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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

Akiko Kawakita [a,*], Souichi Yanamoto [a], Kota Morishita [a], Tomofumi Naruse [a], Saki Hayashida [a], Sakiko Soutome [b], Satoshi Rokutanda [c], Satoshi Inokuchi [d], Takemitsu Matsuo [d], Masahiro Umeda [a]

[a] Department of Clinical Oral Oncology, Nagasaki University Graduate School of Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki City, Nagasaki, 852-8588, Japan
[b] Perioperative Oral Management Center, Nagasaki University Hospital, 1-7-1 Sakamoto, Nagasaki City, Nagasaki, 852-8588, Japan
[c] Department of Dentistry and Oral Surgery, Juko Memorial Nagasaki Hospital, 1-73 Akunora town, Nagasaki City, Nagasaki, 850-0063, Japan
[d] Department of Dentistry and Oral Surgery, Omura City Hospital, 133-22 Kogashima town, Omura City, Nagasaki, 865-8561, Japan

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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.

* Corresponding author.
E-mail addresses: a-kawa@nagasaki-u.ac.jp (A. Kawakita), syana@nagasaki-u.ac.jp (S. Yanamoto), k-morishita@nagasaki-u.ac.jp (K. Morishita), naruse12@nagasaki-u.ac.jp (T. Naruse), sakihaya@nagasaki-u.ac.jp (S. Hayashida), sakiko@nagasaki-u.ac.jp (S. Soutome), satoshi6@nagasaki-u.ac.jp (S. Rokutanda), bb55312206@ms.nagasaki-u.ac.jp (S. Inokuchi), takemitum@jadecom.jp (T. Matsuo), mumeda@nagasaki-u.ac.jp (M. Umeda).

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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

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