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Original research

Discontinuing oral bisphosphonate therapy during dental extraction does not prevent osteonecrosis of the jaw: A multicenter retrospective study of 341 patients with propensity score matching analysis

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ABSTRACT

Objective: Oral bisphosphonates (BPs) are widely used in the treatment of osteoporosis. When tooth extraction is performed, the recommendation is to discontinue oral BP therapy in patients if they have risk factors such as diabetes, treatment with steroids, malignancy, rheumatoid arthritis and renal failure, or have received these agents for a long period. However, there is little evidence to support this recommendation. The aim of this multicenter retrospective study was to assess the preventive effect of discontinuing oral BPs on development of bisphosphonate-related osteonecrosis of the jaw (BRONJ).
Methods: A total of 341 patients receiving oral BPs underwent extraction of 850 teeth from 402 jaws. Various factors were evaluated, including age, gender, diabetes, steroid use, malignancy, rheumatoid arthritis, renal failure, type of oral BP administered, duration of treatment, number of teeth extracted, reason for extraction, site (upper or lower jaw), wound status (open or complete closure), and whether BP therapy was discontinued. The relationship between these factors and development of BRONJ was analyzed by Fisher's Exact test and one-way analysis of variance. Further, propensity score matching analysis was performed to reduce selection biases associated with retrospective data between discontinuing and continuing groups.
Results: BRONJ developed in 7 (2.1%) of 341 patients. Univariate analysis showed that BRONJ developed significantly more often in patients receiving second-generation agents. Discontinuation of BPs was not associated with a reduced risk of BRONJ. After propensity score matching, no factors including discontinuing BPs were correlated with development of BRONJ.
Conclusion: The results of this study do not support discontinuation of oral BPs before tooth extraction to prevent BRONJ.

1. Introduction

Bisphosphonates (BPs) are widely used as first-line therapy for osteoporosis or metastasis of malignant neoplasms to bone. One of the severe late complications of these agents, particularly in those who have received intravenous BPs for a long time, is bisphosphonate-related osteonecrosis of the jaw (BRONJ), which

☆ AsianAOMS: Asian Association of Oral and Maxillofacial Surgeons; ASOMP: Asian Society of Oral and Maxillofacial Pathology; JSOP: Japanese Society of Oral Pathology; JSOMS: Japanese Society of Oral and Maxillofacial Surgeons; JSOM: Japanese Society of Oral Medicine; JAMI: Japanese Academy of Maxillofacial Implants.

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Table 1
Background factors of patients in the discontinuing and continuing groups.

Factor	Category	discontinuing group (284 jaws)	continuing group (118 jaws)	*p*-value
Age	mean ± SD (years)	72.4 ± 10.6	74.1 ± 9.62	0.14
Gender	male	25	18	0.075
	female	259	100	
risk factor	present	165	45	<0.001
	absent	119	73	
Duration of medication	mean ± SD (months)	43.4 ± 36.3	31.3 ± 31.0	0.002
Type of BP	2nd generation	175	67	0.373
	others	109	51	
Site	upper teeth	145	58	0.743
	lower teeth	139	60	
Number of extrated teeth	1 tooth	156	63	0.826
	≥2 teeth	128	55	
wound	complete closure	208	93	0.258
	open	76	25	
cause of extraction	periapical periodontitis	118	36	0.043
	others	166	82	
	marginal periodontitis	78	48	0.013
	others	206	70	
	severe caries	88	34	0.721
	others	196	84	

can affect quality of life [1]. The incidence of BRONJ caused by oral BPs is reportedly rare [2]; however, Japanese patients receiving oral BPs develop this complication more often than their US or European counterparts [3].

BRONJ often develops after tooth extraction. The position paper on the diagnosis and treatment of BRONJ published by the American Association of Oral and Maxillofacial Surgeons in 2009 and its update in 2014 recommended discontinuing oral BPs for 3 months before and 3 months after invasive dental surgery, when systemic conditions allow [4]. The position paper of 2014 suggested that although there are limited data to support or refute the benefit of a drug holiday for osteoporotic patients receiving antiresorptive therapy, there may still be a theoretical benefit for those patients with extended exposure histories of more than 4 years [2]. The aim of this multicenter retrospective study was to investigate the frequency of medication-related osteonecrosis of the jaw and its risk factors in patients who did or did not discontinue oral BP therapy after tooth extraction.

