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Enhancement of bone perfusion through cortical perforations to improve healing of medication-related osteonecrosis of the jaw: a retrospective study☆

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Y. Guo, C. Guo: Enhancement of bone perfusion through cortical perforations to improve healing of medication-related osteonecrosis of the jaw: a retrospective study. Int. J. Oral Maxillofac. Surg. 2021; 50: 740–745.

Abstract. Medication-related osteonecrosis of the jaw (MRONJ) is generally difficult to treat. So far, no optimal strategy for MRONJ has been established. The aim of this study was to determine whether a new surgical technique, i.e. curettage with cortical perforations of healthy adjacent bone that enhances bone perfusion would be more effective than standard curettage in treating patients with MRONJ. Twenty-eight MRONJ patients who underwent curettage treatment with or without cortical perforation technique at our institution between June 2014 and May 2016 were included in this retrospective study. Ten cases treated using cortical perforation technique were completely cured after primary wound closure with mucoperiosteal flap. During a long-term follow-up, two cases from the cortical perforation group relapsed at the mandibular sites 6 and 40 months post-operation, respectively, while in the control group, 77.8% (14/18) cases relapsed due to infected mucosa fistula or bone exposure 1–3 months after treatment. It was concluded that the new treatment approach might be more effective in treating patients with MRONJ caused by antiresorptive drugs. However, more extensive randomized trials are needed to further evaluate its efficacy in clinic.

Key words: MRONJ; treatment outcome; cortical perforation; bone perfusion.

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Medication-related osteonecrosis of the jaw (MRONJ) is an oral complication that can occur after exposure to medications, including bisphosphonates, RANKL ligand inhibitor or anti-angiogenic drugs[1–3]. MRONJ remains a clinical challenge due to uncertain prognosis after treatment[4]. Prevention strategies for MRONJ include maintenance of good oral hygiene, oral antibiotics, as well as local tissue resection[4–6]. Antibiotic therapy is commonly combined with chlorhexidine mouth rinse, hyperbaric oxygen or low-level laser therapy[7,8]. Conversely, surgical treatment includes conservative

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debridement of necrotic bone and major resection of the necrotic lesion[9–11]. Moreover, the success rate of surgical treatment is higher than the one reported for antibiotic therapy[12].

Curettage is a form of therapy that removes superficial inflammatory soft tissue and necrotic bone and usually leads to effective relief of maxillofacial osteomyelitis[13,14]. Yet, this type of treatment is not effective for patients with MRONJ[15,16].

Previous studies have suggested that adequate soft tissue coverage is essential in promoting the healing of MRONJ. For example, the use of pedicled buccal fat pad flap and nasolabial flap has shown to be more effective than simple mucoperiosteal flaps for treating patients with MRONJ[17,18]. Apart from the soft tissue coverage with abundant blood supply, adequate bone lesion resection to reach the normal bleeding edge, supplementary autologous platelet concentrate such as PRP (platelet-rich plasma), PRF(platelet-rich fibrin), and PRGF(plasma rich in growth factors), or reconstructing the jaw defect with vascularized free flap (fibular flap or scapula) indicate that providing sufficient blood supply for the wound can be beneficial to MRONJ symptoms relief[19–22].

Drilling holes on the cortical bone, also known as cortical perforation technique, is often used to enhance the bleeding during the autogenous bone grafting process. The purpose of the present study was to evaluate the healing results of MRONJ patients who received curettage with or without cortical perforation. We hypothesized that the cortical perforations of healthy adjacent bone that enhances bone perfusion would provide favourable structure space for blood transportation from bone marrow or mucoperiosteal flap, which in turn might promote the wound healing process.

Materials and Methods

Study design and sample

A total of 28 MRONJ patients who underwent curettage surgical treatment at Peking University Hospital and School of Stomatology (PKUSS) between June 2014 and May 2016, were selected in this retrospective clinical study. The patients were followed up for 30 months at least. The inclusion criteria were the following: (1) the MRONJ was diagnosed according to the American Association of Oral & Maxillofacial Surgeons definition[4]; (2) those who signed the informed consent. The patients with a medication history of combined bisphosphonates and antiangiogenic drugs were excluded from the study; antiangiogenic target drugs can significantly aggravate the occurrence of MRONJ, and the risk of wound non-healing after curettage surgery is high[23].

