exposure to oral biofilm [3]. Exposed bone can be easily infected by the abundant bacterial and fungal microbiota, which has the potential to cause BRONJ [4]. Bacteria comprise Gram-positives and Gram-negatives and also aerobes, even though the majority were anaerobes or facultative anaerobes. Species of *Actinomyces*, *Fusobacterium*, *Bacillus*, *Staphylococcus*, *Streptococcus viridans*, *Selenomonas*, *Neisseria*, *Prevotella melanogenica* and *Candida* sp. are observed [2, 3]. All cases of BRONJ exhibit bone areas covered with well-developed biofilms [3]. It has also been proven, that bisphosphonates enhance bacterial adhesion and biofilm formation on bone hydroxyapatite [13].

Bisphosphonate-related osteonecrosis of the jaws was first described in 2003 [3, 4, 6, 7]. BRONJ is defined as an avascular area of necrotic bone in the maxillofacial area, with or without exposed bone, that has been evolving for more than eight weeks [3, 4, 6, 11]. Clinical features can also include pain, erythema and pathological jaw fracture. The lesions showing exposed and necrotic bone may remain asymptomatic for a long period, even years [3, 14]. According to the literature, three conditions are needed to define a case of BRONJ: 1) current or previous treatment with a bisphosphonate; 2) exposed, necrotic bone in the maxillofacial region, which has persisted for more than 8 weeks; and 3) no history of radiation therapy to the jaws [3, 4, 7, 14]. The occurrence of a non-exposed variant of osteonecrosis has recently been reported, where the most common findings were jaw bone pain, sinus tract, bone enlargement, and gingiva swelling [4, 7, 15]. Oro-antral fistula and sinusitis may also appear [14, 16].

Differential diagnosis should consider clinical conditions such as alveolar osteitis, sinusitis, gingivitis/periodontitis, periapical pathology and temporomandibular joint disorders [3, 4, 12].

Bisphosphonate-related osteonecrosis of the jaws affects the mandible more often than the maxilla [3, 15–17]. The risk of developing BRONJ increases with the presence of a history of tooth extraction or other dento-alveolar surgery, the use of non-fitting prosthetic appliances, bone exostoses, oral infection, poor oral hygiene, coexisting diabetes mellitus, chemotherapy, steroid therapy, malnutrition, and tobacco use [1–4, 6, 12, 14, 15, 18]. Tooth extraction was the reason for bisphosphonate-related osteonecrosis in 34–86% of cases [6, 19]. The route of administration is also important – the estimated incidence of BRONJ for patients taking i.v. bisphosphonates ranges from 0.8 to 12%, whereas for oral bisphosphonates it ranges from 0.01 to 0.04% [3, 4, 6, 18]. Most of the patients with BRONJ were treated with intravenous BPs, such as zoledronic acid, disodium pamidronate, and sodium alendronate [3, 4, 6, 10, 17]. The duration of bisphosphonate exposure is positively correlated to developing BRONJ, the mean time is 1.5–5 years [11, 17]. Patients at serious risk of BRONJ are likely to be given bisphosphonates parenterally for at least 12 months, or orally for at least 36 months [2].

Radiological features of bisphosphonate-associated jaw necrosis are not specific, because are observed in patients suffering from osteomyelitis, osteoradionecrosis, Paget's disease or bone metastases [18].

Histopathological analysis shows soft tissue and bone necrosis, changes in bone architecture, resorption, fibrosis, hypovascularisation, inflammatory infiltration and bacterial biofilm [18, 20].

To prevent bisphosphonate-associated jaw necrosis when bisphosphonates are recommended it is important that the prescribing physician informs patients of the risk of BRONJ and advises them to attend a dental professional for a full oral assessment [2]. The patient should be dentally fit before commencing bisphosphonate treatment [2, 4, 10, 12, 20]. If extractions or other oral surgical procedures are indicated, BPs treatment should be delayed until the extraction site fully heals (14–21 days) [2, 4]. If a medical

condition makes delay difficult or inadvisable it is likely that most dental problems could be treated after drug treatment has begun, with the most invasive procedures done first, because the risk of BRONJ is associated with long-term use rather than single dosage [2, 4, 18]. Patients with dentures should be examined for areas of mucosal trauma [2, 4, 18].

