



Evaluation of MRONJ Risk and Associated Factors in Patients Receiving Antiresorptive and/or Antiangiogenic Drug Therapy: A Retrospective Cohort Study

Ömer EKİCİ

Department of Oral and Maxillofacial Surgery, Afyonkarahisar University of Health Sciences Faculty of Dentistry, Afyonkarahisar-Türkiye

OBJECTIVE

Due to the increased prevalence of antiresorptive drugs in recent years, the risk of medication-related osteonecrosis of the jaws (MRONJ) development after tooth extraction and other dentoalveolar surgical procedures has increased significantly. The aim of this study is to investigate the risk of MRONJ and related factors after routine oral surgical procedures in patients receiving antiresorptive and antiangiogenic drugs therapy.

METHODS

A retrospective cohort study was carried out in patients receiving antiresorptive and antiangiogenic drugs therapy between 2019 and 2021 at a university's oral and maxillofacial surgery clinic. In all patients, oral surgical procedures were performed according to the guidelines of the American Association of oral and Maxillofacial Surgeons (AAOMS), and the patients were followed for the development of MRONJ. Patients were multidimensionally evaluated for MRONJ risk, including patient-related general-systemic factors, drug-related factors, local anatomical factors, and surgical procedure-related factors.

RESULTS

A total of 76 patients (60 women and 16 men); mean age (59.23 years) was under antiresorptive (86.8% bisphosphonates, and 6.6% denosumab) or antiangiogenic drug (5.3%) treatment for malignant tumor (21.1%) or osteoporosis (78.9%). The mean duration of drug received was 42 months. Tooth extraction (n=66 patients), cyst enucleation (n=6), and pre-prosthetic surgery (n=4) were atraumatically applied to the patients according to AAOMS recommendations. In all patients in the post-operative period wounds healed uneventfully and osteonecrosis was not observed.

CONCLUSION

When conducted according to established guidelines, oral surgical operations can be performed safely and predictably in patients undergoing antiresorptive and antiangiogenic medication treatment, even in high-risk patients.

Keywords: Bisphosphonates; denosumab; osteonecrosis; risk factors; sunitinib.

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Dr. Ömer EKİCİ

Afyonkarahisar Sağlık Bilimleri Üniversitesi Diş Hekimliği Fakültesi,

Ağız, Diş ve Çene Cerrahisi Anabilim Dalı,

Afyonkarahisar-Türkiye

E-mail: dromerekici@hotmail.com

INTRODUCTION

Medication-related osteonecrosis of the jaw (MRONJ) is described as an exposed bone or bone that can be probed with an intraoral or extra-oral fistula in the maxillofacial region that has persisted for more than 8 weeks in a patient with a history of antiresorptive or antiangiogenic therapy and who has not received radiation therapy to the jaw or suffered an apparent metastatic disease of the jaw.[1] Symptoms of MRONJ include dull bone pain, odontalgia, and neurosensory dysfunction such as paresthesia, loosening of teeth, periapical or periodontal fistula, and purulent drainage unexplained from an odontogenic or periodontal cause.[2] MRONJ is more common in patients receiving bisphosphonates, but also occurs in patients treated with denosumab or some antiangiogenic.

MRONJ is particularly important for cancer patients, as high-dose antiresorptive therapy is the mainstay of treatment for metastasized solid tumors and primary bone tumors. Level 1 evidence studies have shown that the overall incidence of tumor patients developing MRONJ under zoledronate therapy is approximately 1%. It has been reported with denosumab at a rate of 0.9–1.7% among cancer patients.[3,4] Benign diseases have a lower risk of developing MRONJ, and the risk of MRONJ in patients treated with bisphosphonates or denosumab has been reported to be only approximately 0.017–0.21%.[5] There have also been reports of MRONJ in patients receiving sunitinib, and the risk may be higher when associated with bisphosphonates.[6] Despite these rather low incidences, the treatment of MRONJ has become more complex in recent years.