Patients were divided into two groups: the control group (18 cases) treated with the conventional approach (sequestrectomy and curettage without cortical perforation) before December 2015, and the experimental group (10 cases) treated with a novel approach (sequestrectomy and curettage with cortical perforations of the residual healthy bone) from December 2015 to May 2016.

The study was approved by the institutional biomedicine ethics committee of

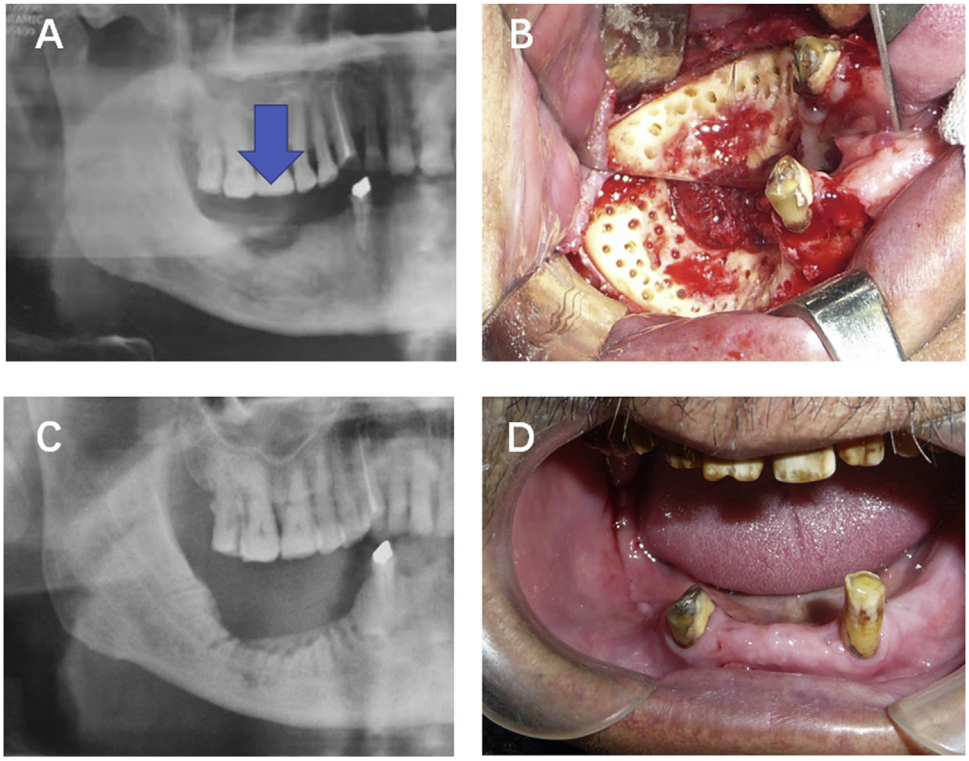

Fig. 1. Cortical perforation technique applied in a medication-related osteonecrosis of the jaw (MRONJ) case of stage II. (A) A 55-year-old male patient with multiple myeloma was treated with thalidomide and zoledronic acid for 15 months. A 2-mm size fistula was detected on the lingual and right side of the mandible, corresponding to the right first molar. PR (panoramic radiography) imaging showed the sequestrum had been separated from the surrounding bone. Arrow indicates the sequestrum. (B) After removal of the inflamed tissue and sequestrum, cortical perforations were prepared using drill under continuous irrigation with saline. (C) Cortical perforations shown in the PR imaging 1 week post-operation. (D) Three months after the operation, the intraoral wound was fully healed and was maintained in good condition until the patient death 2 years later (pulmonary infection caused by chemotherapy) (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

PKUSS (PKUSSIRB-201949114). Informed consent was obtained from all patients.

