

The Awareness and Perceptions of Dentists Regarding Medication-related Osteonecrosis of the Jaw and its Prevention: A Cross-sectional Survey

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Research article

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Abstract

Background: The accurate documentation of a patient's prior medication use by dentists, and their knowledge of the side effects associated with anti-osteoporotic agents can prevent medication-related osteonecrosis of the jaws. This study investigated the awareness of dentists regarding medication-related osteonecrosis of the jaws, with the aim of determining the need for targeted educational interventions for this medical condition within the dental profession.

Methods: An online questionnaire survey was conducted among 1000 dentists registered in an online community in Korea.

Results: Dentists who documented the use of anti-osteoporotic medications by patients were more likely to have no prior experience of encountering previous cases of medication-related osteonecrosis of the jaws; this was evident among dentists who documented the names of these medications (97.5% having no experience versus 95.6% having experience; $P = 0.116$), and those who recorded both medication names and duration of use (67.5% having no experience versus 59.0% having experience; $P = 0.007$). In terms of dentists who advised drug holidays for ≥ 6 months, the proportion with no prior experience of medication-related osteonecrosis of the jaws was also higher than the proportion with prior experience (42.1% versus 32.8%, respectively; $P < 0.001$).

Conclusions: These results suggest that dentists do not respond consistently to the patient's drug history prior to performing dental procedures. This implies the need for mutual cooperation between dentists and physicians, and the development of targeted educational interventions for the dental profession.

Trial registration: Not applicable.

Background

Several medications decelerate or prevent bone loss. However, patients on bone-modifying medications should be treated with caution by dentists because of the possibility of medication-related osteonecrosis of the jaws (MRONJ). Several studies on MRONJ have been conducted since Marx [1] reported the first case almost two decades ago.

In the United States, the prevalence of bisphosphonate-related osteonecrosis of the jaws (BRONJ) in patients on intravenous bisphosphonate therapy has been reported to be 0.7/100,000 (0.8–12%) [2], while a survey in Europe has reported prevalence rates of 95/100,000 (0.095%) and 1/100,000 (0.001%) for intravenous and oral administration, respectively [3]. Another study reported a lower prevalence (0.004%) among patients on oral therapy [4]. Lo et al., on the other hand, documented an increase in prevalence from 0.1–0.21% after more than 4 years of continued bisphosphonate therapy [5]. The prevalence of MRONJ in patients receiving denosumab has been reported to range from 0.017–0.04% [6]. Although prevalence rates vary across countries, the general prevalence of MRONJ appears to be relatively low.

Due to the consistent reports of associations between bone necrosis and both denosumab and angiogenesis inhibitors, the American Association of Oral and Maxillofacial Surgeons has suggested that MRONJ is a more appropriate term than BRONJ [7]. The medical condition of the patient is an important factor in the development of MRONJ, and exposure to bisphosphonates and/or denosumab in patients with malignant tumors can increase the risk by 50–100 times [8, 9].

Dentists have an important role in assessing the risk of MRONJ by accurately documenting their patients' medical and drug history. An inadequate knowledge of this medical condition and subsequent recommendations to discontinue bone-modifying medications (i.e., “drug holidays”) in patients with osteoporosis can have serious consequences. Therefore, the awareness and perceptions of dentists regarding MRONJ should be analyzed in order to identify existing knowledge deficiencies, and inform the development of targeted educational interventions in the dental profession.

Studies in this field are scarce, and the level of awareness among dentists likely varies across countries due to differences in academic scope and definitive treatment protocols. Thus, we investigated the awareness of Korean dentists regarding MRONJ and their advised durations of drug holidays before performing various dental procedures, with the overarching aim of determining the need for mutual cooperation between dentists and physicians, and the development of enhanced educational protocols for the dental profession.

Methods

Ethical approval

This study was approved by the institutional bioethics committee of our university hospital (approval number: 2019-03-015), and conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all study participants.

