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Incidence and Risk Factors of Bisphosphonate-Related Osteonecrosis of the Jaw Following Tooth Extraction: A Systematic Review

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Original Research Article

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Abstract: Tooth extraction is considered to be a potential trigger for the onset of bisphosphonate-related osteonecrosis of the jaw (BRONJ). Therefore, the aim of this systematic review is to assess published evidence in order to identify the incidence and the risk factors influencing the development of osteonecrosis of the jaw after tooth extraction among patients exposed to oral and intravenous (IV) bisphosphonates (BPs). A literature search of Medline via PubMed and Cochrane Library databases was conducted using the keywords 'bisphosphonate-associated osteonecrosis of the jaw' and 'tooth extraction'. Only cohort and case-control studies were included in our research. Twelve articles published between 2007 and January 2017 was reviewed. The studies reported 2325 patients treated with BPs (16% for osteoporosis and 84% for malignant disease) who underwent dental extractions. The mean age of the patients was 65.57 years and the mean duration of BPs administration was 29.83 months. A total of 4673 extractions were involved. The mean duration of follow-up after dental extraction was 41.64 months. Fifty cases (2.15%) of BRONJ was detected (15.69% of them were under oral BPs and 84.31% were treated by IV BPs) which corresponds to 67 extraction sites fairly distributed between maxilla and mandible (p=0.7). 38% of BRONJ patients were under corticosteroid treatment and 22 % were treated by chemotherapy. 10% of osteonecrosis cases have undergone a traumatic extraction with osteotomy. Therefore, the use of BPs is associated with a substantial risk for osteonecrosis of the jaw after dental extraction and patients receiving IV BP are at highest risk.

Keywords: Bisphosphonate-related osteonecrosis of the jaw, tooth extractions, bisphosphonates

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 multiple myeloma, malignancy-induced hypercalcaemia, metastatic bone diseases and osteoporosis [1]. Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is a serious side-effect of BP therapy [2]. However, the majority of cases described in the literature occurred after preceding, so called, trigger events, which were mainly tooth extractions. Therefore, dental practitioners feel in a precarious position when choosing appropriate treatment protocols which aim to avoid BRONJ after tooth extractions and other dento-alveolar surgical procedures [2]. The majority of recommendations are intended to control local infection, while applying perioperative antibiotic prophylaxis and plastic wound closure [2].

The aim of this systematic review is to assess published evidence in order to identify the incidence and the risk factors influencing the development of osteonecrosis of the jaw after tooth extraction among patients exposed to oral and intravenous (IV) bisphosphonates (BPs).

MATERIAL AND METHODS

Search strategy

A literature search of Medline via PubMed and Cochrane Library databases was performed between 2007 and January 2017 using the following Medical Subject Headings (MeSH) 'bisphosphonate-associated osteonecrosis of the jaw' and 'tooth extraction'. Two authors conducted the database searches independently. We used manual restrictions by study type, the advanced automated methods in PubMed, to avoid unnecessary elimination of articles relevant to the search.

Two reviewers independently identified articles eligible for in depth examination by using the following

Inclusion and exclusion criteria

- Osteoporosis and/or malignant tumors with ongoing or previous history of oral and/or intravenous bisphosphonate treatment with necessary tooth extractions or surgical tooth removal.
- Relevant exposures were defined as oral or intravenous use of both nitrogen- and non-nitrogen-containing bisphosphonates.
- Cohort study or case–control study design with an appropriate control group on human subjects.
- The diagnosis of osteonecrosis was based on the physician diagnosis on medical records, clinical findings of exposed necrotic bone of jaw with compatible radiographic findings, or International Classification of Diseases (ICD)-9 code or other diagnostic code for ON in health claim database.
- We excluded case reports, case series, review articles, editorials, meta-analysis, clinical guidelines, and randomized controlled trials.

Any discrepancies between reviewers on articles meriting inclusion were resolved by a consensus meeting of three authors. The study selection is summarized in (Fig 1).