Variables and Data Collection

The treatment type (curettage versus curettage with cortical perforation) was the predictor variable. The outcome variable was the healing status of the skin or mucosal wound defined as the recurrence of exposed bone or fistula at the operated site through clinical examination during at last 30 months of postoperative follow-up. Other study variables recorded from the patient records were demographic characteristics, including age, gender, cancer diagnosis, type of antiresorptive therapy, and predisposing factor for MRONJ onset (e.g., spontaneous or extraction of teeth). The data were retrospectively collected from the patient medical records and analysed.

Cortical perforation technique (CPT)

During the surgery, mucoperiosteal flap with mesial and distal releasing incision was raised along the alveolar ridge that spans across the necrosis region covering up to two healthy teeth to allow optimal exposure of the lesion. Then, debridement of the inflamed granulation tissues and sequestra was performed, followed by peripheral ostectomy of the osteosclerotic area to expose the bleeding margins. In the control group, the bony edges were then smoothened to form a saucer-like depression and achieve the primary wound closure. In the experimental group, cortical perforations were performed as follows: multiple burr holes were made on the residual healthy bone using high-speed fissure burr (diameter = 1.0 mm) under copious irrigation with normal cold saline. The distance between the two perforations was approximately 2 mm. The cortical perforations should reach the bone marrow space and penetrate both the buccal and lingual cortex to allow the infiltration of the adjacent blood supply to the surgical site. The complete closure of the wound was achieved by relieving the tension of the mucoperiosteal flap. Finally, the low-pressure vacuum drain was placed for 24 h to evacuate excess discharge, to prevent potential surgical site infection. The full surgical procedure is shown in Figs 1 and 2.

The therapeutic regimens for all patients included early antibiotic intravenous treatment, which started 24 h before surgery and continued for 6 days after surgery. Clinical follow-up was performed on all patients at regular intervals, including radiographic scans at 3- to 6-month intervals or as clinically indicated.

Statistical Analysis

Descriptive statistics for quantitative variables are presented as the mean ± standard deviation. Independent-sample *t*-tests and χ^2 analyses were performed to examine the association between the outcomes and each factor of interest. The Kaplan–Meier method was used to plot the curves for each relapse in two different treatment groups stratified in terms of staging. Cox proportional hazard regression models were used to independently determine the factors associated with the dependent variable and the MRONJ relapse. The

