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Original Article

Successful prevention of medication-related osteonecrosis of the jaw after dental extractions by socket preservation with alloplast plus tetracycline in patients taking antiresorptive drugs

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Abstract *Background/purpose:* Medication-related osteonecrosis of the jaw (MRONJ) is a serious side effect of antiresorptive, antiangiogenic or targeted agents, and usually occurs after dental extraction. The etiopathogenesis of MRONJ is multifactorial and not fully understood. MRONJ remains difficult to treat. Precluding MRONJ occurrence is therefore essential. We offer our experiences and treatment strategies regarding the successful prevention of MRONJ after tooth extractions in patients taking antiresorptive drugs (ARDs).
Materials and methods: Under ARDs cessation of at least 3 months before and after oral surgery, 106 consecutive patients who underwent 249 dental extractions on 137 occasions were examined according to complete follow-up data. Among them, 42 patients (39.7 %) were classified as higher risk by the Scottish Dental Clinical Effectiveness Program (SDCEP) guidance. All extractions were performed under perioperative antibiotic prophylaxis. Each extraction involved socket preservation with alloplastic bone graft plus tetracycline and then covering it with a flatted Gelfoam and suturing. Post-operative antimicrobial mouthwash was advised.
Results: In 105 patients (99.1 %) with 248 dental extractions (99.6 %), MRONJ was successfully prevented despite most extraction sockets without primary closure. Only one tooth extraction (0.4 %) in a lower-risk patient developed MRONJ due to resuming denosumab one-month post-extraction before completing healing of socket. No one suffered skeletal-related events during the withdrawal of ARDs.

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Conclusion: The study demonstrates a high prevention effect of socket preservation with alloplast plus tetracycline on reducing MRONJ occurrence after tooth extraction. Enough drug holiday and antimicrobial mouthwash plus systemic antibiotics before and after surgery are recommended. Primary closure is likely unnecessary.

Introduction

Medication related osteonecrosis of the jaw (MRONJ) is a well-known severe complication of antiresorptive, antiangiogenic or targeted therapies, and usually develops after tooth extraction.[1—6] Most patients with MRONJ are linked to the cumulative exposure and potency of antiresorptive drugs (ARDs) including bisphosphonates (BPs) and denosumab (Dmab).[3—6] ARDs are widely used for treating osteoporosis, multiple myeloma (MM), malignant hypercalcemia, and bone metastases.[3—7] ARDs are also administered off-label in several rare metabolic bone diseases including juvenile Paget disease, osteogenesis imperfecta, osteopetrosis, diffuse sclerosing osteomyelitis and Langerhans cell histocytosis.[8—10] ARDs invariably reduce bone resorption by prolonged inhibition of bone turnover and targeting osteoclasts, either by inhibiting their function (i.e. BPs) or formation and maturation (i.e. Dmab).[11—14] BPs have a strong affinity for bone and can be embedded in the bone mineral for many years. BPs also show antiangiogenesis and inhibitory effects on macrophages and keratinocytes. Dmab does not bind to bone mineral, but exhibits a rapid onset of action to decrease active osteoclasts within hours of administration. Dmab has a short half-life of 26 days when compared with BPs, which have a half-life of more than 10 years.[11,14] However, the elevation of Dmab dose and dosing frequency for cancer patients generally results in a five-fold increase in half-life.[14] Depending on the underlying disease and ARDs dosage, both bone resorption and bone formation decrease through impaired bone remodeling. The self-healing capacity therefore reduces and MRONJ may occur after jawbone injuries.[11—13]