2. Methods

2.1. Patients

The study population comprised 341 patients receiving oral BP therapy who underwent tooth extraction at Nagasaki University Hospital, Omura City Hospital, or Juko Memorial Nagasaki Hospital, between April 2010 and December 2015. Whether or not oral BPs were discontinued or the extraction wound was left open or complete closure was at the discretion of the attending dentist.

2.2. Variables

Demographic, treatment-related, and dental information was obtained retrospectively from medical records. Demographic factors included age, gender, and risk factors for osteoporosis (diabetes, treatment with steroids, malignancy, rheumatoid arthritis, renal failure); treatment-related factors included type of BP, duration of treatment, discontinuation of BP therapy in relation to tooth extraction; and dental factors included number of teeth extracted, reason for extraction, site (upper or lower jaw), and wound status (open or complete closure). The relationship between these potentially predictive factors and development of BRONJ was investigated.

2.3. Statistical analysis

The statistical analysis was performed using SPSS version 24.0 software (IBM Japan Ltd, Tokyo, Japan). First, the correlation between each variable and development of BRONJ in all patients was analyzed by Fisher's exact test and one-way analysis of variance. Next, propensity score analysis was performed to reduce selection biases associated with retrospective data between discontinuing and continuing groups. A propensity score for discontinuing drug was calculated in each patient using logistic regression with the all predictive variables. The groups (discontinuing vs. continuing) after matching by propensity score were then evaluated to examine the factors relating to development of BRONJ by Fisher's exact test and one-way analysis of variance. In all analyses, a two-tailed p value of <0.05 was considered statistically significant.

2.4. Ethics

Ethics approval was obtained from the institutional review board of Nagasaki University Hospital (Number #16092609).

3. Results

A medical records search yielded 341 patients (43 men, 359 women, a mean age 72.9 years) who underwent extraction of 850 teeth from 203 upper and 199 lower jaws. BP therapy was discontinued in 284 extractions (discontinuing group) and not discontinued in 118 extractions (continuing group). Table 1 shows the background factors in the discontinuing and continuing groups. BP was discontinued more often in patients who had risk factors, who had longer medication period, and when tooth of periapical periodontitis was extracted. On the others hand, BP was continued more often when tooth of marginal periodontitis was extracted.

BRONJ developed in 7 (2.1%) of 341 patients and in 7 (1.7%) of 402 jaws. The lower jaw was involved in 4 patients and the upper jaw in 3 patients. The relationship between each predictive variable and development of BRONJ by univariate analysis is summarized in Table 2. BRONJ occurred significantly more often in patients treated with second-generation agents; other factors, including site (upper/lower jaw), number of teeth extracted, wound status (open/complete closure), and cause of extraction were not associated with development of BRONJ. All patients who developed BRONJ were in the discontinuing group, but there was no significant difference between the two groups with regard to development of

Table 2
Relationship between each predictive variable and development of BRONJ in all patients (univariate analysis).

Factor	Category	BRONJ (−) (395 jaws)	BRONJ (+) (7 jaws)	*p*-value
Age	mean ± SD (years)	72.8 ± 10.4	76.4 ± 5.19	0.360
Gender	male	43	0	1.000
	female	352	7	
risk factor	absent	235	3	0.450
	present	160	4	
Duration of medication	mean ± SD (months)	40.0 ± 35.5	27.4 ± 9.07	0.349
Type of BP	2nd generation	235	7	0.045
	others	160	0	
Site	upper teeth	200	3	0.722
	lower teeth	195	4	
Number of extrated teeth	1 tooth	216	3	0.707
	≥ 2 teeth	179	4	
Wound	complete closure	295	6	0.685
	open	100	1	
Cause of extraction	periapical periodontitis	151	3	1.000
	others	244	4	
	marginal periodontitis	125	1	0.442
	others	270	6	
	severe caries	119	3	0.438
	others	276	4	
medication	discontinue	277	7	0.111
	continue	118	0	

Table 3
Influence of discontinuing oral BPs in patients administrated medication for more than 36 months or having risk factor.