The pathophysiology of MRONJ is uncertain and multifactorial due to inhibition of osteoclasts, decreased vascularity, inflammation and infection, and impaired wound healing.[7] Although the role of trauma is not fully defined, tooth extraction is considered the most common triggering event in the development of MRONJ. Other identified risk factors include length of antiresorptive drug administration, concomitant use of antiangiogenic and antiresorptive drugs, concomitant corticosteroid therapy, diabetes, use of dentures, and poor oral hygiene.[8,9] A very restrictive approach to tooth extraction is recommended because of the up to 33-fold increased risk for MRONJ after extraction.[10] Dentists and oral and maxillofacial surgeons feel endangered when aiming to avoid MRONJ after tooth extraction and other dentoalveolar surgical procedures. Most recommendations aim to control local infection during perioperative antibiotic

prophylaxis and plastic wound closure. However, data on the treatment outcomes of patients treated according to these recommendations are scarce.[11] As far as we know, there is no study in Türkiye investigating the risk of MRONJ in patients receiving antiresorptive and/or antiangiogenic drug therapy. Therefore, the aim of this study was to investigate the clinical course after tooth extraction and other dento-alveolar procedures in patients under antiresorptive/antiangiogenic therapy and to decide whether these surgical procedures can be performed safely and predictably while following treatment recommendations.

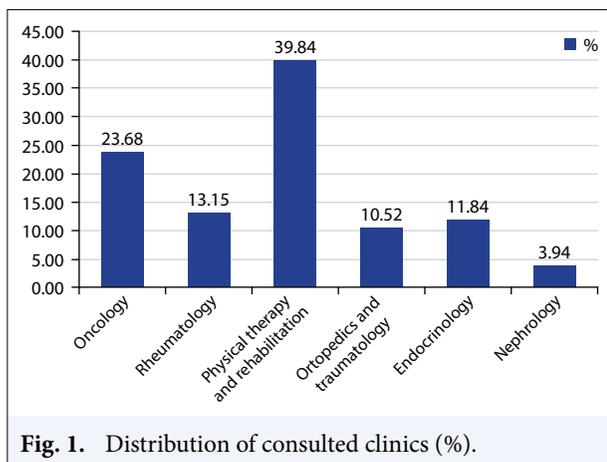
MATERIALS AND METHODS

Study Design and Sample

A retrospective longitudinal cohort study of the risk of post-operative MRONJ development was conducted in patients who applied to Afyonkarahisar Health Sciences University, Faculty of Dentistry, oral, and maxillofacial surgery clinic and used antiresorptive and antiangiogenic drugs between January 1, 2019, and December 31, 2020. The study was approved by the Afyonkarahisar Health Sciences University, Clinical Research Ethics Committee (2020/13–505) and was conducted in accordance with the Helsinki Declaration principles. Written and verbal informed consent was obtained from all patients. Patients using antiresorptive and antiangiogenic drugs and undergoing tooth extraction or similar oral surgery were included in the study. Patients who were treated in an external center and presented with the diagnosis of direct mronj were excluded from the study. All surgical procedures were performed by a single surgeon in accordance with the recommendations of the American Association of Oral and Maxillofacial Surgeons (AAOMS) guideline. All patients were consulted with the physician who prescribed the antiresorptive/antiangiogenic drug before the surgical procedure (Fig. 1). Drug holiday was applied to the patients who were allowed by the relevant physician. Antibiotic treatment was given to all patients after the surgical procedure. Before the surgical procedure, periodontal treatment of the patients was performed when necessary. After the surgical procedure, the patients were followed up clinically and radiologically for a minimum of 6 months in terms of MRONJ findings.

Outcome Variable

The primary outcome variable in patients was whether they developed MRONJ. Factors that may cause osteo-



necrosis in patients were analyzed as secondary variables. These variables were categorized into four groups.

1. General-systemic factors associated with the patient (Age, gender, oral hygiene status, smoking status, systemic diseases, and comorbid diseases associated with MRONJ)
2. Drug-related factors (type of drug, for which disease it is used, route of administration, frequency of use, and duration of use).
3. Local anatomical factors associated with the patient (presence of oral torus/exostosis, use of removable prosthesis, presence of periodontal disease and periapical lesion, and jaw to be operated).
4. Factors related to the surgical procedure (type of surgical procedure, drug holiday status, pre-operative and post-operative antibiotic treatment status, periodontal treatment before the procedure, number of teeth extracted, need for surgical extraction, and socket closure).

Statistical analysis of the data was performed using version 20 of the SPSS statistical program (SPSS Inc, Chicago, IL, USA). Mean and standard deviation values were given in the descriptive statistics of continuous data, and number and percentage values were given in nominal data. The normal distribution of data was evaluated using the Kolmogorov-Smirnov test. Continuous data that were found to fit normal distribution were analyzed by student's t-test. When comparing categorical variables, Chi-square test was employed. $P=0.05$ was considered significant.