MRONJ is defined as having the three features: (1) current or previous treatment with ARDs alone or in combination with immune modulators or antiangiogenic agents; (2) exposed necrotic bone or bone that can be probed through an intra- or extra-oral fistula in the maxilla or mandible persisting for more than eight weeks; and (3) no history of radiotherapy or metastatic disease to the jaws.[3—5] The etiopathogenesis of MRONJ is considered multifactorial, including drug exposure, dental diseases, infection, oral surgery, local trauma, and age, comorbid health conditions, or genetic factors.[15—18] According to the Scottish Dental Clinical Effectiveness Program (SDCEP) guidance about oral health management of patients at risk of MRONJ, current estimates of MRONJ incidence are typically less than 5 % for cancer patients and less than 0.05 % for osteoporosis patients.[17—20] However, the Asian population is considered to have a higher incidence of MRONJ in comparison with the population of other countries.[21] Moreover MM patients have the highest risk of MRONJ with an incidence of 4.9—20.5 %.[7,22] First reported in 2003, MRONJ remains difficult to treat and the gold standard treatment has not been identified.[1,4,15]

As MRONJ is often preceded by dental extractions, many dentists therefore tend to think that dental extraction is a big problem in patients taking ARDs.[1—5,23—25] However, tooth extraction is sometimes necessary and unavoidable for patients suffering toothache due to serious caries or periodontitis. Preventive measures taken during dental extractions can reduce the risk of MRONJ, but no potent evidences indicate that any current risk reduction strategies attempted so far is absolutely effective in reducing the risk of MRONJ development after dental extractions.[23,24] Our previous study has demonstrated the therapeutic effect of guide bone regeneration (GBR) with alloplast plus tetracycline for existing MRONJ.[25] We therefore present a retrospective case series study of preventing MRONJ occurrence after dental extractions by socket preservation as GBR in patients taking ARDs.

Materials and methods

The study was approved by the Institutional Review Board of Chang Gung Memorial Hospital (CGMH). A total of 118 consecutive patients under ARDs therapy were referred by either general dentists or medical practitioners for dental extractions that were performed by the same qualified operator (the corresponding author) at the Oral Pathology and Family Dentistry Department of Kaohsiung CGMH between March 2014 and April 2023. Data were retrieved from the chart notes made at each visit. Investigated items included patient clinicodemographic factors (sex, age, dental and medical diseases), ARDs (drug, dose and duration), and MRONJ risk category by SDCEP guidance. A total of 12 patients were excluded from the study because of ARDs therapy less than one year.

The remaining 106 patients taking ARDs for various conditions, including primary osteoporosis, glucocorticoid-induced osteoporosis in patients with rheumatoid arthritis, osteogenesis imperfecta, multiple myeloma and carcinoma metastasizing to the skeleton or a previous diagnosis of MRONJ were included. No patient had undergone radiation therapy to the head and neck region, and no tooth exhibited signs of ONJ before dental extraction. All patients were thoroughly informed about the benefits and risks of dental

extraction and socket preservation measures. All procedures were performed with the patient's informed consent.

All patients obtained permission from their prescribing physicians or oncologists to interrupt ARDs of at least 3 months since the last administration before tooth extraction. After enough drug holiday, the patient was prescribed with antibiotic prophylaxis once before tooth extraction. Only a single extraction or multiple extractions in the same quarter was performed under the same procedure. Patients requiring multiple extractions in the different quarter were planned for a sequent procedure after complete mucosal healing of the first extraction. All dental extractions were performed with minimal invasion, and inflamed granulation tissue was curetted completely. The standard socket preservation measures consisted of packing with alloplastic bone substitute (micromacroporous biphasic calcium phosphate, MBCP) plus tetracycline powder and covering it with a flattened Gelfoam and suturing for fixation, and then biting on a gauze swab about 1 h for hemostasis. The use of systemic antibiotics and antimicrobial mouthwashes after surgery was prescribed. Further ARD cessation of 3 months after surgery was advised.

Patients were given a leaflet outlining the usual post-extraction instructions and a weekly follow-up schedule during the first month and then monthly for at least 3—6 months until complete wound healing. They were examined whether clinical or radiographic features of MRONJ developed, such as painful jaw swelling, non-healing mucosal ulcers, alveolar abscesses with fistula formation, exposed necrotic bone, focal osteolysis, and periodontal alteration of adjacent teeth, thickening of lamina dura or widening of periodontal ligament space.[24] The treatment strategy was considered a failure if extraction socket unhealed or MRONJ developed.