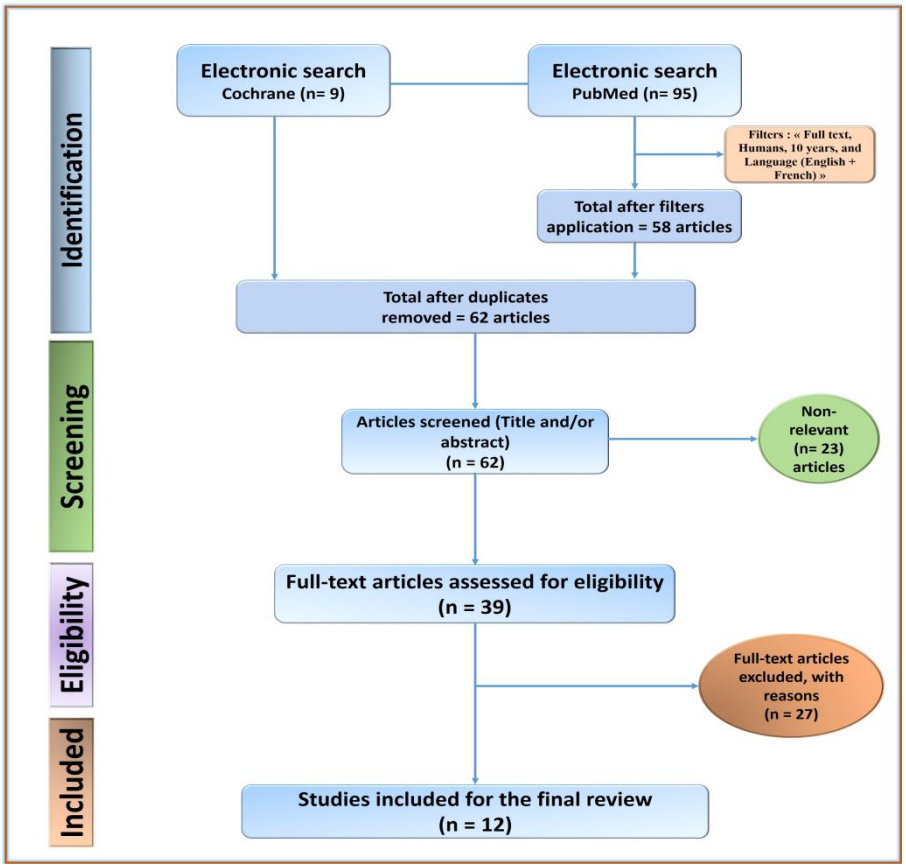

Fig-1: Schema of studies selection

Data extraction and synthesis

We extracted data for study location, population characteristics such as age range, underlying diseases, number of participants, and type of BPs used in the study and route of administration, diagnosis of outcome and potential risk factor.

RESULTS

Search results and study characteristics

Using our search criteria, we identified 104 studies, of which 95 were from PubMed and 9 from Cochrane. We excluded 65 citations based on screening titles and abstracts using predefined criteria mentioned in the method section. A total of 39 articles were retrieved from full-text review, and 27 were excluded due to various reasons. Notably, the majority of studies were excluded due to a lack of appropriate controls. Finally, 12 studies met the inclusion criteria.

The 12 included studies were comprised of 2325 patients treated with BPs (16% for osteoporosis and 84% for malignant disease) who underwent dental extractions. Of the included studies, seven are

prospective cohort studies, three retrospective cohort studies and only two case control studies.

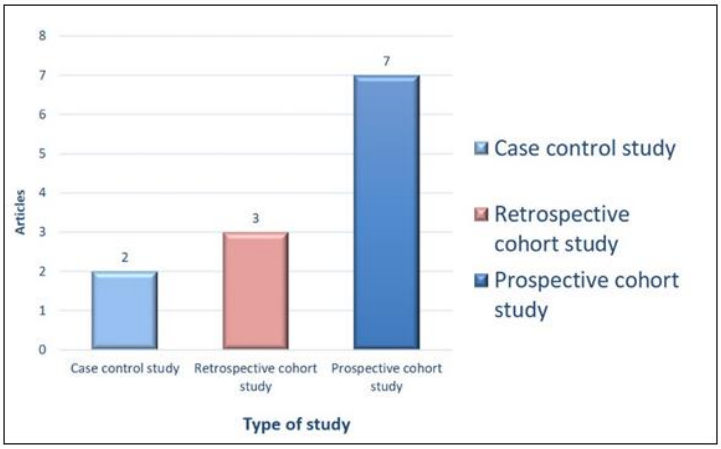

Fig-2: Study design

Details of the studies are summarized in (Tab 1). The studies varied with their settings, study populations, sample sizes, exposure and outcome definitions. The types of BPs and route of administration also varied with studies (Fig 3 and 4).