Subjects

According to the health insurance statistics of 2017, approximately 25,300 dentists practice in Korea. This study was conducted among dentists registered on DentPhoto (<http://www.dentphoto.com/>), the largest online community of dentists in Korea.

Survey method

The survey was initiated online in April 2020, and closed automatically after the participation of 1000 dentists. Our questionnaire used existing research data and was prepared by adapting it [23]. The questionnaire recorded general characteristics of the dentists, such as sex, age, clinical experience, and type of practice. The type of practice was categorized as either private (i.e., dentists engaged in private

practice) or non-private (e.g., employed dentists, public dentists, etc.). Questions were also included to determine the following: whether dentists recorded details of current or prior usage of bone-modifying agents (e.g., drug name and duration of therapy before implant placement and tooth extraction); required period of drug discontinuation; specific management protocols employed while treating patients on bone-modifying medications; and prior experience of treating MRONJ patients.

Statistical analysis

The statistical software SPSS 21.0 (IBM, Armonk, NY, USA) was used for data analysis. Frequency and cross analyses were performed to evaluate knowledge pertaining to MRONJ among dentists. Data were presented as percentages (%) for categorical variables. Differences between dentists with and without a prior experience of treating a patient with MRONJ were evaluated using the χ^2 test. The level of statistical significance was set at $P < 0.05$.

Results

General characteristics of survey respondents

The majority of survey respondents were male (78.7%), and almost half (46.6%) were 41–50 years of age. Dentists engaged in private practice accounted for 85.3% of survey respondents, with the remainder being engaged in non-private practice. Over a quarter (25.6%) had 11–15 years of experience in dental practice (Table 1).

Table 1
General characteristics of survey respondents

Variable		N	%
Sex	Male	787	78.70%
	Female	213	21.30%
Age (y)	≤30	32	3.20%
	31–40	298	29.80%
	41–50	466	46.60%
	51–60	172	17.20%
	≥61	32	3.20%
Type of practice	Private clinic ^a	853	85.30%
	Non-private clinic ^b	147	14.70%
Clinical experience (y)	≤5	102	10.20%
	6–10	179	17.90%
	11–15	256	25.60%
	16–20	212	21.20%
	≥21	251	25.10%
Abbreviations: y, year			
^a Dentists engaged in private practice			
^b Employed dentists, public dentists, etc.			
Data are expressed as numbers and percentages			

Awareness among dentists and specific management protocols

Most (96.9%) of the dentists reported that they regularly documented the medication history (including bone-modifying agents) of patients before implant placement and tooth extraction. Over half (65%) recorded both the drug name and duration of use, while 16.3% of the respondents only documented the

drug name. Referral letters were requested by 59.1% of respondents prior to dental surgery procedures. The majority (45.7%) of respondents advised their patients to discontinue anti-osteoporotic agents for 3–5 months before the procedure; 14.9% and 39.4% of respondents advised durations of <3 months and ≥ 6 months, respectively.

Different durations of drug holidays, depending on the type of bone-modifying agent (bisphosphonate, denosumab, selective estrogen-receptor modulators, or parathyroid hormone) used, were advised by 46.7% of respondents. MRONJ was most often reported to be caused by bisphosphonate therapy (27.6%); denosumab therapy was only cited by 1.3% of respondents. Almost three-quarters (70.7%) of respondents reported no prior experience of treating patients with MRONJ (Table 2).

Table 2
Dentists' awareness of MRONJ and protocol followed before dental procedures

Variable	N	%
Do you record if the patient is taking anti-osteoporotic drugs?		
Yes	969	96.90%
No	31	3.10%
Do you record the name of the drug and duration of its use?		
No	187	18.70%
Name only	163	16.30%
Name and duration	650	65.00%
Do you ask for a doctor's referral letter?		
Yes	591	59.10%
No	409	40.90%
How long do you advise to discontinue the anti-osteoporotic agent before the procedure?		
<3 months	149	14.90%
3–5 months	457	45.70%
≥6 months	394	39.40%
Do you recommend different drug holidays depending on the type of drug (bisphosphonate, denosumab, SERM, PTH)?		
Yes	467	46.70%
No	533	53.30%
If you have encountered case/s of MRONJ, what type of medication caused it?		
Bisphosphonate	276	27.60%
Denosumab	13	1.30%
SERM	4	0.40%
No experience	707	70.70%
Abbreviations: MRONJ, medication-related osteonecrosis of the jaw; SERM, selective estrogen-receptor modulators; PTH, parathyroid hormone.		
Data are expressed as numbers and percentages.		