Results

Patient clinico-demographic data and the results of the study are summarized in Tables 1 and 2. A total of 106 patients receiving ARDs more than one year with a wide range of ages (21—91 years) and female predominance (89/106, 84 %) with a mean age of 68 years and male patients (16 %) with a mean age of 71 years. The youngest patient was a 21-year-old male with osteogenesis imperfecta under oral BP over 3 years. The majority on ARDs were due to primary osteoporosis (84.0 %), and others included glucocorticoid-related osteoporosis (10.4 %), skeletal-related events in 3 breast cancer and 2 MM (4.7 %), and osteogenesis imperfecta (0.9 %). Twenty-nine patients (27.4 %) with one or more cancers included 17 breast cancer, 3 multiple myeloma, 3 colon cancer, 2 thyroid cancer, 1 hepatocellular carcinoma, 1 cervical cancer, 1 endometrial adenocarcinoma, 1 leukemia, 1 non-Hodgkin's lymphoma, and 1 osteosarcoma. Other comorbidity included cardiovascular diseases (50.0 %), cerebral disturbance (21.7 %), rheumatoid arthritis (19.8 %), diabetes (15.1 %) and uremia (2.8 %).

The 106 patients were classified into the lower risk group (64/106, 60.3 %) and higher risk group (42/106, 39.7 %) according to the potential risk of developing MRONJ by SDCEP guidance (Table 2). The lower risk group was treated for non-malignant bone diseases (primary osteoporosis) on oral BPs (33/106, 31.1 %) or intravenous BPs (8/106, 7.5 %) for less than 5 years, or on Dmab (23/106, 21.7 %) but no concurrent systemic glucocorticoids or chemotherapy. The higher risk group was treated for non-malignant bone diseases on oral or intravenous BPs for more than 5 years (24/106, 22.6 %), and BPs or Dmab with concurrent systemic glucocorticoids (11/106, 10.4 %), and ARD plus anti-angiogenic drugs for management of cancers (5/106, 4.7 %), and a previous MRONJ history (2/106, 1.9 %).

Table 1 Demographic information in 106 patients under antiresorptive therapy.

Variables	Patients (%)
Female	89 (84.0 %)
Male	17 (16.0 %)
Mean age years (range)	68 (21—91)
Primary osteoporosis	89 (84.0 %)
Glucocorticoid related osteoporosis	11 (10.4 %)
Oncological diseases with skeletal-related events	5 (4.7 %)
Osteogenesis imperfecta	1 (0.9 %)
Cardiovascular disease	53 (50.0 %)
Oncological diseases[a]	29 (27.4 %)
Cerebral disturbance (Stroke, Parkinson's disease, Dementia)	23 (21.7 %)
Rheumatoid arthritis, osteoarthritis	21 (19.8 %)
Diabetes mellitus	16 (15.1 %)
End-stage renal disease	3 (2.8 %)
Total cases	106 (100 %)

[a] Oncological diseases included 17 cases of breast cancer, 3 cases of multiple myeloma, 3 cases of colon cancer, 2 cases of thyroid cancer, and 1 case of hepatocellular carcinoma, 1 case of cervical cancer, 1 case of endometrial adenocarcinoma, 1 case of leukemia, 1 case of non-Hodgkin's lymphoma, and 1 case of osteosarcoma.

A total of 106 consecutive subjects underwent 249 tooth extractions on 137 occasions. In 105 patients (99.1 %) with 248 dental extractions (99.6 %), including all higher-risk patients, MRONJ was successfully prevented, despite most sockets by secondary intension. On radiographs of all healing sockets, the same results of healthy trabecular bone with neovascularization within the grafted area have fully regenerated (Fig. 1). Only one extraction socket (1/249, 0.4 %) in a 57-year-old female with uremia and osteoporosis on previous Dmab therapy for 2 years developed ONJ due to early Dmab reinstitution one-month post-extraction before complete healing. The time to resolution of this MRONJ site lasted about 8 months.