During bisphosphonates treatment it is generally recommended that high-risk procedures should be avoided, and there should be a reliance on restorative treatment including root canal treatment and non-invasive periodontal surgery. In teeth that cannot be restored, removal of the crown and endodontic treatment of the remaining roots should be considered [2, 4, 10].

Currently, BRONJ management remains controversial, and there is no definitive standard of care for this disease. In fact, several articles in the recent literature discuss a range of topical to surgical treatments [6]. In order to direct rational treatment guidelines and collect data to assess the prognosis in patients who have used either i.v. or oral bisphosphonates, it is suggested that the following staging categories are used:

1. Patients at risk: No apparent exposed/necrotic bone in patients who have been treated with either i.v. or oral bisphosphonates. These patients do not require any treatment. However, they should be informed of the risks of developing BRONJ, as well as the signs and symptoms of the disease process. Regular dental assessment, prophylaxis, and conservative treatment is recommended.

2. Patients with BRONJ

Stage 1: Exposed/necrotic bone in patients who are asymptomatic and have no evidence of infection. These patients benefit from the use of oral antimicrobial rinses, such as chlorhexidine 0.12%. No surgical treatment is indicated.

Stage 2: Exposed/necrotic bone in patients with pain and clinical evidence of infection. These patients benefit from the use of oral antimicrobial rinses in combination with long-term antibiotic therapy. Most of the isolated microbes have been sensitive to the penicillin group of antibiotics. Quinolones, metronidazole, clindamycin, doxycycline, and erythromycin have been used with success in those patients who are allergic to penicillin.

Stage 3: Exposed/necrotic bone in patients with pain, infection and pathologic fracture or extra-oral fistula. Surgical debridement/resection in combination with antibiotic therapy and local antimicrobial treatment is recommended [3, 4, 17, 20]. Regardless of the disease stage, mobile segments of bony sequestrum should be removed [4, 17, 21]. In patients with pathological mandibular fractures, a segmental resection and immediate reconstruction with a reconstruction plate is recommended [17].

Material and methods

Seven patients (4 female and 3 male) affected by BRONJ (stage 2) were included in the study. Seven sites of BRONJ were located in the mandible and two were located in the maxilla. Five patients had been treated with i.v. BPs, two had



Fig. 1. BRONJ in the maxilla, clinical view (patient 1)

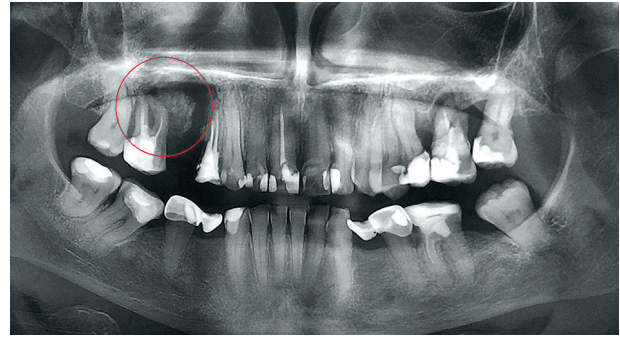


Fig. 2. Bone sequestrum visible on panoramic X-ray (patient 2)

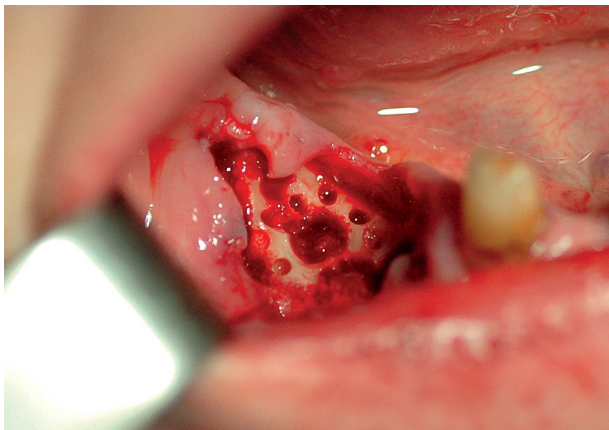


Fig. 3. Bone after surgical debridement (patient 3)