Awareness and specific management according to prior MRONJ experience

Dentists who documented anti-osteoporotic medication use were more likely to have no prior experience of encountering previous cases of MRONJ (Table 3). This was evident among dentists who documented medication names (97.5% having no experience versus 95.6% having experience; $P = 0.116$), and those who recorded both medication names and duration of use (67.5% having no experience versus 59.0% having experience; $P < 0.007$). Among dentists who advised drug holidays for <3 months, a smaller proportion had no prior experience of encountering previous cases of MRONJ (12.4% having no experience versus 20.8% having experience; $P < 0.001$). Similarly, a smaller proportion of dentists advising a 3–5 month-discontinuation period had no prior experience (45.4%) compared to those with prior experience (46.4%; $P < 0.001$). However, a greater proportion of dentists with no prior experience of encountering MRONJ cases advised drug holidays for ≥ 6 months, compared to those with prior experience (42.1% versus 32.8%; $P < 0.001$). There was no significant difference in the proportion of dentists with prior experience of MRONJ cases among those advising different drug holidays based on drug type.

Table 3
Awareness and management protocol according to prior MRONJ experience

		MRONJ experience ^a		<i>P</i>
		No	Yes	
Sex	Male	541 (76.5%)	246 (84.0%)	0.009
	Female	166 (23.5%)	47 (16.0%)	
Age (y)	≤30	5 (0.7%)	27 (9.2%)	<0.0001
	31–40	226 (32%)	72 (24.6%)	
	41–50	350 (49.5%)	116 (39.6%)	
	51–60	102 (14.4%)	70 (23.9%)	
	≥61	24 (3.4%)	8 (2.7%)	
Type of practice	Private clinic ^b	605 (85.6%)	248 (84.6%)	0.705
	Non-private clinic ^c	102 (14.4%)	45 (15.4%)	
Clinical experience (y)	≤5	64 (9.1%)	38 (13%)	0.030
	6–10	135 (19.1%)	44 (15%)	
	11–15	193 (27.3%)	63 (21.5%)	
	16–20	150 (21.2%)	62 (21.2%)	
	≥21	165 (23.3%)	86 (29.4%)	
Do you record if the patient is taking anti-osteoporotic drugs?	Yes	689 (97.5%)	280 (95.6%)	0.116
	No	18 (2.5%)	13 (4.4%)	
Do you record the name of the drug and duration of its use?	No	115 (16.3%)	72 (24.6%)	0.007

	Name only	115 (16.3%)	48 (16.4%)	
	Name and duration	477 (67.5%)	173 (59.0%)	
Do you ask for a doctor's referral letter?	Yes	423 (59.8%)	168 (57.3%)	0.466
	No	284 (40.2%)	125 (42.7%)	
How long do you advise to discontinue the anti-osteoporotic agent before the procedure?	<3 months	88 (12.4%)	61 (20.8%)	0.001
	3–5 months	321 (45.4%)	136 (46.4%)	
	≥6 months	298 (42.1%)	96 (32.8%)	
Do you recommend different drug holidays depending on the type of drug (bisphosphonate, denosumab, SERM, PTH)?	Yes	319 (45.1%)	148 (50.5%)	0.120
	No	388 (54.9%)	145 (49.5%)	
If you have encountered case/s of MRONJ, what type of medication caused it?	Bisphosphonate	-	276 (94.2%)	-
	Denosumab	-	13 (4.4%)	
	SERM	-	4 (1.4%)	
	No experience	-	0 (0%)	
Abbreviations: y, year; MRONJ, medication-related osteonecrosis of the jaw; SERM, selective estrogen-receptor modulators; PTH, parathyroid hormone				
^a Differences between dentists with and without prior MRONJ experience were evaluated using the χ^2 test. The level of statistical significance was set at $P < 0.05$. Data are presented as N (%).				
^b Dentists engaged in private practice				
^c Employed dentists, public dentists, leave of absence, etc.				