Discussion

In this retrospective case series, an interval of at least 3 months before and after surgery, 105 patients (99.1 %) with 248 dental extractions (99.6 %), MRONJ was successfully prevented by use of socket preservation with alloplastic

Table 2 MRONJ incidence after dental extractions in the lower risk group and higher risk group classified by SDCEP guidance based on their medical conditions, type and duration of antiresorptive therapy in 106 patients.

Lower risk	n	MRONJ incidence	Higher risk	n	MRONJ incidence
Patients treated for non-malignant diseases of bone with oral BPs less than 5 years. (Not concurrently treated with systemic GCs)	33	0	Patients treated for non-malignant diseases of bone with oral BPs or IV BPs for more than 5 years.	24	0
Patients treated for non-malignant diseases of bone with IV BPs less than 5 years. (Not concurrently treated with systemic GCs)	8	0	Patients treated for non-malignant diseases of bone with BPs or Dmab and concurrently treated with systemic GCs.	11	0
Patients treated for non-malignant diseases of bone with Dmab. (Not concurrently treated with systemic GCs)	23	1	Patients treated with anti-resorptive or anti-angiogenic drugs (or both) for management of cancers.	5	0
			Patients with a previous diagnosis of MRONJ.	2	0
Total cases	64	1		42	0
%	60.3	0.9		39.7	0

n = Number of patients; MRONJ = Medication-related osteonecrosis of the Jaw; IV = intravenous; BPs = Bisphosphonates; Dmab = Denosumab; GCs = Glucocorticoids.
SDCEP: Scottish Dental Clinical Effectiveness Program, Oral health management of patients at risk of MRONJ, March 2017.[20]

bone graft plus tetracycline after tooth extraction. Particularly, MRONJ was completely precluded in the higher risk cohort, with a preventive effectiveness of 100 %. Only one tooth extraction (0.4 %) in a lower-risk patient with osteoporosis under previous Dmab for 2 years developed MRONJ due to Dmab reinstitution one-month post-extraction before completing socket healing. Although Dmab only has a short half-life about one month, its bone remodeling effect can last about six months that may elevate the risk of MRONJ before socket healing.[14] According to SDCEP guidelines, resumption of Dmab treatment after invasive dental procedures should be delayed until the soft tissues or extraction sockets have fully healed.[19,20] Such claim corresponds with many studies supporting the fact that prophylactic dental preparation is a must before the first dose of ARDs, including extraction site with complete epithelization or adequate bone healing.[3—5] However, there is limited evidence to demonstrate that a drug holiday is unnecessary or may be potentially harmful during dental surgery.[26] In the skeletal metastases cohort study, increasing the time since the last administration of ARDs was associated with a decreased occurrence of MRONJ, and the optimal cut-off was 3 months prior to dental extractions.[24] These findings indicate that enough drug holiday before and after dental extraction is recommended. In our previous study and over two decades of clinical practice, the present researchers have found that drug holiday can provide great benefit to help the healing process of existing MRONJ.[25] This is likely due to progressive recovery of the impaired bone turnover, or antiangiogenesis and cytoinhibitory effects against macrophages after stopping ARDs that all contribute to the critical aspects of defense and wound healing.[11—14] All patients in the study tolerated the duration of withdrawal of ARDs and no one developed SREs.

The main reason for tooth extraction in patients taking ARDs is the eradication of dental infection that cannot be cured by conservative measures. The presence of dental infection or periodontitis is acknowledged as a significant risk factor for MRONJ.[27,28] Therefore, the use of antimicrobial mouthwash and antibiotic prophylaxis before and after surgery are recommend despite limited evidence.[23] The diminution of dental infection and periodontitis or dental trauma will reduce the bone remodeling demands and, thus, improve the likelihood of healing process.[23,24]

After a tooth extraction, a cascade of healing process starts which can result in about 25 % of bone resorption.[29] The resorption process may increase the possibility of MRONJ. Such as the bone uptake BPs will be liberated and become active again when the bone in which they are deposited is resorbed.[12,14] Studies indicate that early bone loss after extraction can be significantly reduced by socket seal surgery with GBR before dental implantation. Our previous studies have demonstrated the successful treatment of existing MRONJ or peri-implantitis by use of GBR with alloplast plus tetracycline powder.[25,30] The present study further ascertain its preventive effect after dental extraction in reducing MRONJ occurrence.