Category	withdrawal of oral BP	BRONJ (−)	BRONJ (+)	*p*-value
duration of medication	discontinue	110	5	1.000
≥36 months (n = 147)	continue	31	1	
having risk factor	discontinue	85	3	1.000
(n = 131)	continue	42	1	

the condition. Further, when the occurrence rate of BRONJ was calculated in the limited numbers of patients who had been taking BPs for more than 3 years and those who had risk factors, discontinuing BPs did not reduce the risk of BRONJ (Table 3).

A propensity score was calculated in each patient using logistic regression with the all 10 variables associated with discontinuing drug. The concordance index (c index) was 0.640 and the Hosmer-Lemeshow test was not significant ($p = 0.196$) indicating a strong ability to differentiate between patients receiving or not receiving oral care and good calibration, respectively. Propensity score (which reflected the probability that a patient would discontinue drug) ranged from 0.3454 to 0.9700 in the discontinuing group and from 0.3548 to 0.8927 in the continuing group.

The propensity score analysis resulted 220 patients matched (110 in the discontinuing group and 110 in the continuing group) as shown in Table 4. After propensity score matching, univariate analysis revealed that no variables were correlated with development of BRONJ (Table 5).

4. Discussion

In a survey of more than 13,000 members of the Kaiser Permanente integrated managed care consortium, the reported prevalence of BRONJ in members receiving oral BP therapy was 0.1%, but increased to 0.21% in those with an oral BP exposure of more than 4 years [5]. Felsenberg and Hoffmeister reported a prevalence of BRONJ in patients treated with BPs for osteoporosis of 0.00038% based on reports of 3 cases to the German Central Registry of Necrosis of the Jaw [6], while Malden and Lopes derived an incidence of 0.004% from 11 cases of BRONJ reported in a population of 90,000 patients living in southeast Scotland [7].

Some risk factors for BRONJ have been reported but tend to relate to intravenous BPs used in patients with cancer. Duration of therapy and dentoalveolar surgery have also been investigated as risk factors when using oral BPs. The prevalence of BRONJ increases over time in patients receiving oral BPs for osteoporosis, from nearly 0% at baseline to 0.21% after 4 years of treatment [2]. Dentoalveolar surgery, including tooth extractions and implant procedures, is considered a major risk factor for developing medication-related osteonecrosis of the jaw. Several studies have reported that tooth extraction is a common predisposing factor in the development of BRONJ, with 52%–61% of patients reporting this as the precipitating event [8–10]. In a case-control study of patients with cancer exposed to zoledronate, tooth extraction was associated with a 16-fold increased risk for osteonecrosis of the jaw [11] In a longitudinal cohort study of patients exposed to intravenous BPs, tooth extraction was associated with a 33-fold increased risk for osteonecrosis of the jaw [8]. The risk of developing BRONJ after tooth extraction in patients with cancer and exposed to intravenous BPs ranges from 1.6% to 14.8% [12–14]. In contrast, the risk of BRONJ in patients receiving oral BPs after tooth extraction seems to be relatively low; 0.5% [15], 2,5% [16], 3.0% [17], and 3.7% [18] in recent literatures. Other risk factors for osteonecrosis of the jaw include poor oral hygiene, chronic inflammation, diabetes mellitus, ill-fitting dentures, and use of glucocorticoids and certain other drugs, including antiangiogenic agents [2].

The current retrospective study investigated the frequency of and risk factors for BRONJ after tooth extraction in patients receiving oral BP therapy, and compared the occurrence rate of BRONJ between patients who discontinued this medication before and after the procedure and those who did not. BRONJ occurred in 7 (2.1%) of 341 patients after tooth extraction. This rate is higher than that reported in the USA, European Union, or Australia. Patients who used second generation BP, in particular alendronate, showed higher percentage of development of BRONJ in this study by univariate analysis before propensity score matching. The reason why BRONJ was found so often in patients treated with alendronate is unclear, but this was a retrospective study and some confounding factors may be present.

In the statistical analysis of observational data, propensity score matching is a statistical technique that attempts to estimate the effect of a treatment, policy, or other intervention by accounting for the covariates that predict receiving the treatment [19]. Propensity score matching reduces the bias due to confounding variables that could be found in an estimate of the treatment effect obtained from

Table 4
Background factors of patients in the discontinuing and continuing groups after propensity score matching.