Discussion

The results of this study showed that most dentists only recorded the name of the osteoporotic drug, without documenting the duration of use. While the required period for a drug holiday is different for each

drug, most dentists did not advise different drug holiday durations depending on drug type. Dentists recording both the name and duration of bone-modifying medications, as well as those requesting referral letters from doctors, more often had no prior experience with MRONJ cases. Therefore, the results of this study suggest that MRONJ can be prevented by maintaining a thorough medical record for patients on bone-modifying medications, and requesting a doctor's referral letter prior to the performance of any dental procedures.

Furthermore, it was observed that drug holidays ≥ 6 months are more effective than 2–3-month drug holidays for the prevention of MRONJ. This period is longer than that recommended in the literature [7, 10]. Hence, the optimal duration of a drug holiday cannot be determined from the results of our study alone, and further long-term studies are required for definitive conclusions to be drawn.

Due to the aging demographic not only in Korea, but also worldwide, an increasing number of elderly individuals with multiple co-morbidities are expected to undergo various dental procedures, including implant placement. Thus, an awareness of the potential interactions in treatment regimens advised by multiple doctors in specialized fields, as well as optimal communication between healthcare professionals, will become increasingly important. Poor patient compliance and varied side effects of bone-modifying agents are the primary obstacles in the treatment of osteoporosis [11, 12]. On the other hand, excessive use of bone-modifying agents can also increase the risk of MRONJ. MRONJ is a rare but serious complication following treatment with certain medications, and is defined as the presence of exposed bone in the oral and maxillofacial regions (or extra- or intra-oral fistulas) lasting more than 8 weeks. Patients do not have any prior history of radiation or treatment with bone-resorption inhibitors or angiogenesis inhibitors for tumor metastasis to the jawbones [7].

The exact mechanism of development of MRONJ is unclear, in spite of several proposed hypotheses. Additionally, varied opinions regarding the efficacy of surgical and non-surgical treatments have been presented [8, 9, 13, 14]. In addition to bisphosphonates, several drugs such as denosumab, steroids, and angiogenesis inhibitors can cause MRONJ [7, 15]. Denosumab is an anti-human receptor activator of the nuclear factor kappa-B ligand, and inhibits the activity of osteoclasts. It is used to treat osteoporosis caused by bone absorption disorders [16], similar to bisphosphonates [8], and its efficacy and convenience of administration has recently led to its increased use in Korea [17]. Denosumab is also associated with a risk for MRONJ, but the risk of fracture may increase either temporarily or permanently when its use is discontinued [7].

Thus, the disadvantages of drug discontinuation should be weighed against its advantages; this requires that dentists request a doctor's referral letter prior to any dental procedure in patients at risk for MRONJ. In addition, detailed investigations and records of bone-modifying agents must be requested and maintained. Drug holidays are not recommended for certain drugs, as well as patients with severe osteoporosis [10, 18]. As the determination of a drug discontinuation protocol depends on both individual patient factors and the specific drug in question, this may be beyond the scope of dentistry; therefore, a doctor's referral letter should always be obtained. However, the results of our study showed that the

proportion of dentists requesting referral letters was relatively low. In addition, the proportion of dentists that encountered cases of MRONJ was higher than the general prevalence of MRONJ. This suggests that dentists are highly likely to encounter patients at risk for MRONJ, thus highlighting the importance of adequate knowledge pertaining to this condition, and proper dental management protocols.