Alloplast displays osteoconductive capabilities and provides bone augmentation to decrease early bone resorption.[25,29] The most common material used in alloplastic bone substitutes is hydroxyapatite (HA) which is the primary structural component of bone and has the ability to adhere to normal bone and helps in its remodeling as well as enables hemostasis.[29] Instead of unnecessary surgery from autograft or possible disease transmission from allograft or xerograft, alloplast may be the first choice for patients taking ARDs.[29] Apart from the broad-spectrum antimicrobial activity, several tetracyclines can exert many non-antibiotic effects such as anticollagenase activity, inhibition of connective tissue degradation, incorporation into bones to form a stable calcium complex, and influence over bone remodeling. Therefore, tetracyclines have been reported as potential agents to prevent bone loss and maintain near normal rates of bone formation.[25]

Primary closure after tooth extraction in patients taking ARDs was recommended despite limited evidences.[23] The

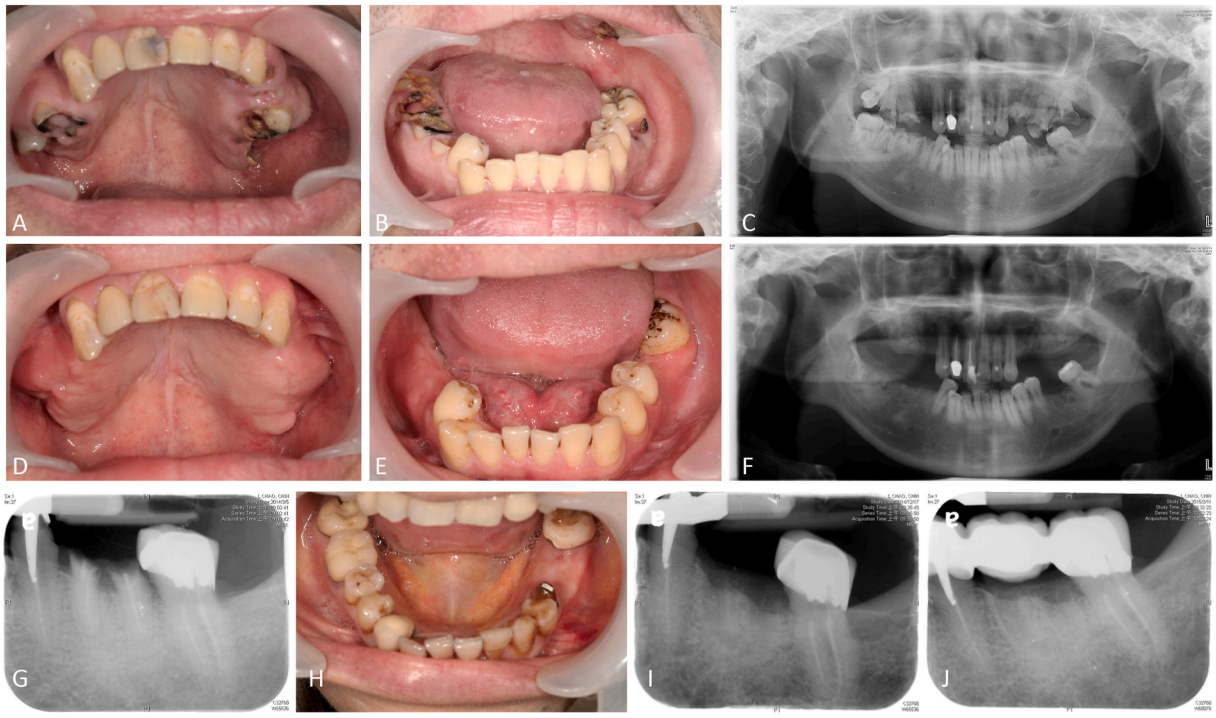

Figure 1 Examples of successful prevention of MRONJ after dental extractions by socket preservation with alloplast plus tetracycline in two high risk patients. A 23-year-old male with severe rheumatoid arthritis under methotrexate, prednisolone, tocilizumab and oral bisphosphonate therapy over 4 years (A—F) and a 58-year-old female with malignant lymphoma, rheumatoid arthritis and previous MRONJ of right maxilla due to treatment with prednisolone and zoledronic acid plus denosumab over 5 years (G—J). (A—C) Clinical photographs and panoramic radiograph in September 2014 showed eleven residual roots and two third molars that were needed extractions before making dentures. (D—F) Healing of all extraction sockets with complete epithelization and adequate bone regeneration within the grafted areas of four quarters under a sequent procedure during December 2014 to May 2015. (G) Periapical film in March 2014 showed residual roots of left lower first molar that was needed extraction before making a new bridge. (H and I) Complete healing of extraction socket with bone regeneration within the grafted area in December 2014. (J) Well bone formation below a new bridge in February 2015.

sufficient wound closure after GBR procedure can provide safe coverage for the bone graft and reduce the risk of recurrent infection. In the study, primary closure was hard to be achieved in most extraction sockets by an atraumatic operation accompanied with conservative alveolectomy. However, MRONJ was successfully prevented despite extraction socket healing by secondary intension. Therefore, primary closure is likely unnecessary. Instead, the use of antimicrobial mouthwash and systemic antibiotics before and after surgery should be implemented under all efforts.[23,31]

