Clinical Report

A Clinical Retrospective Study of Surgical Treatment for Medication-Related Osteonecrosis of the Jaw

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(Accepted for publication, June 8, 2016)

Abstract: In 2014, the American Association of Oral and Maxillofacial Surgery recommended surgical treatment for medication-related osteonecrosis of the jaw (MRONJ) patients classified as stage 3 or those with mobile segments of bony sequestrum. However, there is limited information regarding the healing mechanism in MRONJ surgical treatments. This study aimed to retrospectively elucidate clinical outcomes of the surgical treatment of MRONJ patients. This study included 26 patients (7 men, 19 women; age: 42–92 years; mean ± standard deviation, 75.3 ± 11.7 years) who were classified as stage 3 or had mobile segments of bony sequestrum, and intake of the offending drug was ceased. The sequestrum was removed with surrounding vital bone, and segmental resection was performed in one patient with a pathological mandibular fracture. The outcome was classified into one of the following three categories: “Healing,” “Improvement,” “Unchanged,” and “Exacerbation.” The mean postoperative follow-up period was 16.6 months (3.0–57.9 months), and complete healing was observed in 21 patients (80.8%), improvement of the lesion was observed in four patients (15.4%), and the outcome of one patient was unchanged (3.8%). The procedure described here may be recommended with relatively high clinical success rate for the patients with MRONJ requiring surgical treatment.

Key words: Medication-related osteonecrosis of the jaw, Drug holiday, Sequestrum

Introduction

Bisphosphonates (BPs) inhibit bone resorption and are commonly used for treating bone-resorbing diseases such as osteoporosis, malignancy-related hypercalcemia, multiple myeloma, and bone metastasis from solid cancers1). BPs are unstable equivalents of pyrophosphates that selectively bind to bone and selectively act on osteoclasts during high bone turnover, resulting in an antiresorptive effect2). Despite the advantageous clinical effects of BP for treating several diseases, some adverse reactions have been reported including bisphosphonate-related osteonecrosis of the jaws (BRONJ)3–5). Similarly, denosumab, an antihuman RANK ligand (RANKL) monoclonal antibody that was developed to inhibit osteoclasts during the treatment of bone-resorbing diseases, is reported to cause osteonecrosis of the jaw (ONJ)6–7); this has been recently termed medication-related ONJ (MRONJ)8).

In 2014, the American Association of Oral and Maxillofacial Surgery (AAOMS) published recommendations for stage-specific treatment of MRONJ8). These recommendations reflected those stated in 2007 and 2009 for BRONJ, namely, supportive conservative therapy and surgical treatment for patients classified as stage 3 or those with mobile segments of bony sequestrum.

However, clear evidence regarding the mechanism of the healing process in MRONJ treatment has not been previously reported. In this study, we retrospectively evaluated the histopathological and radiological aspects of postoperative outcomes of surgical treatment in MRONJ patients.

Materials and Methods

Patients

This retrospective, clinical study included 26 patients diagnosed with MRONJ who required surgery and were referred to and treated in the Division of Oral and Maxillofacial Surgery at Kagawa Prefectural Central Hospital in Japan between January 2011 and December 2015.

The study inclusion criteria were based on the AAOMS 2014 update, stating that patients requiring surgery included those with...
stage 3 disease or mobile segments of bony sequestrum. The update defines MRONJ stage 3 as “exposed and necrotic bone, or fistulae that probe to bone, with evidence of infection” and at least one of the following: “exposed necrotic bone extending beyond the region of the alveolar bone, i.e., inferior border and ramus of the mandible, maxillary sinus, and zygoma in the maxilla,” “pathologic fracture,” “extra-oral fistula,” “oral antral/oral nasal communication,” and “osteolysis extending to the inferior border of the mandible or sinus floor.”

Conservative treatment with oral antibiotics and oral rinsing was performed before surgery, but this did not lead to healing of the defect. The extent of necrosis was evaluated using computed tomography (CT) and panoramic image.

The aim of the surgery was to remove the sequestrum as well as the surrounding vital bone. Thereafter, the affected bone was resected until healthy, perfused (bleeding) bone was observed (Fig. 1). In case of sequestration formation with a pathological fracture, segmental resection of the extensive necrotic bone and pathological fracture in the mandible was performed with safety margins extending to the living bone. Furthermore, the BP or denosumab treatment was interrupted 3 months before the operation, and a different treatment regimen was chosen in consultation with the physician in charge of treatment of MRONJ.