The determination of bone-modifying medication type and its duration of use, potential alternative medications, and a drug holiday of 2–3 months before dental procedures is essential for preventing MRONJ [7, 10]. In our study, the optimal drug holiday duration reported by the respondents varied, and the percentage advising the guideline-recommended 2–3-month holiday was relatively low. A post-analysis study concluded that drug holidays should be advised for “patients at low risk of fracture,” who are defined by the following criteria: T-score > -2.5; no current fracture; age less than 70 years; and no diseases or medications that could increase fracture risk [19]. Drug holidays should be considered for patients with a 5-year history of alendronate use or a 3-year history of zoledronic acid (or risedronate) use [19, 20]. The duration of drug holiday should be decided based on the results of bone mineral density assessment, fracture risk, and T-score [20]. The management of the osteoporotic condition with other bone-modifying medications is advised after discontinuation of denosumab during drug holidays or dental treatment [21, 22]. Drug holidays are not required with other bone-modifying medications such as hormone replacement therapy, selective estrogen-receptor modulators, and teriparatide [21]. Therefore, it is important that dentists obtain a doctor's referral letter before initiating treatment.

Several prior studies examining the awareness of dentists regarding BRONJ have been conducted in different countries. A survey of 120 dentists in Romania reported that the majority were aware of bisphosphonate therapy and its complications, but were not familiar with the pathophysiology, diagnosis, and treatment of BRONJ [23]. A survey of 204 Brazilian dentists and dental students reported a lack of knowledge regarding bisphosphonates and awareness pertaining to BRONJ [24]. In a survey of 120 dentists and dental students in Spain, 30 (50%) students and 41 (68.36%) dentists were determined to have up-to-date knowledge regarding BRONJ [25]. In a survey of 129 British dentists, more than 90% admitted a lack of awareness regarding drugs (other than bisphosphonates) that cause MRONJ. Furthermore, the lack of a standardized protocol was reported as the primary reason for difficulties in managing such patients [26]. A recent study conducted in 2019 reported that only 31.5% of the surveyed physicians and dentists were aware of ONJ. The authors suggested that the level of knowledge and awareness regarding BRONJ could be increased through education [27]. In the present study, we found that the level of awareness of dentists regarding MRONJ was high; nevertheless, the documentation of patients' history pertaining to bone-modifying agent type and duration of use was insufficient. Hence, dentists should be made aware of the standard guidelines for treatment of such patients through regular educational programming.

Our study had some limitations. First, only 1000 dentists were surveyed; therefore the results may not be generalizable to all dentists in Korea. Second, due to the limited scope of the questions, it was not possible to elucidate the dentists' knowledge of MRONJ pathogenesis. Third, respondents in this survey were not aware of the available guidelines for implementing drug holidays. Fourth, the type of medication

responsible for MRONJ could not be definitively ascertained. Nevertheless, the results of this survey can serve as a basis for further detailed, larger, long-term studies to reveal more causal relationships.

Conclusions

Elderly individuals often have multiple co-morbidities that require multidisciplinary management. Due to an aging demographic, dentists are likely to encounter an increasing number of elderly patients with osteoporosis who require implant surgery. Thus, the successful management of such patients will require an approach which encourages cooperation between doctors and dentists, and the development of educational programs to increase knowledge and awareness of MRONJ.

List Of Abbreviations

BRONJ, bisphosphonate-related osteonecrosis of the jaws

MRONJ, medication-related osteonecrosis of the jaws

PTH, parathyroid hormone

SERM, selective estrogen-receptor modulators

Declarations

Ethics approval and consent to participate

This study was approved by the institutional bioethics committee of our university hospital (IRB approval number: 2019-03-015), and conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all study participants.

Consent for publication

The consent we obtained from study participants was written. We put the following phrase at the top of the questionnaire. We swear that the results of this questionnaire will be used for research purposes and will not be used for any purpose other than research. If you agree to this, please fill out and submit the questionnaire. Then, a sample of the questionnaire was submitted to the IRB and approved by the IRB.

Competing interests

There is no competing interests

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Authors' contributions

ALH performed all work involved in this study (including study conception, hypothesis, experimental design, data collection and analysis, and write-up of manuscript) and approved the final manuscript.

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