RESULTS

General-systemic Factors Related to the Patient

Data on the socio-demographic characteristics and general health status of the patients are presented in

Table 1 Patient-related demographic and general systemic factors

	n	%
Gender		
Female	60	78.9
Male	16	21.1
Age		
<50	14	18.4
50–59	18	23.7
60–69	24	31.6
70<	20	26.3
Education status		
Illiterate	10	13.2
Primary school	48	63.2
Secondary school	4	5.3
High school	10	13.2
University	4	5.3
Tooth brushing frequency		
<Once/day	38	50
Once/day	16	21.05
Twice/day	22	28.94
Smoking		
Yes	31	40.78
No	45	59.21
Presence of systemic disease		
Yes	42	55.3
No	34	44.7
Comorbid diseases		
Diabetes mellitus	5	6.57
Anemia	8	10.52
Cancer/chemotherapy	20	26.31
Corticosteroid use	8	10.52
Kidney failure	4	5.26
Rheumatoid arthritis	6	7.89
Estrogen therapy	2	2.63
None	23	30.26
Total	76	100

Table 1. Most of the participants in the study were women. (The male/female ratio was about 1/4). Most of the patients were over 50 years old. The minimum age of the patients was 19 and the maximum age was 82 (Mean age 59.23 ± 14.89). Three quarters of the participants were illiterate or primary school graduates. Half of the participants brushed less than one tooth a day, while 40.78% were smokers. In addition, 69.73% of the participants had a comorbid disease related to MRONJ (Table 1).

Drug-Related Factors

Drug-related factors that may cause MRONJ in patients are presented in Table 2. Half of the patients were

Table 2 Antiresorptive/antiangiogenic drug-related factors

	n	%
Drug type		
Alendronic acid	38	50
Ibandronic acid	14	18.4
Zoledronic acid	14	18.4
Denosumab	6	6.6
Antiangiogenic drugs	4	5.3
Drug indication		
Osteoporosis	60	78.9
Breast CA met	4	5.3
Lung CA met	4	5.3
Colon CA met	4	5.3
Prostate CA met	2	2.6
Liver-pancreas-spleen CA met	2	2.6
Way of use		
Oral	50	65.8
IV	22	28.9
Subcutan	4	5.3
Frequency of use		
Once a week	42	55.3
Once a month	26	34.2
Once in 3 months	4	5.3
Once in 6 months	4	5.3
Duration of drug		
<1 year	35	46.05
1–4 years	19	25
>4 years	22	28.94
Total	76	100

CA: Cancer; met: Metastasis; IV: Intravenous

using Alendronic acid, followed by zoledronic acid and ibandronic acid equally with 18.4%. While 6.6% of the patients were using denosumab, 5.3% were using an antiangiogenic drug. While 78.9% of the patients were being treated for osteoporosis, the others were being treated for bone metastases of internal organ tumors. About 65.8% of the patients were taking the drug orally, 28.9% IV and 5.3% subcutaneously. The majority of the patients were taking medication on a weekly and monthly basis. While the duration of drug use in 71.05% of the patients was less than 4 years, the duration of use of 28.94% was more than 4 years (Table 2).

Local-Anatomical Factors Related to the Patient

Only 10.5% of patients had a bone exostosis/torus that could cause trauma. In addition, 42.1% of the patients were using a removable prosthesis, which could pose a risk of trauma. About 90.79% of the patients had periodontal disease such as gingivitis or periodontitis. In 28.95% of the patients, there was a periapical lesion in

Table 3 Local-anatomical and surgical procedure related factors

	n	%
Local-anatomical factors		
Oral torus/exostosis		
Yes	8	10.5
No	68	89.5
Use of removable prosthesis		
Yes	32	42.1
No	44	57.9
Periodontal disease		
Yes	69	90.79
No	7	9.21
Periapical lesion		
Yes	22	28.95
No	54	71.05
Jawbone		
Maxilla	32	42.1
Mandible	30	39.5
Maxilla and Mandible	14	18.4
Surgical procedure-related factors		
Surgical procedure		
Tooth extraction	66	86.8
Cystectomy	6	7.9
Pre-prosthetic surgery	4	5.3
Drug holiday before surgery		
Yes	59	77.63
No	17	22.37
Antibiotic therapy before surgery		
Yes	63	82.89
No	13	17.11
Periodontal treatment before surgery		
Yes	30	39.47
No	46	60.53
Number of teeth extracted per patient		
1	36	50
2	22	30.6
3	6	8.2
>3	8	11.2
Additional surgical procedure		
Yes	14	19.45
No	58	80.55
Socket closure		
Open socket	39	54.16
Approximation with sutures	22	30.55
Full closure	11	15.27
Periodontal treatment after surgery		
Yes	76	100
Total	76	100

the teeth associated with the surgical site. While the surgical procedure was in the mandible in 39.5% of the patients, it involved both jaws in 18.4% (Table 3).

