

Efficacy of a nonsurgical treatment regimen in patients with bisphosphonate-related osteonecrosis of the jaws in Saudi Arabia

SAGE Open Medicine
2: 2050312114522995
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DOI: 10.1177/2050312114522995
smo.sagepub.com


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Abstract

Objectives: The objective of this study was to evaluate the effectiveness of a nonsurgical treatment regimen in the long-term control of necrotic areas of the jaws and pain in such patients.

Methods: A total of 96 patients suffering from the disease were included in this study. All patients received nonsurgical treatment regimen for 10 days, and repeated every 3 months for 2 years. The size of the osteonecrotic lesions was measured and the pain level was self-assessed with a visual analog scale.

Results: The patients showed a statistically significant ($F = 16.1$; $p < .01$; $r^2 = .95$) gradual decrease in the size of exposed bone areas during the nonsurgical therapy (from 12.5 to 8.8 mm). Pain scores ranged from 0 to 3 score scale. Complete resolution of the disease was observed in some patients.

Conclusions: This conservative nonsurgical treatment regimen seems to provide successful treatment in reduction of the sizes of exposed bone areas in the majority of patients.

Keywords

Bisphosphonates, osteonecrosis, jaws, nonsurgical treatment regimen, Saudi Arabia

Date received: 20 August 2013; accepted: 6 January 2014

Introduction

Osteoporosis is much more common in some regions of Saudi Arabia, and the burden of management in an aging population will increase in coming decades.¹ This condition is usually treated by bisphosphonates. Bisphosphonate-related osteonecrosis of the jaws (BRONJ) is a recently (last decade) described adverse side effect of bisphosphonate therapy.² Patients who are receiving intravenous, nitrogen-containing bisphosphonates for treatment of osteoporosis, multiple myeloma or metastatic carcinoma to the skeleton are at greatest risk for osteonecrosis of the jaws (ONJ). These patients represent 94% of published cases.² The mandible is more commonly affected than the maxilla (2:1 ratio), and 60% of cases are preceded by a dental surgical procedure.²

The BRONJ has been defined as “a condition characterized by exposure of bone in the mandible or maxilla persisting for more than 8 weeks in a patient who has taken or currently is taking a bisphosphonate and who has no history of radiation therapy to the jaws.”³ It presents with halitosis, pain and neuropathy, and erythema and suppuration. Clinically, the disease is characterized by exposed alveolar

bone that occurs spontaneously or becomes evident following an invasive dental surgical procedure such as tooth extraction, periodontal surgery, apicoectomy, or dental implant placement.^{4,5} In 2003, several cases of ONJ were reported in patients receiving bisphosphonate therapy.^{5–7} Since then, the number of reported cases has been increased, and the literature now includes several hundreds of cases.³ Bisphosphonate-associated ONJ (Figure 1) usually appears as areas of necrotic exposed bone surrounded by inflamed gingiva or mucosa.⁸ It usually has a significant adverse effect on the quality of life for most patients.^{9–11} Complete prevention of this complication is not currently possible. However,

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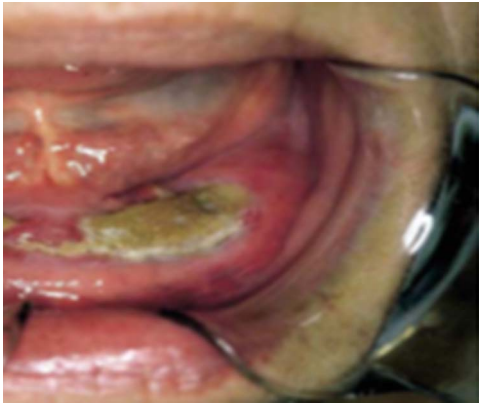


Figure 1. Bisphosphonate-related exposed necrotic bone in the mandible.

pre-therapy dental care reduces this incidence, and nonsurgical dental procedures can prevent new cases.¹²

Several recommendations have been proposed for treating ONJ, but no consensus on a standard of care has been reached, nor is there any agreement on a surgical versus nonsurgical approach to therapy.^{3,11–14} This probably results from the lack of reported randomized clinical trials comparing different management strategies designed to allow the area of exposed bone to recover.³

Montebugnoli et al.³ evaluated the efficacy of two different procedures for treating patients with ONJ and adopted an objective parameter to quantify the efficacy of each protocol. The preliminary results of such a study did not show any significant difference between surgical and nonsurgical approaches and suggested that an antibiotic regimen was effective in the short-term management of these patients.