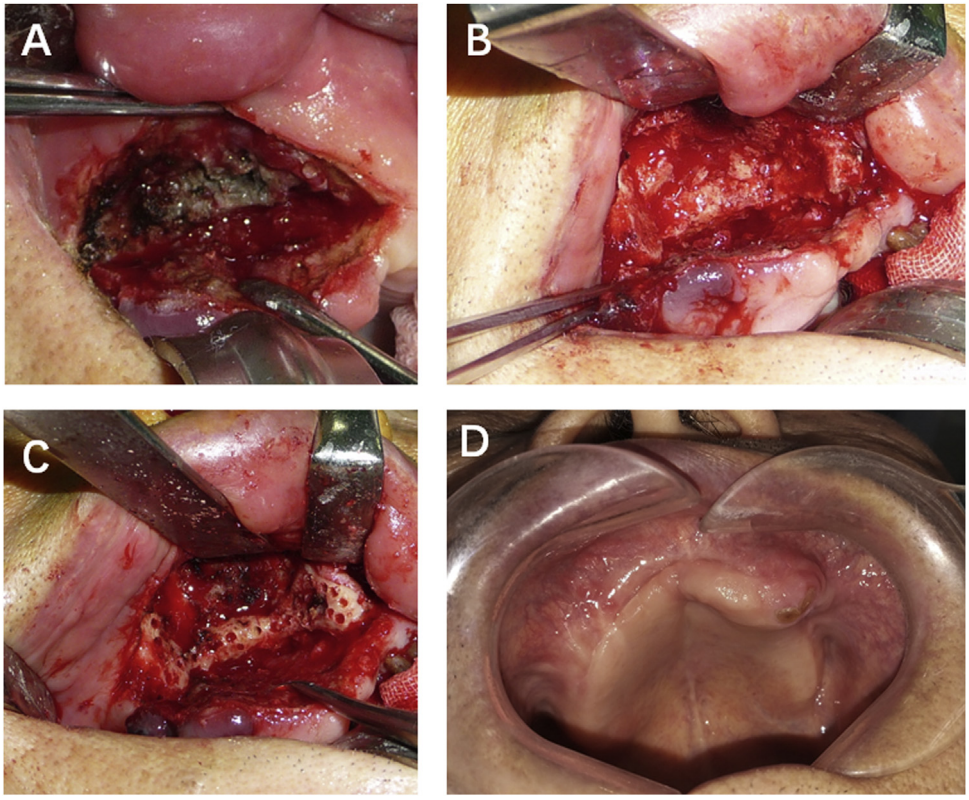

Fig. 2. Cortical perforation technique applied in a medication-related osteonecrosis of the jaw (MRONJ) case of stage III. (A, B) An 83-year old male patient with prostate cancer and bone metastasis was treated with zoledronic acid for 2 years. Consequently, the patient suffered non-healing of teeth sockets after spontaneous teeth loss (14/13/12/11/21/22). Sequestrum had been exposed and removed during operation. (C) Cortical perforations were prepared on the remaining bony field. (D) Postoperative 3.5 years photo reveals complete soft tissue healing without any fistula formation, and the patient recovered to the normal status of chewing function with a suitable denture.

Table 1. Distribution of demographic data and other co-variables by group ($n = 28$).

Variable	Control group (curettage; $n = 18$)	Experimental group (curettage and cortical perforation; $n = 10$)	P
Sample size	18	10	
Age (years)			0.653*
Mean ± SD	62.17 ± 2.80	63.50 ± 3.38	
Gender			0.649‡
Male	10 (55.56)	6 (60)	
Female	8 (44.44)	4 (40)	
Treatment duration (months)			0.579*
Mean ± SD	39.89 ± 6.43	34.44 ± 8 .62	
Anatomic location			0.328‡
Mandibular	7 (38.89)	6 (60)	
Maxillary	8 (44.44)	4 (40)	
Maxilla and mandible	3 (16.67)	0	
Disease stage			0.412‡
2	5 (27.78)	5 (50)	
3	13 (72.22)	5 (50)	
Duration until MRONJ relapse (months)	5.71 ± 1.13	17.29 ± 5.75	0.010*
Treatment result			0.005‡
Healed	4 (22.22)	8 (80)	
Relapse	14 (77.78)	2 (20)	

Data presented as *n* (%), unless otherwise noted. IQR, interquartile range; MRONJ, medication-related osteonecrosis of the jaw; SD, standard deviation.
* Independent-sample *t*-test.
‡ χ^2 test.

P-values were two-sided and subject to a significance level of 0.05.

Results

Twenty-eight patients with MRONJ were included in the study (Table 1, Supplementary Table S1). All of the patients completed the 30 months follow-up. Among the 28 patients, 12 were males and 16 were females, with an average age of 62.68 years (44–83 years). In the control group, the mean age was 62.17 ± 2.80 years, while it was 63.50 ± 3.38 years in the experimental group. The mean duration of antiresorptive therapy was 37.21 ± 26.34 months until the diagnosis of MRONJ; in the control group, the mean duration was 39.89 ± 6.43 months, while in the experimental group, it was 34.44 ± 8.62 months. In addition, in the control group, there were five and 13 patients within the disease stage II and III, respectively; in the experimental group, there were five and five patients within the stage II and III, respectively. In the case of MRONJ relapse, the mean time after surgery for all patients was 16.25 ± 7.59 months. In the control group, the mean time was 5.71 ± 1.13 months compared with 17.29 ± 5.75 months in the experimental group. Moreover, cases within both stage II and stage III showed a better prognosis and a lower risk of relapse in the experimental group than the cases in the control group (Fig. 3).

The treatment success was significantly higher in the experimental group ($P = 0.005$; Table 1). In further univariate analysis of variables in the healed and relapsed group, variables including age, gender, type of antiresorptive agent, duration of antiresorptive therapy until the occurrence of MRONJ, the site, and stage of MRONJ did not differ significantly, except for the type of surgical treatment (Table 2). Furthermore, multivariate analyses were carried out through the adjusted regression analysis. The results showed that only the type of surgical treatment has a significant value in the relapse of MRONJ (Table 3).