The comorbid health conditions including age, diabetes, uremia, cancer chemotherapy and concurrent steroid therapy are reported to increasing the risk of MRONJ.[32—34] The exact mechanism of diabetes mellitus as a risk factor for MRONJ remains unclear. The main reasons may originate from diabetes complications including microvascular ischemia, endothelial cell dysfunction, reduced bone remodeling, increased apoptosis of osteoblasts and osteocytes, and changes in the immune cell function that all likely decrease bone quality and increase the risk of MRONJ.[33] BPs are eliminated from human body by the kidneys.[12] Chronic kidney disease in patients taking BPs may contribute to an increased MRONJ risk because the reduced renal function results in a higher BPs retention and deposition in bones. Studied has reported that the stage of BPs related ONJ (BRONJ) and the estimated glomerular filtration rate (eGFR) of kidney showed a statistically significant correlation.[14] With older age and lower renal function, BRONJ is more severe and there may be a decreased response to treatment.[14,34] However, this status is not found in MRONJ patients taking Dmab, because Dmab is cleared by reticuloendothelial system with minimal renal excretion.[13,14]

The prevention and early diagnosis of MRONJ is fundamental to minimizing the risk and progression of MRONJ. Therefore, the continuity and coordination of patient-centered multidisciplinary care is essential.[35—37] Declining incidence of MRONJ in cancer patients with bone metastases has been validated through the implementation of prophylactic dental intervention before ARDs use, increased dental awareness, regular dental surveillance, and optimizing ARDs therapy or nonsurgical dental procedures to prevent new cases.[36] This would need to comprise a closed responsibility treatment loop with all benefits directed to the patient. However, most of physicians, even some oncologists, did not feel the necessity of dental preparation before and during ARDs treatment. The poor cooperation among oncologists, physicians and dentists might likely increase MRONJ risk.[3,4,38]

This is the first reported use of socket preservation as GBR after dental extraction to successfully prevent MRONJ. Further investigations with larger numbers of patients taking ARDs in randomized controlled clinical trials are advised prior to recommending dental extraction with GBR to prevent MRONJ. Despite the positive results of this study, the prevention of MRONJ through avoidance of dental extraction and other triggers is the preferred strategy.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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