Oral Surgical Treatment Related Factors

In the study, tooth extraction was performed in 66 patients, cyst enucleation was performed in 6 patients, and preprosthetic surgical procedures such as epulis/fibroma excision and alveoplasty were performed in four patients. In 77.63% of the patients, with the permission of the physician who prescribed the drug, the drug was suspended for a while (average 3 months) before the procedure (drug holiday). Antibiotics were prescribed to prevent infection in 82.89% of the patients before the surgical procedure, and periodontal treatment was performed in 39.47% of the patients. Except for simple surgical procedures such as tooth extraction, in approximately 20% of the patients, flap removal was performed like surgical extraction. While the socket was left open in 54.16% of the patients who underwent tooth extraction, suturing was applied in 30.55% and complete closure was applied in 15.27%. After the surgical procedure, antibiotics were prescribed to all patients according to their condition (Table 3).

In the study, patients were followed up for a minimum of 6 months in terms of postoperative wound healing. No mucosal healing problem or osteonecrosis was observed in any of the patients in the post-operative period.

DISCUSSION

In recent years, due to the increasing prevalence of antiresorptive drugs such as denosumab, other than bisphosphonates, tooth extraction and other dentoalveolar surgical procedures are becoming more important for dentists and maxillofacial surgeons in patients taking antiresorptive/antiangiogenic drugs. Tooth extraction and dentoalveolar surgical procedures are considered risk factors for the onset of MRONJ.[12] Some guidelines even recommend avoiding extractions and dentoalveolar surgery whenever possible under bisphosphonate intake.[13] MRONJ is a growing problem, as prescription levels of MRONJ-related drugs have risen notably in recent years and are expected to increase further. In this study, patients using antiresorptive/antiangiogenic drugs were comprehensively evaluated for the development of MRONJ and risk factors.

Age and gender are reported to be variable risk factors for MRONJ. The high prevalence of MRONJ in women is likely due to the underlying disease for which the agents were prescribed (e.g., osteoporosis and breast cancer).[1] Consistent with the literature in this study, 78.9% of the patients were women and

it was approximately 4 times more than men. The mean age of the patients was 60 years and it was observed that these patients were quite advanced (81.6% over 50 years old). Comorbid conditions associated with MRONJ risk include anemia (hemoglobin <10 g/dL) and diabetes. Corticosteroids have been linked to a higher risk of MRONJ.[8] The kind of cancer is also cited as a risk factor.[10] Tobacco usage has been cited as a risk factor for MRONJ in a variety of studies.[1] In the present study, 70% of patients had a comorbid disease such as diabetes, anemia and cancer. Corticosteroid intake was present in 10.52% of the patients. In addition, 40% of them were smokers. It is observed that the education level of the patients in the study is quite low. Almost all of the patients were not informed about MRONJ by the physician who prescribed the drug, and they did not know that the drug could cause osteonecrosis of the jaws as a side effect.

Potent nitrogen bisphosphonates may persist for years because they bind to the hydroxylapatite of bone.[14] Therefore, most patients who initially use bisphosphonates switch to Denosumab. The risk is around 1% among cancer patients who have had intravenous (iv) zoledronate.[15] The risk of MRONJ is 100 times higher in cancer than in osteoporotic patients taking the same drug.[1] All patients in the study, except for osteoporosis, were under cancer treatment. Most of them were using antiresorptive drugs such as IV bisphosphonate (28.9%) or denosumab (6.6%) for bone metastases of solid tumors such as lung, breast, and colon cancer. In this study, four patients were using antiangiogenic drugs for visceral tumors. It has been reported that especially in patients using bisphosphonates, when the duration of treatment exceeds 3 years, patients are faced with an increased risk of osteonecrosis. In this study, the duration of drug use in 43.8% of the patients was over 3 years.