Discussion

MRONJ is a relatively common form of osteomyelitis of the jaw, which is usually caused by antiresorptive and anti-angiogenic drugs that are prescribed to patients with various medical conditions, such as osteoporosis, bone metastases, multiple myeloma, etc.[24]. The vasculature is considered as the primary source of oxygen, nutrients, hormones, and growth factors, which have an essential role in bone development, regeneration, and remodelling[25]. The suppression of angiogenesis and bone remodelling within the alveolar bone may quickly lead to the accumulation of inflammation and/or infection, which are a significant risk factors for the occurrence of MRONJ[26–29]. Once alveolar trauma or chronic inflammation occurs, impaired bone marrow stromal cells (BMSCs) from the central area and peripheral area of MRONJ lesion cannot function properly, which significantly affects the new bone formation and wound healing[30,31]. Thus, rebuilding the blood supply that carries BMSCs and growth nutrients could be essential for an effective MRONJ treatment.

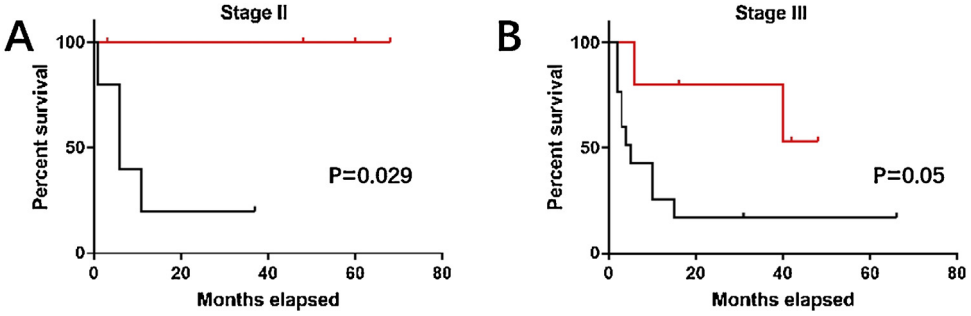

Fig. 3. Graphical depiction of Kaplan–Meier analysis comparing relapse timing differences in control (black lines) and experimental (red lines) groups in stage 2 (A) and stage 3 (B) with *P* values indicated in the pictures (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

Table 2. The relationship between the study variables compared with primary outcome variable (relapse) using univariate analysis (medication-related osteonecrosis of the jaw (MRONJ) relapse; $n = 28$).

Variable	Hazard ratio	95% CI	*P*
Age (<50 vs >50 years)	0.714	0.230–2.222	0.561
Gender (female vs male)	0.803	0.296–2.179	0.667
Type of antiresorptive drugs (pamidronate vs zoledronate)	0.672	0.255–1.768	0.423
Duration of antiresorptive therapy until MRONJ (months)	1.005	0.988–1.023	0.569
Site of MRONJ (mandible vs maxilla vs mandible and maxilla)	1.834	0.833–4.037	0.132*
Stage of MRONJ (stage II vs stage III)	2.050	0.659–6.383	0.215
Type of surgical treatment (curettage vs cortical perforation)	0.121	0.026–0.565	0.007*

CI, confidence interval.
* Univariate analyses are performed first to select those factors that with $P < 0.2$ for further multivariate analysis.

Table 3. The relation between the study variables compared to primary outcome variable (relapse) using multivariate analysis (medication-related osteonecrosis of the jaw (MRONJ) relapse; $n = 28$).

Variable	Hazard ratio	95% CI	*P*
Site of MRONJ (mandible vs maxilla vs mandible and maxilla)	1.486	0.767–3.289	0.312
Type of surgical treatment (curettage vs cortical perforation)	0.126	0.098–0.351	0.01

CI, confidence interval.

In the present study, we established a new surgical approach that was based on curettage with cortical perforations of healthy adjacent bone for treating patients with MRONJ. The goal was to supply a healthy bone marrow cavity or cortical bone with new blood, nutritional factors (BNFs) and MSCs via bone perforations, which could, in turn, promote the wound healing process. Additional studies are required to further confirm this hypothesis. Briefly, the treatment was applied to 10 patients; it was easy to perform and was more effective compared with standard curettage (which was based on stable wound healing procedure). The treatment was nearly the same as its use in the autogenous bone grafting process for enhancement of bone perfusion.