Factor	Category	discontinuing groupn (110 jaws)	continuing group (110 jaws)	*p*-value
Age	mean ± SD (years)	73.5 ± 11.1	73.8 ± 9.64	0.846
Gender	male	12	11	1.000
	female	98	99	
risk factor	present	34	44	0.205
	absent	76	66	
Duration of medication	mean ± SD (months)	32.4 ± 25.2	32.6 ± 31.5	0.846
Type of BP	2nd generation	67	64	0.784
	others	43	46	
Site	upper teeth	59	55	0.686
	lower teeth	51	55	
Number of extrated teeth	1 tooth	60	59	1.000
	≥2 teeth	50	51	
wound	complete closure	76	78	0.833
	open	34	32	
cause of extraction	periapical periodontitis	39	36	0.776
	others	71	74	
	marginal periodontitis	34	40	0.476
	others	76	70	
	severe caries	37	34	0.773
	others	73	76	

Table 5
Relationship between each predictive variable and development of BRONJ after propensity score matching (univariate analysis).

Factor	Category	BRONJ (−) (217 jaws)	BRONJ (+) (3 jaws)	*p*-value
Age	mean ± SD (years)	73.6 ± 10,4	77.3 ± 6.66	0.537
Gender	male	23	0	1.000
	female	194	3	
risk factor	absent	140	2	1.000
	present	77	1	
Duration of medication	mean ± SD (months)	32.6 ± 28.7	28.0 ± 6.93	0.537
Type of BP	2nd generation	128	3	0.274
	others	89	0	
Site	upper teeth	109	1	1.000
	lower teeth	110	2	
Number of extrated teeth	1 tooth	118	1	0.595
	≥ 2 teeth	99	2	
Wound	complete closure	152	2	1.000
	open	65	1	
Cause of extraction	periapical periodontitis	73	2	0.268
	others	144	1	
	marginal periodontitis	74	0	0.553
	others	143	3	
	severe caries	70	1	1.000
	others	147	2	
medication	discontinue	197	3	0.247
	continue	110	0	

simply comparing outcomes among units that received the treatment versus those that did not. In the current study, 220 of 402 jaws were matched by propensity score matching. However, after propensity score matching, no variables including discontinuing medication were correlated with development of BRONJ, probably because of a small number of cases developing BRONJ.

The position paper of the Japanese Society for Bone and Mineral Research, Japan Osteoporosis Society, Japanese Society of Periodontology, Japanese Society for Oral and Maxillofacial Radiology, and Japanese Society of Oral and Maxillofacial Surgeons published in 2010 recommended discontinuing oral BP therapy for 3 months before and 2 weeks to 2 months after tooth extraction in patients with risk factors (such as corticosteroid therapy, diabetes, smoking, and poor oral hygiene) and in those who have received oral BP therapy for more than 3 years [20]. The position paper published by the American Association of Oral and Maxillofacial Surgeons in 2014 also recommends a drug holiday for patients with osteoporosis who undergo tooth extraction after receiving oral BPs for more than 4 years [2]. In the current study, 7 patients who developed BRONJ had discontinued their oral BP medication before tooth extraction. The effect of discontinuing medication was examined in patients who had risk factors for BRONJ or who had received oral BP therapy for more than 3 years, given that oral BPs tended to be discontinued more often in these groups of patients. Discontinuing medication had no effect on development of BRONJ in these higher-risk patients. Taguchi et al. reported that discontinuing oral BP for 3 months or more possibly increased risk of fracture to 5.3% in osteoporosis patients [21]. Curtis et al. also described that discontinuing of BP increased hip fracture in osoteoporosis patients who received oral BP therapy for more than 2 years [22]. It should be borne in mind that discontinuing oral BPs before tooth extraction may decrease quality of life for patients by preserve infected teeth for several months, and increase the risks for worsening of osteoporosis and bone fracture.

This study has some limitations, including being retrospective and involving a relatively small number of patients, which precludes any valid conclusions being drawn. However, its results suggest that discontinuing oral BPs does not prevent BRONJ after tooth extraction. We consider that oral BPs are not necessarily required to withdraw in patients with osteoporosis undergoing tooth extraction. Larger studies are needed in the future to address this issue.

5. Conclusions

The results of this multicenter retrospective study do not support discontinuation of oral BPs before tooth extraction to prevent BRONJ in patients receiving this therapy.

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