Dentoalveolar surgery is thought an important factor in the occur of MRONJ.[10,16] About 66.7% of the lesions occur in the mandible. This might be due to variations in anatomical structure between the maxillary and mandibular bones.[17] In this study, the most common procedure was tooth extraction. While a single tooth was extracted in half of the patients, more than three teeth were extracted in 11.2% of the patients. Both jaws were undergone to similar dentoalveolar surgery. About 42% of the patients were using removable prostheses and 10% of patients had bone exostosis that could cause trauma. In patients receiving bisphosphonates, mucosal healing is im-

perfect and trauma caused by prostheses can lead to bone infection. A two-fold increased risk of MRONJ was reported in prosthetic wearers in 1621 patients treated with bisphosphonates.[10] Another research reported that 27.5% of 80 MRONJ patients had denture pressure ulcers.[18]

The timing of discontinuation of antiresorptive agents is still for discussion, but it has been reported that early discontinuation of bisphosphonates in MRONJ treatment is associated with faster resolution of symptom.[19] According to the AAOMS, discontinuation of antiresorptive therapy may be considered until bone exposure is resolved.[1] In this study, 77.63% of the patients had a 'drug holiday' before the surgical procedure. Dental care before the initiation of antiresorptive drugs and following guidelines emphasizing the need for active dental care in these patients have been shown to reduce the risk of MRONJ.[20,21] Biofilm formation on exposed bone may require long-term antibiotic therapy or even surgical treatment.[22] Hence, when necessary, periodontal treatment of the patients was performed before the procedure. Pre-operative antibiotic therapy was administered to most patients. All surgical procedures were performed atraumatically. Antibiotics, analgesic/anti-inflammatory, and mouthwash were prescribed to all patients after the surgical procedure.

Treating individuals with MRONJ is still a difficult task, and it has been a contentious subject since the occurrence of the disease.[23] The best method is to prevent MRONJ by evaluating risk factors and taking measures to minimize the risk of osteonecrosis in patients under antiresorptive therapy. In a cohort of patients with a low-risk profile, namely, osteoporotic patients receiving only oral bisphosphonates, Mozzati et al.[24] reported that they had a 100% success rate in atraumatic tooth extraction combined with antibiotic prophylaxis in subgroups with (n=334 patients) and without (n=366 patients) plastic wound closure. A recent study reported an high success rate (uneventful recovery at 96.8% and 209/216 extraction sites) in high-risk patients with underlying malignant disease receiving intravenous bisphosphonate therapy.[25] Heufelder et al.[11] reported a 97% rate for complete mucosal healing (n rate 114/117 extraction sites), taking very similar preventive measures in a comparable patient cohort. In this study, wound healing was uneventful in all patients in the post-operative period and no complications were observed. Moreover, some of these patients were at high risk and underwent multiple surgical procedures.

Study Limitations

The retrospective design and sample size of the study are the limitations of the study. The minimum follow-up period was judged to be 6 months, which was a shorter-than-desired length, but this constraint was compensated by a mean follow-up period of 10 months. The study's strength is that therapy and clinical follow-up were conducted by a single surgeon using the same treatment protocol. The study comprehensively revealed possible risk factors in patients taking antiresorptive/antiangiogenic drugs and showed that the risk of MRONJ can be reduced or completely eliminated after surgical procedures performed in accordance with AAOMS principles.

CONCLUSION

The results of this study show that although the patient cohort contained at-risk patients with underlying malignant disease who received intravenous bisphosphonate or denosumab therapy, the emergence of osteonecrotic lesions was prevented when the procedures were performed in accordance with international guidelines such as AAOMS. We recommend a minimally traumatic method involving removal of the bone margins and closure of the mucosal wound as standard procedures in patients receiving antiresorptive and antiangiogenic drug therapy. In these patients, periodontal treatment and oral hygiene education before the surgical procedure, antibiotic treatment before and after the procedure are effective methods in controlling the infection. In addition, we think that taking a break from the antiresorptive drug for a while by consulting the physician who prescribed the drug may reduce the risk of MRONJ. Clinical guidelines recommend that patients be in optimal oral health possible at which they start MRONJ-related medications. It should be noted that preventing MRONJ as much as possible is a much better option than treating it.

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Ethics Committee Approval: The study was approved by the Afyonkarahisar Health Sciences University Clinical Research Ethics Committee (no: 2020/13-505, date: 06/11/2020).

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