Lemond et al. suggested that radical resection followed by free flap surgery should be reserved for symptomatic patients with MRONJ at an advanced stage and a good prognosis[18]. Still, the use of less invasive surgery is more acceptable for selective patients with a better prognosis. The perfusion reduction of both the bone-covering soft tissue and the bone itself should be carefully considered before and during the surgery. Sufficient bone removal to normal edge and application of antibiotics help to achieve the local and systemic control of infection. Besides, the use of a drainage device can reduce secondary infection due to the excess discharge after surgery. Protecting the inferior alveolar nerve during operation is essential for MRONJ patients to maintain a good quality of life. The accurate assessment of the location of the lesion and the mandibular neural canal using CBCT (cone-beam computed tomography) is beneficial to avoid nerve injury during the cortical perforation procedure. Ultrasonic piezoelectric surgery may be helpful in reducing the risk of nerve injury[32].

Since the introduction of antiangiogenic target therapies, the life expectancy in metastatic renal cell cancer patients has almost tripled, leading to longer exposure to bisphosphonates treatment and increased occurrence of MRONJ. It has also been reported that the treatment duration before the occurrence of MRONJ was shortened in patients at advanced stage who were prescribed with antiresorptive-antiangiogenic drugs over those who received antiresorptive drug only[23,33]. Our preliminary results showed that standard curettage is ineffective for patients receiving antiresorptive-antiangiogenic medication. Therefore, the type and duration of the patients' medication should be carefully considered when choosing the surgical treatment and the extent of radical resection. In the present study, no patients were given angiogenesis-targeted drugs, or checkpoint inhibitors, while bisphosphonate drugs were discontinued for at least 2 months at the time of surgery. The combination of angiogenesis-targeted drugs and bisphosphonate drugs can rapidly aggravate MRONJ symptoms, and whether this method can be used for such patients requires further exploration[23].

This study has a few limitations. This was a retrospective style, non-randomized study with a relatively small sample size. More extensive randomized trials are needed in the future.

Funding

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Competing interests

This research is free of any conflicts of interest.

Ethical approval

The study was approved by the institutional biomedicine ethics committee of our hospital (PKUSSIRB-201414057) and conformed to the Declaration of Helsinki.

Patient consent

Written informed consent was obtained from all participants.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijom.2020.07.036.

References

1. Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL. Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. *J Oral Maxillofac Surg* 2004;**62**:527–34.
2. Ruggiero SL, Dodson TB, Assael LA, Landesberg R, Marx RE, Mehrotra B. American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws – 2009 update. *J Oral Maxillofac Surg* 2009; **67**:2–12.
3. Guo Y, Wang D, An J, Peng X, Cai Z, Guo C. Clinical analysis of 24 cases of bisphosphonate-related osteonecrosis of the jaw. *Zhon-*

ghua Kou Qiang Yi Xue Za Zhi 2014;**49**:517–20.