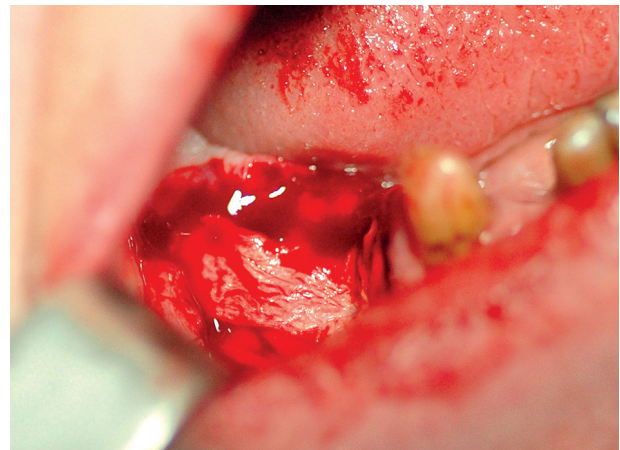


Fig. 4. Bone surface covered with Collatamp EG (patient 3)



Fig. 5. Clinical view of the patient after 3 weeks (patient 1)

been treated orally. In all of the cases, BRONJ was clinically diagnosed (Fig. 1) and confirmed radiographically (Fig. 2).

Scaling was performed with each patient one day before surgery. Beginning the day before surgery, each patient took clindamycin 0.6 g twice.

Granulation tissue and necrotic bone was removed to visible healthy bone under local anaesthesia 4% articaine (Fig. 3).

When separated sequestra were seen, a sequestrectomy was performed. A gentamicin-collagen sponge (Collatamp EG) was placed on the exposed bone (Fig. 4), and the mucoperiosteal flap was mobilised. Double-suture was used: continuous resorbable monofilament (Monosyn 4/0) was used to suture the periosteum, then simple detached stitching with non-resorbable monofilament (Dafilon 3/0) was performed to obtain a hermetic closure at the wound margins. Written instructions for proper oral hygiene for maintenance of the surgical site were given to all patients. They received antibiotic therapy, including oral clindamycin 0.6 twice a day for six days and doxycycline for the next 10 weeks as well as chlorhexidine oral rinses 4 times daily. Solcoseryl Dental Adhesive Paste was used after rinsing as topical dressing on the wound.

Monitoring of mucosal healing was carried out post-operatively one day after and twice a week for the next 3 months. Sutures were removed 3 weeks after surgery. The patients were always examined by detecting the clinical signs of BRONJ: pain, swelling, nonhealing, exposed necrotic bone, and/or fistulas with connection to the bone.

Results

Seven patients with stage 2 BRONJ were included in the study and were treated in the Oral Surgery Department of the Medical University of Lublin, Poland. Four patients were women, and three were men. The minimum age was

66.5 years, the maximum age was 78.3 years. The mean age at presentation was 72.7 years. Patients had been treated with i.v. or oral BPs for an average of 33 months at the time of diagnosis. After a BRONJ diagnosis, patients discontinued the use of BPs. Drug holidays were determined by the oncologist when needed.

Of the 9 treated sites, 7 were located in the mandible and 2 in the maxilla. Tooth extraction was the cause of BRONJ in 7 sites. In 2 sites BRONJ appeared spontaneously.

In four patients no intraoperative or postoperative complications were observed during the first three weeks. Three patients showed mild pain and swelling at the first post-surgical visit. The discomfort resolved spontaneously after three days. In one patient on the day 3 after surgery wound dehiscence was noticed; however, the patient did not agree to suturing of the wound again.

Three weeks after the surgery, when the sutures were removed, 6 sites of BRONJ were treated successfully (Fig. 5). In two patients partial mucosal closure was observed. In these patients there was an area of exposed but asymptomatic bone with no evidence of infection (BRONJ stage 1). The patients used chlorhexidine mouth rinse, chlorhexidine topical gel and Solcoseryl. Two months after surgery the exposed areas were completely covered with oral epithelium. In one patient who did not agree to closure of the wound dehiscence after three months there was still BRONJ stage 1, however, the bone was epithelialised by about 80%.

Resolution of disease was defined as the maintenance of mucosal closure without clinical signs of residual infection or exposed bone at the time of evaluation.

Discussion

Bisphosphonates are drugs used to prevent and treat secondary skeletal-related events that are due to bone consuming disease of bone metastasis of solid cancer. The goal of treatment with BPs is to improve patients' quality of life. BRONJ is a term that has recently emerged to describe an important complication in some patients receiving this class of drugs.