This study was approved by the Ethics Committee of Kagawa Prefectural Central Hospital (Approval No.492). Written informed consent was obtained from the patient for publication of this study and any accompanying images.

Outcomes

The postoperative clinical and functional statuses of patients were assessed for 3 months or longer using clinical and radiographical examinations. Histopathological analysis of the bone specimens demonstrated no metastatic disease, and confirmed a diagnosis of MRONJ in all cases.

Patients with follow-up periods >3 months were evaluated 6 months after surgery, and the presence or absence of changes in disease state was assessed.

The evaluation method proposed by Reich et al. was used and includes the following:

a) “Healing:” the objective symptoms disappeared
b) “Improvement:” an improvement relative to the stage at pre-treatment (postoperative stage < preoperative stage)
c) “Unchanged:” no change in the stage before and after treatment (postoperative stage = preoperative stage)
d) “Exacerbation:” progression of the disease in spite of surgical intervention (postoperative stage > preoperative stage)

Patient characteristics (Table 1)

Age and sex

Twenty-six patients, of which seven (26.9%) were male and 19 (76.9%) were female (male: female ratio 0.37), satisfied the inclusion criteria. The mean age was 75.3 years (standard deviation: 11.7 years, range: 42-92 years).

Primary cause of the disease

The treatment of osteoporosis was the most common indication for BP and/or denosumab, and this was observed in 20 patients (76.9%). The indications for treatment in the remaining patients included multiple myeloma (n = 3, 11.5%), breast carcinoma (n = 2, 7.7%), and prostate carcinoma (n = 1, 3.8%).

Location

The lesion was located in the maxilla in eight (30.8%) patients and mandible in 18 (69.2%) patients.

Stage classification

With regard to the AAOMS stage classification, 21 patients...
were stage 3 (80.8%) and five were stage 2 (19.2%). None of the MRONJ patients requiring surgical treatment had stage 0 or 1 disease.

**Triggering factor**

The following triggering factors of MRONJ were identified: tooth extraction (n = 14, 53.8%), periodontal disease (n = 3, 11.5%), natural occurrence (n = 2, 7.7%), denture incompatibility (n = 2, 7.7%), pericoronitis of the wisdom tooth (n = 1, 3.8%), dental implant infection (n = 1, 3.8%), and unknown cause (n = 3, 11.5%).

**Results**

**Surgical outcome (Table 1)**

The mean follow-up period was 16.6 months (3.0-57.9 months), twenty-five patients underwent sequestrum removal surgery, while one patient with a mandibular pathological fracture underwent segmental resection. With regard to the outcome of the surgery, complete healing was observed in 21 patients (80.8%), improvement of the lesion was observed in four patients (15.4%), and the condition remained unchanged in one patient (3.8%).

**Representative case reports**

**Case 1 (Figs. 2, 3)**

An 85-year-old woman presenting with swelling and pain in the right lower molar area was referred to a general dental practitioner who diagnosed her with an infection and extracted the lower first molar as it could not be saved. She experienced exacerbation of pain and swelling with a suppurative fistula approximately 1 month later, and was referred to the dental and oral surgery department of Kagawa university hospital for anti-inflammatory treatment. Thereafter, she was referred to the Division of Oral and Maxillofacial Surgery at Kagawa Prefectural Central Hospital in February 2014 when the pain continued to worsen and she experienced right mental nerve paralysis. The patient had a history of osteoporosis and had been undergoing oral BP (risedronate) treatment for more than 2 years. Extraoral examination revealed slight facial redness in the right submental to mandibular body region, and hypoesthesia in the area supplied by the right mental nerve. Intraoral examination revealed pain on contact and gingival swelling on the right side of the mandible, with the presence of a suppurative fistula. Panoramic radiography showed extensive osteolysis in the right mandibular body area, while computed tomography showed cortical osteolysis of the right mandible. Based on the criteria of the AAOMS, a diagnosis of stage 3 MRONJ was made. The patient received various types of oral and intravenous antibiotics and mouthwashes, and the fistula was cleaned. However, her symptoms did not completely resolve after treatment. In March 2014, a decision to remove the extensive necrotic bone and surrounding vital bone was made, followed by placement of a reconstruction plate via an extraoral approach under general anesthesia. The affected bone was then removed using piezosurgery until healthy, perfused (bleeding) bone was observed. The surgical site was completely healed 6 months postoperatively.

Figure 2. An 85-year-old female patient with medication-related osteonecrosis of the jaw (MRONJ) stage 3 disease. Facial view at the time of the first visit to our hospital. The patient had slight facial redness at the right submental to mandibular body region.

