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Incidence of bisphosphonate-related osteonecrosis of the jaw in high-risk patients undergoing surgical tooth extraction

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ABSTRACT

As the most suitable approach for preventing bisphosphonate-related osteonecrosis of the jaw (BRONJ) in patients undergoing surgical tooth extraction is still under discussion, the present study evaluates the incidence of BRONJ after surgical tooth extraction using a standardized surgical protocol in combination with an adjuvant perioperative treatment setting in patients who are at high-risk for developing BRONJ.

High-risk patients were defined as patients who received intravenous bisphosphonate (BP) due to a malignant disease. All teeth were removed using a standardized surgical protocol. The perioperative adjuvant treatment included intravenous antibiotic prophylaxis starting at least 24 h before surgery, a gastric feeding tube and mouth rinses with chlorhexidine (0.12%) three times a day. In the follow-up period patients were examined every 4 weeks for the development of BRONJ. Minimum follow-up was 12 weeks.

In 61 patients a total number of 184 teeth were removed from 102 separate extraction sites. In eight patients (13.1%) BRONJ developed during the follow-up. A higher risk for developing BRONJ was found in patients where an additional osteotomy was necessary (21.4% vs. 8.0%; $p = 0.0577$), especially for an osteotomy of the mandible (33.3% vs. 7.3%; $p = 0.0268$). Parameters including duration of intravenous antibiotic prophylaxis, the use of a gastric feeding tube and the duration of intravenous BP therapy showed no statistical impact on the development of BRONJ. Furthermore, patients currently undergoing intravenous BP therapy showed no higher risk for BRONJ compared with patients who have paused or completed their intravenous BP therapy ($p = 0.4232$).

This study presents a protocol for surgical tooth extraction in high-risk BP patients in combination with a perioperative adjuvant treatment setting, which reduced the risk for postoperative BRONJ to a minimum. However, the risk for BRONJ increases significantly if an additional osteotomy is necessary, especially in the mandible.

1. Introduction

Bisphosphonates (BP) are potent inhibitors of bone resorption and are currently the therapy of choice for many different bone diseases or associated complications, including osteolytic bone disease, malignancy-induced hypercalcaemia, metastatic bone diseases and osteoporosis, as BP therapy significantly reduces skeletal complications (Berenson et al., 2006; Bilezikian, 2009; Body, 2006; Body et al., 2007; Cosman, 2009). As a significant drawback of BP therapy, bisphosphonate-related osteonecrosis of the jaw (BRONJ) is a well-known complication (Otto et al., 2012). Although it was originally described in 2003 (Marx, 2003), the exact aetiology is still incompletely understood and is the subject of current research (Russell et al., 2007). The main effect of BPs is based on the reduction of bone resorption by inhibiting osteoclast function and by inducing apoptosis in osteoclasts (Russell et al., 2007). Furthermore, BPs show a direct inhibition of the growth and healing potential of mucosal cells which might further promote BRONJ (Cornish et al., 2011).

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Marx was the first to describe an avascular necrosis of the jaw of 36 patients receiving intravenous BP therapy with pamidronate or zoledronic acid (Marx, 2003). In his experience, removal of teeth was the initiating event in 28 cases (77.7%). The first peer-reviewed case series of BRONJ was published by Rugierro et al., in 2004. They reported BRONJ in 63 cases with a history of chronic bisphosphonate therapy. Fifty-six patients received intravenous BP therapy and seven patients received oral therapy. As already described by Marx, dentoalveolar treatment was the main risk factor for BRONJ as 54 patients (86%) had a history of a recent dentoalveolar procedure.

Since then, various studies have confirmed these findings. Filleul et al. (2010) reported, in a large review of 138 articles, a total number of 2400 patients with BRONJ, where dental extraction was the triggering event in 67% of the cases. According to these results the BRONJ Position Paper of the American Association of Oral and Maxillofacial Surgeons (AAOMS) was published, considering extraction as one of the independent local risk factors inducing BRONJ (Ruggiero et al., 2009b).

In order to reduce the risk of BRONJ, patients should receive a detailed dental examination and, if necessary, dental treatment before starting bisphosphonate therapy (Khosla et al., 2007; Vescovi et al., 2011; Walter et al., 2009), especially as the treatment of established BRONJ still remains challenging (Vassiliou et al., 2010).