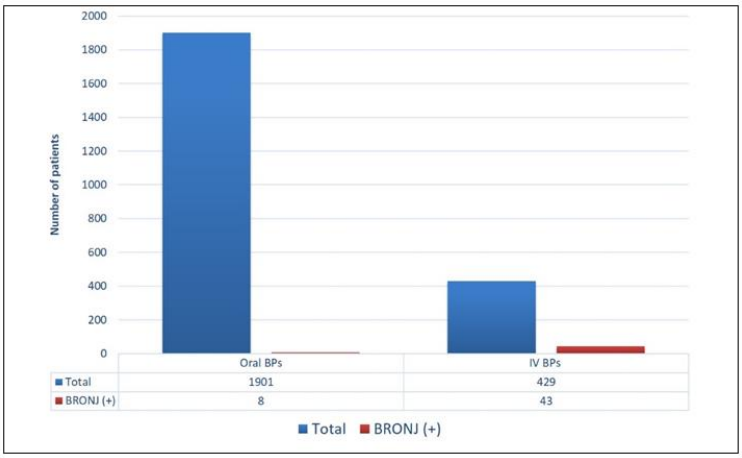

Fig-3: Route of BPs administration

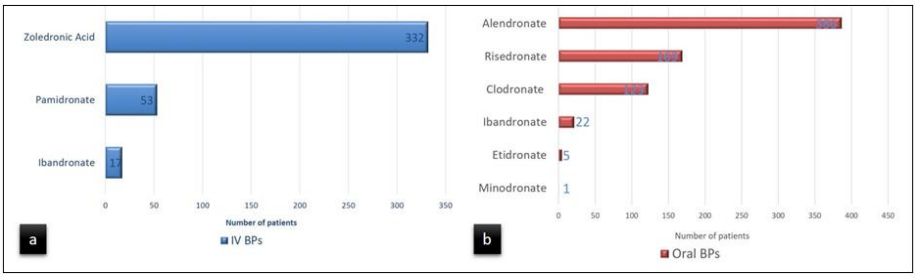

Fig-4: Type of Bisphosphonate

Table-1: Summary of studies on the association between use of bisphosphonates and risk of osteonecrosis of jaw

Author (location, year)	Design	Setting and study population	Sample size	Exposure (patient)	Teeth extraxted	Outcome definition
Otto S [2] (Germany, 2015)	Retrospective cohort	Osteoporosis (29) and/or malignant (43)	72 (53 F and 19 M)	Oral (27) and/or IV BPs (45)	216 teeth (119 in the maxilla and 97 in the mandible)	5 patients (7 extraction sites) → wound healing disturbances
Vescovi P [3] (Italy, 2015)	Prospective cohort	Osteoporosis and/or malignant tumors	36 (12 M, 24 F)	N/A	82	Minimal bone exposure was observed in 2 cases
Bodem J.P [1] (Germany, 2015)	Prospective cohort	Malignant disease	61	IV BPs	102 : 55 maxilla and 47 mandible)	8 patients developed BRONJ (stage I)
Sanshis J.M [4] (Spain, 2014)	Prospective cohort	Malignant disease	36 (20 F, 16 M)	IV Bps	62 teeth (27 maxilla, 35 mandibula)	14.5% developed BRONJ
Taylor T [5] (UK, 2013)	Retrospective cohort	195 Non oncologic pathology 7 malignant disease	225	Oral (202) or IV BPs (23)	N/A	(8/23) of patients prescribed IV BPs developed BRONJ following dental extraction, oral BP group : 2.5% (5/202 patients).
Migliorati CA. [6] (Canada, 2013)	Prospective cohort	Osteoporosis (40) Bone cancer metastasis (13)	53 (43 F, 10 M)	Oral and IV BPs	N/A	One case of ostonecrosis (mandibular site)
Vescovi P [7] (Italy, 2012)	Prospective cohort	95 : oncologic disease 122 : non onclogic	217 (38 M, 179 F)	Oral or IV BP therapy.	589 (285 mandibular, 304 maxillary)	A minimal bone exposure was observed in 5 cases.
Hasegawa T [8] (Japan, 2012)	Prospective cohort	139 : primary osteoporosis 62 : of secondary Osteoporosis.	201 patients (18 M and 183 F).	Oral or IV BP therapy.	434	One case (BRONJ stage 1).
Mozzati M [9] (Italy, 2012)	Prospective cohort study	Osteoporosis, rheumatoid arthritis, and Paget's disease.	700 (23 M and 677 F)	Oral BPs	1480 (864 in the mandible and 616 in the maxilla)	No evidence of postoperative BRONJ in any of the extractions in the study group at follow-up
Yamazaki T [10] (Japan, 2012)	Retrospective cohort study	Osteoporosis and malignant disease.	126 (103 F, 23 M)	Oral (99) and IV (27) BPs.	N/A	5 cases developed ONJ
Mozzati M [11] (Italy, 2011)	Case control study	Oncologic pathologies	100 (25 M, 75 F)	IV BPs	G1 :118 G2 : 104	Two patients in the control group (without PRF) developed BRONJ
Mozzati M [12] (Italy, 2011)	Case control	Osteoporosis Rheumatoid arthritis Paget disease	500 (15 M and 485 F)	Oral BPs	1000 teeth (456 in the mandible and 544 in the maxilla).	No intraoperative complications were observed in either of the two groups. Also, no evidence of postoperative BRONJ could be found in any of the extraction sites