4. Ruggiero SL, Dodson TB, Fantasia J, Goodday R, Aghaloo T, Mehrotra B, O'Ryan F. American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw – 2014 update. *J Oral Maxillofac Surg* 2014;**72**:1938–56.
5. Khan AA, Morrison A, Hanley DA, Felsenberg D, McCauley LK, O'Ryan F, Reid IR, Ruggiero SL, Taguchi A, Tetradis S, Watts NB, Brandi ML, Peters E, Guise T, Eastell R, Cheung AM, Morin SN, Masri B, Cooper C, Morgan SL, Obermayer-Pietsch B, Langdahl BL, Dabagh RA, Davison KS, Kendler DL, Sándor GK, Josse RG, Bhandari M, Rabbany ME, Pierroz DD, Sulimani R, Saunders DP, Brown JP, Compston J. Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. *J Bone Miner Res* 2015;**30**:3–23.
6. Schwartz HC. American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw – 2014 update and CTX. *J Oral Maxillofac Surg* 2015;**73**:377.
7. Freiberger JJ, Padilla-Burgos R, McGraw T, Suliman HB, Kraft KH, Stolp BW, Moon RE, Piantadosi CA. What is the role of hyperbaric oxygen in the management of bisphosphonate-related osteonecrosis of the jaw: a randomized controlled trial of hyperbaric oxygen as an adjunct to surgery and antibiotics. *J Oral Maxillofac Surg* 2012;**70**:1573–83.
8. Vescovi P, Merigo E, Meleti M, Fornaini C, Nammour S, Manfredi M. Nd: YAG laser biostimulation of bisphosphonate-associated necrosis of the jawbone with and without surigcal treatment. *Br J Oral Max Surg* 2007;**45**:628–32.
9. Sacco R, Sacco G, Acocella A, Sale S, Sacco N, Baldoni E. A systematic review of microsurgical reconstruction of the jaws using vascularized fibula flap technique in patients with bisphosphonate-related osteonecrosis. *J Appl Oral Sci* 2011;**19**:293–300.
10. Sacco R, Sacco N, Hamid U, Ali SH, Singh M, Blythe JS. Microsurgical reconstruction of the jaws using vascularised free flap technique in patients with medication-related osteonecrosis: a systematic review. *Biomed Res Int* 2018;**2018**:9858921.
11. Wilde F, Heufelder M, Winter K, Hendricks J, Frerich B, Schramm A, Hemprich A. The role of surgical therapy in the management of intravenous bisphosphonates-related osteonecrosis of the jaw. *Oral Surg Oral Med O* 2011;**111**:153–63.
12. Rupel K, Ottaviani G, Gobbo M, Contardo L, Tirelli G, Vescovi P, Lenarda RD, Biasotto M. A systematic review of therapeutical approaches in bisphosphonates-related osteonecrosis of the jaw (BRONJ). *Oral Oncol* 2014;**50**:1049–57.
13. McLeod NMH, Patel V, Kusanale A, Rogers SN, Brennan PA. Bisphosphonate osteonecrosis of the jaw: a literature review of UK policies versus international policies on the management of bisphosphonate osteonecrosis of the jaw. *Br J Oral Max Surg* 2011;**49**:335–42.
14. Nezafati S, Ghavimi MA, Yavari AS. Localized osteomyelitis of the mandible secondary to dental treatment: report of a case. *J Dent Res Dent Clin Dent Prospects* 2009;**3**:67–9.
15. Guo YX, Wang DC, Wang Y, Peng X, Mao C, Guo CB. Clinical features of osteonecrosis of jaws after bisphosphonates therapy for bone metastasis of breast cancer. *Beijing da xue xue bao Yi xue ban J Peking Univ Health Sci* 2016;**48**:80–3.
16. Hayashida S, Soutome S, Yanamoto S, Fujita S, Hasegawa T, Komori T, Kojima Y, Miyamoto H, Shibuya Y, Ueda N, Kirita T, Nakahara H, Shinohara M, Umeda M. Evaluation of the treatment strategies for medication-related osteonecrosis of the jaws (MRONJ) and the factors affecting treatment outcome: a multicenter retrospective study with propensity score matching analysis. *J Bone Miner Res* 2017;**32**:2022–9.
17. Rotaru H, Kim M-K, Kim S-G, Park Y-W. Pedicled buccal fat pad flap as a reliable surgical strategy for the treatment of medication-related osteonecrosis of the jaw. *J Oral Maxillofac Surg* 2015;**73**:437–42.