To date, such clinical trials entail objective difficulties to a scientific approach, that is, randomizing groups of oncology patients whose quality of life is strictly related to bisphosphonate drugs. There is also a paucity of recent data on treatment of ONJ particularly in the Saudi population. Hence, in this study, we enrolled a large number of patients suffering from ONJ and followed them prospectively for a longer period of time, with the aim of evaluating whether a nonsurgical treatment regimen, suggested by Montebugnoli et al.,³ is effective in the long-term control of necrotic areas of the jaws and pain in Saudi population.

Aim of the study

This study aims at evaluating a long-term nonsurgical treatment regimen for Saudi patients suffering from BRONJ.

Patients and methods

A total of 96 patients (42 males and 54 females) with BRONJ and under treatment with different types of bisphosphonates (zoledronate, 45 patients; pamidronate, 27

Table 1. Type of bisphosphonate that patients were taking.

N	Zoledronate	Pamidronate	Alendronate
96	45	27	24

Table 2. Duration of treatment with bisphosphonates at the beginning of regimen therapy (month).

n	10–19 months	20–29 months	30–40 months	100–180 months
96	40	30	15	11

Table 3. Diseases that patients were complaining of or treating.

n	Osteoporosis	Metastatic carcinoma	Breast cancer	Prostate cancer
96	75	3	10	8

Table 4. Precipitating factors or procedures of ONJ.

N	Tooth extraction	Torus mandibularis	Implants	Spontaneously
96	53	11	12	20

ONJ: osteonecrosis of the jaws.

Table 5. Location of osteonecrosis.

N	Maxillary	Mandibular
96	29	67

patients; and alendronate, 24 patients) were allocated consecutively from those attending the oral and maxillofacial surgery clinic, faculty of dentistry, King Abdulaziz University, Jeddah, Kingdom of Saudi Arabia, during the past 5 years. Their age range was 48–85 years. Of these, 57 patients had osteoporosis, 31 had metastatic breast carcinoma, and 8 had metastatic prostate carcinoma. The time from the appearance of osteonecrosis and the beginning of bisphosphonates treatment ranged between 8 and 180 months. Exposed bone developed after tooth extraction in 53 patients, after trauma to torus mandibularis in 11 patients, after implant placement in 12 patients, and it appeared spontaneously in 20 patients. A total of 67 cases affected the mandibles, and 29 cases were maxillary. Patients continued bisphosphonates therapy after diagnosis of the disease (Tables 1–5).

On examination and diagnosis of ONJ, the diameter of the lesion is measured in millimeters using a usual graduated probe. The patient's pain was self-evaluated using a visual analog scale (VAS) graduated from 0 to 10 (Figure 2).

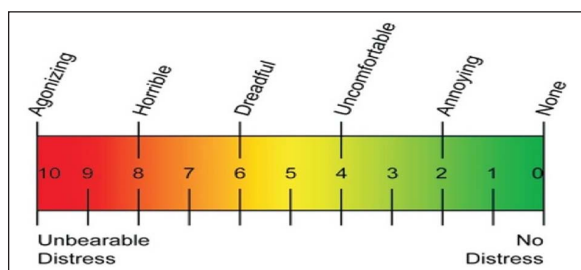


Figure 2. Visual analog scale (VAS).

Table 6. Diameter of exposed bone (mm).

Item	59 cases	16 cases	10 cases	11 cases
At the beginning of therapy	10 mm	20 mm	30 mm	40 mm
3 months after therapy	5 mm	15 mm	20 mm	30 mm
1 year	5 mm	9 mm	8 mm	20 mm
2 years	0 mm	5 mm	5 mm	7 mm

All patients received minimally invasive treatment regimen suggested first by Moretti et al.¹⁵ in the form of professional oral hygiene measures every 3 months. Antiseptic oral rinses twice a day, switching between chlorhexidine digluconate 0.12% (Corsodyl; GlaxoSmithKline, Brentford, Middlesex, UK) and essential oils (Listerine; Johnson and Johnson, New Brunswick, NJ, USA) to avoid bacterial resistance were also recommended. A combination antibiotic therapy formed of amoxicillin clavulanate potassium/metronidazole was prescribed, and patients were instructed only to use it in emergent cases of severe infections.