A. Intraoral examination revealed pain on contact and gingival swelling of the right side of the mandible, with presence of a suppurative fistula.

B. Panoramic image showed extensive osteolysis in the right mandibular body area.

C. Axial CT image revealed cortical osteolysis of the right mandible.

D. Three dimensional CT image showed bone loss due to the absorption of the buccal cortical bone.

F. After a diagnosis of stage 3 MRONJ, the patient underwent removal of the extensive necrotic bone as well as surrounding vital bone, followed by placement of a reconstruction plate via an extraoral approach.
After removal of the sequestrum and surrounding vital bone, a panoramic X-ray image showed a large radiolucent area extending from the second premolar to the wisdom tooth in the right mandible. Gradual bone regeneration in the left lower molar region was observed, and a radiographic image taken 1 year after surgery showed complete filling of the mandibular cavity by newly generated bone. The patient was well at the 2-year follow-up.

Case 2 (Fig. 4)

A 92-year-old woman was referred to the Division of Oral and Maxillofacial Surgery, Kagawa Prefectural Central Hospital in February 2014 with a 6-month history of spontaneous pain in the left molar region. The left lower second molar had been extracted by a private dentist in September 2013, and the patient had undergone antibiotic treatment and curettage of the socket in the department of dental and maxillofacial surgery in a general hospital. She had a medical history of osteoporosis and had been undergoing oral BP (risedronate) treatment for more than 10 years.

Extraoral examination showed facial redness in the left...
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Table 1. Summary of the 26 patients included in our study

<table>
<thead>
<tr>
<th>Drug</th>
<th>Location</th>
<th>Triggering factor</th>
<th>Stage at diagnosis</th>
<th>Surgical treatment</th>
<th>Outcome</th>
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Figure 5 Histopathological examination.
A. Loupe image: shows a mixture of sequestration and viable bone.
B. Several multinucleated, giant osteoclasts (arrow head) are observed on the bone surface, along with several Howship’s lacuna, indicating bone resorption.
C. Reactive bone formation is observed. Active osteocytes with rich reticulum (arrow) and osteoblasts are observed in large numbers.
D. Non-viable bone and extensive osteonecrosis. Osteocytes are lost.
submandibular region with trismus, while intraoral examination revealed gingival swelling of the left mandibular molar with a suppurrative fistula. Panoramic radiography showed extensive osteolysis in the left mandibular body area, and computed tomography revealed cortical osteolysis of the left mandible along with a pathological mandibular fracture. Based on the criteria of the AAOMS, a diagnosis of stage 3 MRONJ was made. Despite conservative treatment for 3 months, the spontaneous pain was observed to worsen. Therefore, in March 2014, a decision was made to perform segmental resection of the extensive necrotic bone and pathological fracture in the mandible with safety margins via an extraoral approach under general anesthesia. The affected bone was removed until healthy, perfused (bleeding) bone was observed. The patient underwent repositioning and reconstruction with an osteosynthesis locking plate at the time of resection, and was well at the 2-year follow-up.

**Histological evaluation**

Loupe image showed a mixture of sequestration and viable bone (Fig.5A). Microscopic examination showed necrotic bony trabeculae with empty osteocyte lacunae. The necrotic bone was surrounded by bacterial colonies and exhibited irregular peripheral resorption and prominent reversal lines (Fig. 5D). Empty Howship’s lacunae were frequently observed at the periphery of the bone, suggesting that the osteoclasts had undergone apoptosis after internalizing bisphosphonates. These findings confirmed a diagnosis of BRONJ. Viable bone areas and numerous multinucleated osteoclasts were observed at the periphery of the bony trabeculae and in the intertrabecular spaces (Fig.5B). Active osteocytes and osteoblasts were observed on the periphery of the bone surface, suggesting the occurrence of proper bone remodeling (Fig.5C). The intertrabecular spaces were infiltrated by inflammatory cells including neutrophils, lymphocytes, and plasma cells.

**Discussion**

MRONJ can be caused by various agents, and the risk depends on the type, dosage, and duration of the medication. The risk of ONJ in cancer patients in clinical trials was 0-0.019% (0-1.9 cases per 10,000 cancer patients)\(^8\), while the risk of ONJ in cancer patients on denosumab treatment was comparable to that of patients receiving zoledronate\(^13,19\). The risk of ONJ among osteoporosis patients treated with zoledronate or denosumab (0.017-0.04%) was similar to that of patients enrolled (0-0.02%)\(^9\). The duration of BP or antiresorptive therapy remains a risk factor for ONJ. Among patients receiving zoledronate or denosumab treatment, the risk of ONJ incidence increased two to three times when these agents were used for more than 3 years\(^13\). A further increase in the number of MRONJ patients is expected in the future, although its treatment is still under discussion.

