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, Souichi Yanamoto, Kota Morishita, Tomofumi Naruse, Saki Hayashida, Sakiko Soutome, Satoshi Rokutanda, Satoshi Inokuchi, Takemitsu Matsuo, Masahiro Umeda

Department of Clinical Oral Oncology, Nagasaki University Graduate School of Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki City, Nagasaki, 852-8588, Japan
Perioperative Management Center, Nagasaki University Hospital, 1-7-1 Sakamoto, Nagasaki City, Nagasaki, 852-8588, Japan
Department of Dentistry and Oral Surgery, Juko Memorial Nagasaki University Hospital, 1-73 Akanor town, Nagasaki City, Nagasaki, 850-0063, Japan
Department of Dentistry and Oral Surgery, Omura City Hospital, 133-22 Nagashima town, Omura City, Nagasaki, 865-8561, Japan

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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
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 all the 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).

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

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

<table>
<thead>
<tr>
<th>Category</th>
<th>withdrawal of oral BP</th>
<th>BRONJ (−)</th>
<th>BRONJ (+)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>duration of medication</td>
<td>≥36 months (n = 147)</td>
<td>discontinue</td>
<td>110</td>
<td>5</td>
</tr>
<tr>
<td>having risk factor</td>
<td>n = 131</td>
<td>continue</td>
<td>31</td>
<td>1</td>
</tr>
</tbody>
</table>

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 dental alveolar 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]. Dental alveolar 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 the 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
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 osteoporosis 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 preserving 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.

References