They were followed up every 3 months for 2 years. At each recall visit, the maximum diameter of the exposed area was measured carefully and recorded. Pain was also reevaluated using the VAS. Any mobile area of necrotic bone was removed gently with tissue pliers, and the rough surface of the bone was smoothed using piezosurgery tips (P10 insert, Piezosurgery; Mectron, Genova, Italy). During each visit, mucosal surfaces were evaluated, as well as periodontal probing, thermal tooth vitality, halitosis, and tissue swelling. Prosthetic devices were controlled and, if necessary, modified to remove traumatic triggers on the tissues.

Patients who experienced pain or showed purulent discharge were given an antibiotic therapy consisting of amoxicillin/clavulanate potassium as 1 g tablets every 8 h for the first 3 days and every 12 h for the next 7 days, and metronidazole 500 mg every 12 h for 10 days. Alternatively, if a patient was allergic to penicillin, the antibiotic therapy consisted of ciprofloxacin 500 mg every 12 h, and metronidazole 500 mg every 12 h for 10 days. Patients were instructed to come back for inspection in case of sudden complication, such as infection or persistent pain. The antibiotic therapy was repeated only when pain or infection was still present or reported during the follow-up visits.

This nonsurgical regimen was authorized by the Research Ethics Committee of King Abdulaziz University, Faculty of Dentistry (KAUFD). Results were statistically analyzed and tabulated.

Results

Patients were followed up every 3 months for 2 years. The diameter of exposed bone was carefully measured, and patients were instructed to come back for inspection in case of sudden complication. The one-way analysis of variance (ANOVA) did not reveal any statistical difference in the initial extent of exposed bone between the mandible (13.2 ± 12.9 mm) and maxilla (10.4 ± 9.5), between men (12.7 ± 10.5 mm) and women (12.3 ± 13.2 mm), or with regard to the type of bisphosphonate therapy (zoledronate, 13.3 ± 12.2 mm; pamidronate, 17.0 ± 14.7 mm; and alendronate, 3.5 ± 4.6 mm). Few patients particularly those using zoledronate showed mobile areas of necrotic bone and was removed gently with tissue plier, and the rough surface of the bone was smoothed.

The linear model did not identify any significant relationship between the initial area of exposed bone and patient age or duration of bisphosphonate therapy. Only the results from the general linear model showed a statistically significant time-related decrease (Table 6) in the size of exposed bone areas during the nonsurgical therapy from 12.5 ± 12.0 mm to 8.8 ± 10.3 mm ($F = 16.1$; $p < .01$; $r^2 = .95$), and mean from 25 to 4.25 mm. Complete resolution of the disease was observed in some patients (59 cases) after 2 years (Table 6).

The significant change in the size of exposed bone was not significantly influenced by the type or duration of bisphosphonate therapy or by the initial size or location of the exposed bone. The pain scores with ONJ, at the first examination, at 3 months after beginning the nonsurgical therapy, at 1 year, and at the last examination, were subjectively assessed using a VAS. Pain scores ranged from 0 to 3 score scale. A total of 12 patients (6 males and 6 females) receiving zoledronate required three courses of antibiotics at different intervals.

Discussion

Bisphosphonates are life-saving drugs for oncology patients. Bisphosphonate-related ONJ is a well-documented side effect of the therapy.¹⁶ Ethical considerations prevent analyzing these agents in randomized trials. Numerous clinical protocols have been proposed for treating such lesion. Nevertheless, there is no consensus on the best protocol for treating the areas of exposed bone.^{3,11,13,14} Eckert et al.¹⁷ used surgery and antibiotics (amoxicillin/clavulanic acid) to treat 21 patients with bisphosphonate-associated ONJ and found that the clinical symptoms of osteonecrosis recurred in 10 cases (47.6%) after primary treatment.