18. Lemound J, Muecke T, Zeller A-N, Lichtenstein J, Eckardt A, Gellrich N-C. Nasolabial Flap Improves Healing in Medication-Related Osteonecrosis of the Jaw. *J Oral Maxillofac Surg* 2018;**76**:877–85.
19. Kim HY, Lee SJ, Kim SM, Myoung H, Hwang SJ, Choi JY, Lee J-H, Choung PH, Kim MJ, Seo BM. Extensive surgical procedures result in better treatment outcomes for bisphosphonate-related osteonecrosis of the jaw in patients with osteoporosis. *J Oral Maxillofac Surg* 2017;**75**:1404–13.
20. Bedogni A, Saia G, Bettini G, Tronchet A, Totola A, Bedogni G, Ferronato G, Nocini PF, Blandamura S. Long-term outcomes of surgical resection of the jaws in cancer patients with bisphosphonate-related osteonecrosis. *Oral Oncol* 2011;**47**:420–4.
21. Caldroney S, Ghazali N, Dyalram D, Lubek JE. Surgical resection and vascularized bone reconstruction in advanced stage medication-related osteonecrosis of the jaw. *Int J Oral Maxillofac Surg* 2017;**46**:871–6.
22. Lopez-Jornet P, Sanchez Perez A, Amaral Mendes R, Tobias A. Medication-related osteonecrosis of the jaw: Is autologous platelet concentrate application effective for prevention and treatment? Asystematic review. *J Craniomaxillofac Surg* 2016;**44**:1067–72.
23. Fusco V, Porta C, Saia G, Paglino C, Bettini G, Scoletta M, Bonacina R, Vescovi P, Merigo E, Re GL, Guglielmini P, Fede OD, Campisi G, Bedogni A. Osteonecrosis of the jaw in patients with metastatic renal cell cancer treated with bisphosphonates and targeted agents: results of an Italian multicenter study and review of the literature. *Clin Genitourin Cancer* 2015;**13**:287294.
24. Guo YX, Wang DC, Wang Y, Peng X, Guo CB. Imaging features of medicine-related osteonecrosis of the jaws: comparison between panoramic radiography and computed tomography. *Oral Surg Oral Med Oral Pathol* 2016;**122**:E69–76.
25. Filipowska J, Tomaszewski KA, Niedzwiedzki L, Walocha JA, Niedzwiedzki T. The role of vasculature in bone development, regeneration and proper systemic functioning. *Angiogenesis* 2017;**20**:291–302.
26. Bi Y, Gao Y, Ehirchiou D, Cao C, Kikuiri T, Le A, Shi S, Zhang L. Bisphosphonates cause osteonecrosis of the jaw-like disease in mice. *Am J Pathol* 2010;**177**:280–90.
27. Kikuiri T, Kim I, Yamaza T, Akiyama K, Zhang Q, Li Y, Chen C, Chen W, Wang S, Le AD, Shi S. Cell-based immunotherapy with mesenchymal stem cells cures bisphosphonate-related osteonecrosis of the jaw-like disease in mice. *J Bone Miner Res* 2010;**25**:1668–79.
28. Kim S, Williams DW, Lee C, Kim T, Arai A, Shi S, Li X, Shin K, Kang MK, Park N, Kim RH. IL-36 induces bisphosphonate-related osteonecrosis of the jaw-like lesions in mice by inhibiting TGF-beta-mediated collagen expression. *J Bone Miner Res* 2017;**32**:309–18.
29. Guo Y, Yuan Y, Wu L, Ho TV, Jing J, Sugii H, Li JXH, Feng J, Guo C, Chai Y. BMP-IHH-mediated interplay between mesenchymal stem cells and osteoclasts supports calvarial bone homeostasis and repair. *Bone Res* 2018;**6**:30.
30. He LH, Xiao E, An JG, He Y, Chen S, Zhao L, zhang T, Zhang Y. Role of bone marrow stromal cells in impaired bone repair from BRONJ osseous lesions. *J Dent Res* 2017;**96**:539–46.
31. Katsarelis H, Shah NP, Dhariwal DK, Pazianas M. Infection and medication-related osteonecrosis of the jaw. *J Dent Res* 2015;**94**:534–9.
32. Blus C, Giannelli G, Szmukler-Moncler S, Orru G. Treatment of medication-related osteonecrosis of the jaws (MRONJ) with ultrasonic piezoelectric bone surgery. A case series of 20 treated sites. *Oral Maxillofac Surg* 2017;**21**:41–8.
33. Ghidini G, Manfredi M, Giovannacci I, Mergoni G, Sarraj A, Mureddu M, Giunta G, Bonanini M, Meleti M, Vescovi P. Medication-related osteonecrosis of the jaw: risk factors in patients under biphosphonate versus patients under antiresorptive-antiangiogenic drugs. *Minerva Stomatol* 2017;**66**:135–40.

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