M: male; F: female; BPs: bisphosphonate; IV: intravenous; BRONJ: Bisphosphonate-related osteonecrosis of the jaw

The mean age of the patients was 65.57 years and the mean duration of BPs administration was 29.83 months. A total of 4673 extractions were involved. The mean duration of follow-up after dental extraction was 41.64 months.

Fifty cases (2.15%) of BRONJ was detected (15.69% of them were under oral BPs and 84.31% were treated by IV BPs) (Tab 2) which corresponds to 67 extraction sites fairly distributed between maxilla and mandible with a p value = 0.7 (Tab 3). Male patients were at a significantly increased risk of developing a BRONJ compared to the female with $p < 0.01$ (Tab 4).

Table-2: Route of BP administration and incidence of BRONJ

Variable	BRONJ	No BRONJ
oral (n=1901)	8	1893
IV (n=429)	42	387
The chi-square statistic is 150.7466. The p-value is 0.000 This result is significant at $p < 0.05$.		

Table-3: BRONJ incidence by site

Variable	BRONJ	No BRONJ
Maxilla (n=1696)	17	1679
Mandible (n=1817)	16	1801
The chi-square statistic is 0.1398. The p-value is 0.708463. This result is not significant		

Table-4: BRONJ incidence by gender

Variable	BRONJ	No BRONJ
Male (n=265)	20	245
Female (n=2038)	21	2017
The chi-square statistic is 56.95. The p-value is 0.00000084 <0.01 This result is significant at $p < 0.05$		

Breast cancer, kidney cancer, prostate cancer, multiple myeloma and bone metastasis consisted of the largest part of BRONJ population (Fig 5).

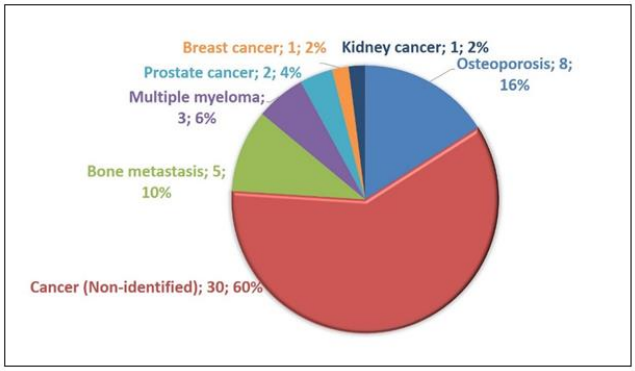

Fig-5: Underlying disease among patient with BRONJ

38% of BRONJ patients were under corticosteroid treatment and 22 % were treated by chemotherapy. 10% of osteonecrosis cases have undergone a traumatic extraction with osteotomy (Fig 6).