On the other hand, our results showed a remarkable decrease in the size of exposed bone areas during the nonsurgical therapy from a mean 25 to 4.25 mm (12.5 ± 12.0 mm to 8.8 ± 10.3 mm, $F = 16.1$; $p < .01$; $r^2 = .95$), and showed also complete resolution of the disease in some patients. There is also no recurrence, although we used a minimally invasive nonsurgical regimen suggested by Moretti et al.¹⁵ This might be explained¹² on the basis that bisphosphonates are highly concentrated in the jaws. Coupled with chronic invasive dental diseases and treatments and the thin mucosa over bone, the small capillaries within the bone become involuted, and the bone becomes avascular. A spontaneous breakdown of the overlying mucosa, some form of injury, or an invasive surgery to the jaws usually causes this necrotic bone to become exposed which then fails to heal. Ficarra et al.¹⁸ were the first to suggest antibiotic treatment associated with hygiene protocol, and the value of this therapy has been supported by more recent articles.^{19,20} These actually coincide with our results in using limited minimally invasive nonsurgical protocol, whereas extensive radical surgical resection rarely results in wound closure and sometimes contributes to worsening of the disease.²¹

More precisely, debridement of the affected area and covering the exposed bone with soft tissue flaps or bone-contouring procedures has often proven to be risky, leading to more exposed bone, worsening of the symptoms, and increased risk for a pathologic fracture of the jaw. This can be explained on the basis that the uncertain outcomes of surgical treatment probably stem from the ability of bisphosphonates to bind hydroxyapatite and thus to be absorbed by bone, making it impossible to surgically remove the necrotic bone to a safe margin.¹² In addition, surgery may create a bone wound that will not heal, because of the bisphosphonate therapy itself; secondary osteonecrosis may then develop from the surgical margins.¹⁵ In such cases, the post-surgical relapse of the pathology can create greater bone exposure and a worsening of the condition. The intrinsic risks associated with these surgical procedures, which are typically performed in patients who are already compromised by their oncologic pathology, should persuade physicians to limit surgical intervention to only those cases that are refractory to conservative management.

The use of antibiotics is justified because bacteria play an important role in developing and maintaining the osteonecrotic process.^{22,23} Bacterial cofactors appear to be directly involved in the maintenance and development of the necrotic lesions, and these factors may also be responsible for significant inhibition of epithelial regeneration over the exposed bone.^{21,24}

Therefore, the present prospective longitudinal study evaluated the effectiveness of a minimally invasive hygiene protocol in a larger group of patients for a longer period of time, restricting antibiotic therapy to the acute phase, to determine whether this approach allowed long-term control of both necrotic bone and patient discomfort. It is important

to note that the size of the necrotic area is not a healing parameter, because it is strictly associated with other factors, such as soft tissue shrinkage due to the control of infection and inflammation. However, it should be considered that the mucosa does not grow on necrotic bone, and the effect of any variation of the soft tissues on the extent of the lesions should be minimal, especially if compared with the loss of one or more areas of bone sequestrum developed by some patients.

We do not know how long patients can live with exposed bone or how long they will maintain their quality of life with our minimally invasive protocol of nonsurgical management of ONJ. The unpredictable results associated with surgery support our nonsurgical minimally invasive regimen for treatment of ONJ, and also support a decision to avoid difficult surgery in patients who are already highly compromised by their oncologic pathology. We propose that surgery be considered only in selected cases that have proven to be refractory to long-term medical treatment, although it was not the case in our study. In addition, the antibiotic therapy should be limited to the acute painful phases of the condition, because we do not know whether repeated long-term cycles of antibiotics would produce bacterial resistance.

Based on the finding of Montebugnoli et al.³ that there was no difference between surgical and nonsurgical management of ONJ, so using the conservative nonsurgical regimen in this study saved the patients from the detrimental effects of surgery in such conditions.

Conclusion

This conservative and minimally invasive treatment regimen used in this study may provide successful treatment in the vast majority of patients suffering from ONJ, provided that they are adequately informed, motivated, and followed. Nonsurgical treatment of bisphosphonate-associated osteonecrosis is considered useful for controlling the disease.

Recommendations

It is well recommended that, before starting bisphosphonate therapy, all patients should be referred to a dental practitioner for an oral examination and treatment of any pathology, which may include conservative treatments, periodontal surgery, tooth extraction, and prosthetic procedures. Generally, the best solution for bisphosphonate osteonecrosis remains prevention.

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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