The international consensus for MRONJ treatment includes conservative measures initially\(^8\), followed by surgical therapy if no effect is observed. The reported success rates vary considerably, including approximately 12-100%\(^16,18\), 54% of 33 patients\(^17\), and 23% of 29 patients\(^18\). However, comparisons of different studies are limited by the fact that different criteria may be used to define the success of treatment outcomes. Some studies define success as the absence of infection and cessation of disease progression, while others define a successful treatment outcome as normal oral mucosa without any sign of exposed bone. Hoff et al.\(^18\) and Lazarovici et al.\(^19\) in their retrospective analyses of patients treated conservatively or with superficial debridement reported complete healing in only 23% and 18% of patients, respectively. The low rates of complete healing following conservative or minimal surgical treatment (only sequestrectomy) of established MRONJ have resulted in an increased interest in the performance of more extensive surgery for this disease. In our study, removal of sequestrum as well as the surrounding vital bone was performed after cessation of the medication. In case of sequestration formation, oral soft tissues can be used to easily close the socket of the removed sequestrum and bony edge completely. After the affected bone is removed and the bony edges are rounded off, a mucoperiosteal flap is elevated and moved for closure. The use of good surgical technique with adequate removal of sequestrum and soft tissue closure results in a predictable treatment outcome, with some authors reporting a success rate of 85-100% with uncomplicated intraoral wound healing after surgical treatment\(^16,20,21\). Although closure using the local skin flap has exhibited high success rates\(^22,23\), our treatment method benefits from being minimally invasive and having the same effect without requiring a local flap.

Osteoclasts, a specific target cell of BP, play a central role in physiological and pathological bone resorption. However, this medication inhibits their differentiation and function and increases their apoptosis, leading to decreased bone resorption and remodeling\(^24,26\). Weinstein et al. reported greater presence of osteoclasts in biopsy specimens collected from the iliac bone of healthy postmenopausal women receiving oral BP therapy than in those from patients who were receiving placebo\(^27\). A number of giant and hypernucleated osteoclasts with 20-40 nuclei, of which approximately 30% were apoptotic, were observed to detach from the bone surface, suggesting that BPs prolonged the apoptosis of osteoclasts while cell fusion continued to generate distinctive morphology such as giantism and hypernucleation. In patients undergoing BP treatment, the drug is believed to inactivate and induce apoptosis of osteoclasts, instead of reducing their numbers. In case 2 of our study, giant and hypernucleated osteoclasts were not observed, suggesting that the effect of the BP had been lost during long-term withdrawal.

Moreover, osteoclasts have been known to indirectly assist...
bone formation, wherein osteoclastic bone resorption results in the release of some growth factors in the bone which stimulate osteoblasts to produce bone. The interaction of osteoclasts with osteoblasts is thought to be essential for bone turnover. Thus, the loss of osteoclasts is likely to impair the activity of osteoblasts, resulting in bone turnover arrest and osteonecrosis. On the other hand, the direct effects of BP on osteoblasts have also been investigated. Zoledronate inhibited the growth and viability of osteoblasts,[28,29], which in turn inhibits bone healing. In a representative case[1] included in the present study, bone healing of the mandible after cessation of medication and sequestrum removal was apparent radiologically. Additionally, strong osteoblast activity was also observed histologically, suggesting that a "drug holiday" or discontinuation of drugs may be effective in the treatment of MRONJ. The treatment of MRONJ may be associated with damage to osteoblasts, and this hypothesis is supported by a study that reported that the parathyroid hormone may improve MRONJ by stimulating osteoblasts[30]. However, in patients treated with BP therapy, a drug holiday seems to be maximally effective for restoring bone turnover of the jaw and supporting the treatment of MRONJ. Although sequestrum removal surgery with a drug holiday is a useful method for MRONJ treatment, these measures should only be selected based on the general condition of the patient and the local state. The treatment measures used in this study showed a good healing rate of 96.2% (complete healing: 80.8%; improvement: 15.4%) and should be, therefore, considered a more effective treatment in the requiring surgery patients with free sequestration in our surgical strategy.

In conclusion, this clinical retrospective study of treatment of MRONJ showed that sequestrum may be formed despite a drug holiday, and the use of a surgical technique to adequately remove it, accompanied by soft tissue closure, results in predictable treatment outcomes.

Competing interests
The authors have declared that no COI exists.

References