There is strong evidence that infection is closely related to BRONJ etiopathogenesis, especially regarding the constant findings of *Actinomyces* sp. colonies in histological examinations of the lesions. In patients taking bisphosphonates, the site of tooth extraction favours infection because of lower inflammatory response and vascularisation of the tissues, increased bacterial adhesion to bisphosphonate-coated bone and persistence of exposed bone to oral cavities consequent to inhibition of both bone resorption and epithelial covering [3]. Use of perioperative antibiotics and a chlorhexidine mouthwash have been suggested to reduce the risk of postoperative BRONJ where invasive dental treatment is necessary [2–4].

As most of the microorganisms isolated from BRONJ lesions are sensitive to penicillin, oral amoxicillin has been the therapeutic choice. Quinolones, metronidazole, clindamycin, doxycycline and erythromycin have been used in patients allergic to penicillin. These drugs must be administered over a long-term period, which can vary from

several months to more than a year. Chlorhexidine has been beneficial in the control of surface bacteria, which can help the recovery of bone-exposed regions in BRONJ. It is important to recall that, besides bacteria, fungi, especially *Candida* spp., have also been found in BRONJ lesions a fact that deserves attention when deciding on antimicrobial therapy. Among the protocols applied in BRONJ treatment, chlorhexidine seems to be the main tool against fungal agents [4].

Systemic antibiotics are part of the standard therapy after debridement of infected bone, but their efficacy may be limited due to impaired blood supply and a low penetration rate at the site of infection. Furthermore, long-term treatment and high doses are associated with severe side effects. In contrast, antibiotic-impregnated bone void fillers can act as local anti-infective drug release systems, which not only fill up the dead space after surgical debridement but also deliver high antibiotic concentrations at the site of potential infection, without increasing serum antibiotic levels [22, 23]. Collatamp is a gentamicin-impregnated collagen matrix that is used as a topical adjunct for perioperative antibiotic prophylaxis. The gentamicin-collagen sponge (Collatamp EG, Syntacoll, Saal/Donau, Germany) used in this study consists of a matrix of purified bovine collagen type I impregnated with 2.0 mg/cm² gentamicin sulphate [24].

Gentamicin is an aminoglycoside with broad bactericidal activity against many aerobic Gram-negative and some aerobic Gram-positive organisms. Gentamicin is the most commonly used aminoglycoside antibiotic and is indicated for moderate-to-severe bacterial infections caused by sensitive agents, primarily Gram-negative bacteria. Gentamicin is typically used in combination with a penicillin or cephalosporin for treatment of severe infections with *Staphylococcus aureus*, viridians group streptococci, *Pseudomonas aeruginosa*, *Enterobacter*, *Klebsiella*, and other bacteria [25].

Adequate debridement and placement of collagen film eluting antibiotics locally produces excellent results and is a safe technique in the management of bone infections [23, 24, 26]. These sponges can be used easily and there is no need for a second surgery for the removal of these antibiotic carriers because they are bioabsorbable. The potential for systemic side effects appears minimal. The implantation of Collatamp EG is safe and well tolerated [24, 26].

Good postoperative results can be achieved by the complete mucosal sealing of the alveolar socket within the surgical extraction, which prevents the bacterial contamination of the jaw [18].

In conclusion, our data on the use of antibiotic therapy together with surgical debridement and local placement collagen-gentamicin sponge indicate positive results regarding the surgical treatment of BRONJ, even if the analysed sample is small.

The investigated material can, overall, provide adequate protection against bacterial infection in all challenging, at risk, patients with chronic osteomyelitis/osteitis during the first weeks after implantation and to support the bone healing process.

However, it is important to note that the positive results have a total follow-up period ranging from 48 to 50 months. The long follow-up period represent a good indication in continuing this kind of analysis. Therefore, we suggest that surgical treatment on patients taking BPs is necessary because it improves and accelerates the healing process. Hermetic closure of the muco-periosteal flap and the use of systemic antibiotic therapy as well as local gentamycin prevents bacterial contamination of the bone.

The authors declare no conflict of interest.

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Address for correspondence

Joanna Jakiel
Oral Surgery Department
Medical University of Lublin
Karmelicka 7
20-081 Lublin, Poland
e-mail: joanna.m.jakiel@gmail.com

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