Principally, procedures that cause exposure of the jaw bone should be avoided under BP therapy (Ruggiero et al., 2009b), however, if tooth extraction is unavoidable it should be performed according to a standardized extraction protocol that includes a specific preoperative and postoperative approach to reduce the risk of BRONJ. The relative risk of BRONJ after tooth extraction is up to 50 times higher than in BP patients without tooth extraction (Hoff et al., 2008). As a simple tooth extraction is reported to be associated with a higher rate of BRONJ, any tooth extraction should be performed as a surgical extraction with a thorough closure of the alveolar socket by a mucosal flap (Hasegawa et al., 2013; Khosla et al., 2007).

Although various studies have been published regarding the best prophylactic methods for the prevention of BRONJ, there is still disagreement on the importance of the different risk factors associated with tooth extraction and on the appropriate surgical approach. Hence, the aim of the present study was to evaluate the incidence of BRONJ after surgical tooth extraction using a standardized protocol in combination with an adjuvant perioperative treatment setting in patients who had received intravenous BP therapy.

2. Materials and methods

This study was approved by the local Ethics Committee (Ethics number S-420/2012) and was carried out according to the Declaration of Helsinki. Written informed consent was obtained from all patients. The study was designed as a monocentric cohort study. As this study focused on patients who are at high-risk for developing BRONJ according to the AAOMS, we only included patients with either ongoing or completed therapy with intravenous BPs due to a malignant disease. We evaluated the incidence of BRONJ following surgical tooth extraction under standardized conditions. Additional inclusion criteria were: no radiation therapy in the medical history and no clinical or radiological evidence of BRONJ Stage 0–III according to the AAOMS (Ruggiero et al., 2009a).

All patients were treated using a standardized surgical extraction protocol under local or general anaesthesia depending on the number of extracted teeth, the general health status of the patient and patient's compliance. Surgical tooth extraction was performed as follows: (I) elevation of a mucosal flap by *epiperiosteal* preparation with bilateral release incisions, if necessary; (II) extraction of tooth; and (III) tension-free closure of the alveolar socket. If tooth extraction was not possible using forceps only, an additional osteotomy was performed including removal of facial and/or lingual/palatine bone if necessary.

The perioperative adjuvant treatment included intravenous antibiotic prophylaxis (1.5 g of ampicillin-sulbactam 3 times per day) starting at least 24 h before surgical treatment and continued postoperatively for a recommended period of 5 days. Patients with known allergy to penicillin were given 600 mg clindamycin, 3 times per day. Furthermore, for optimizing oral hygiene, we recommended a gastric feeding tube to the patients and a mouth rinse with antimicrobiological solution (chlorhexidine 0.12%) three times a day.

In the follow-up period, all patients were examined every 4 weeks in our outpatient department including a thorough oral inspection. Possible development of BRONJ was noted and if present classified into different stages 0–III according to the guidelines of the AAOMS (Ruggiero et al., 2009a).

The statistical analysis is of exploratory nature. The outcome variable was defined as the absence of BRONJ during the follow-up. Median, first and third quartiles, minima and maxima, and relative and absolute frequencies were calculated for exploratory analyses. A multiple logistic regression analysis was performed to identify independent variables, which are associated with the therapeutic success defined as absence of BRONJ after extraction or osteotomy. In addition univariate analyses (Chi-squared test) were performed.

Statistical analyses were conducted using SPSS version 19.0.0 (IBM SPSS Statistics; SPSS Inc., Chicago, IL, USA). Due to the exploratory nature of the study, no adjustment was made for multiple testing, and *p*-values less than 5% were interpreted as statistically significant.

Table 1
Clinical parameters of 8 patients with development of BRONJ after surgical tooth extraction.

Patient	Number of extraction sites: maxilla	Number of extraction sites: mandible	Duration of intravenous antibiotic prophylaxis [days]	Duration of intravenous BP therapy [month]	Duration of gastric feeding tube [days]	Localization of BRONJ [number]	Additional osteotomy at BRONJ site [number]
R.A.	1	2	8	53	4	Man (2)	Yes (2)
N.T.	3	1	12	12	7	Max (1)	Yes (1)
K.B.	3	2	9	12	0	Max (1)	No (1)
M.A.	1	0	6	92	4	Max (1)	No (1)
E.E.	2	2	3	20	0	Max (1) Man (1)	No (2)
R.H.-B.	2	1	10	11	6	Max (1)	No (1)
K.K.	0	1	7	26	5	Man (1)	No (1)
M.I.	0	1	7	16	4	Man (1)	No (1)
Total	12	10	Mean: 7.8	Mean: 30.3	Mean: 4.9	Max (5) Man (5)	Yes (3) No (7)

BP: bisphosphonate; BRONJ: bisphosphonate-related osteonecrosis of the jaw; man: mandible; max: maxilla.