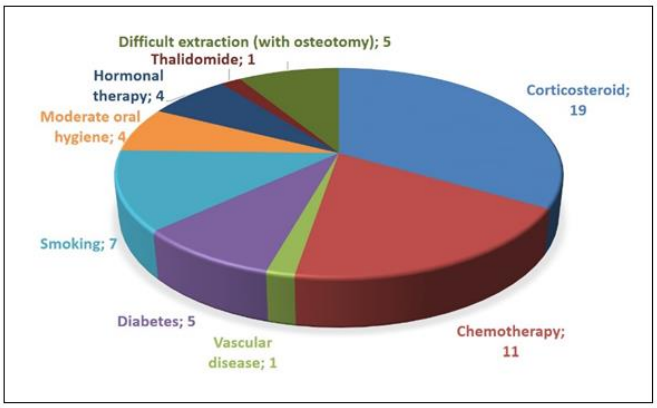

Fig-6: Risk factors and development of BRONJ

DISCUSSION

Since 2003 it had been known, that beside the great therapeutic benefit, BP therapy can trigger a serious complication which involves the maxillofacial area and is classified as BRONJ [13]. It was defined in 2007 as an area of exposed bone in the maxillofacial region that does not heal within 8 weeks after identification, in a patient who received BPs and had not received radiation therapy to the craniofacial region [3]. The etiology of BRONJ still remains unclear and the pathogenesis seems multifactorial and associated with medication-related risk factors, local and systemic factors, as well as genetic predisposition [1, 3]. The precise mechanisms responsible for the development of ONJ are not well defined. Ischemic necrosis has been suggested to play a role in the pathogenesis of ONJ; however, patent vessels have been noted in most histological examinations. Direct toxicity of BPs has also been suggested because BPs adheres strongly to bone and inhibit osteoclastic activity, leading to a net reduction in bone turnover. Infection is an almost universal finding in histological examination of ONJ and is thought to be a major precipitating factor. Gram negative bacteria with lipopolysaccharides may stimulate proinflammatory cytokine and promote bone resorption [14].

The most commonly reported factor responsible for promoting BRONJ is dental extraction [8]. Hoff et al in a consistent series of 4019 oncological patients identified dental extraction as a significant risk factor for BRONJ (incidence: 10.5%) [15]. For non-oncological patients, Manfredi et al reported that a history of oral surgery at the site affected by MRONJ was detected in 72% of the patients (n = 18): of these, 2 patients received dental implants during BP therapy and 16 patients reported teeth extractions in the months before BRONJ appearance [16].

Several studies have consistently shown that the incidence of BRONJ in patients receiving oral BP with osteoporosis was very low (0.01% to 0.04%) compared with intravenous BP (0.8% to 12%) [3, 17]. The most likely reason for this decrease is that less than 1% of the dose of a BP taken orally is absorbed by the gastrointestinal tract, whereas more than 50% of the dose of a BP administered intravenously is bioavailable for incorporation into the bone matrix [8]. Thus, patients at high risk of developing BRONJ are those with malignant disease receiving high doses of intravenous bisphosphonate therapy and/or with a history of chemotherapy or concomitant use of systemic corticosteroids [18]. Chronic glucocorticoid therapy has adverse effects on bone metabolism, including impaired osteoblastic differentiation and function. Furthermore, the additional immunosuppressive and antiangiogenic effects of glucocorticoids can play an important role in the development of BRONJ [19]. In addition, many other risk factors have been implicated in the development of BRONJ, including systemic factors such as concomitant cancer, diabetes, or osteoporosis; the simultaneous administration immune suppressors; smoking; alcoholism; denutrition; or deficient oral health [3].

As treatment of manifest BRONJ remains challenging, many authors have established several prophylactic measures to avoid the development of BRONJ. In general, a thorough dental examination is recommended, and if necessary dental treatment is completed before starting BP therapy [1]. In addition, all surgical procedures that might cause exposure of jaw bone should be strictly avoided under ongoing BP therapy. Hence, conservative treatments have been advised in such patients, including fillings, endodontic treatment of remaining teeth and roots, or splinting in the case of teeth with grade I or II mobility (Miller classification) [4]. If, however, despite all prophylactic measures, a tooth extraction is inevitable (grade III mobility, or in the presence of infection and recurrent abscesses), it should be done under special precautions since the risk of BRONJ is increased up to 50-fold compared with patients without tooth extraction [1].

Several authors proposed different clinical preventive protocols for tooth extractions in patients under BP therapy. Ferlito *et al*. proposed a surgical approach characterized by the removal of alveolar bone with piezosurgical instruments and supported by correct antimicrobial therapy (antibiotics and mouthwash). In a total of 43 patients, no signs of necrotic exposed bone in any patient were observed after a 12-month follow-up [20]. Vescovi et al proposed in a successful protocol for tooth extractions in patients under BP therapy supported by Nd:YAG low-level laser therapy (LLLT). In a total of 82 extractions, minimal bone exposure was observed in 2 cases, treated with Er: YAG laser vaporization and then completely healed [3]. Mozzati et al. compared two different surgical protocols with and without detachment of full thickness flap and sutures for tooth extraction in patients treated with oral BPs. No intraoperative complications were observed in either of the two groups, and there was no evidence of postoperative BRONJ in any of the extractions at follow-up. Therefore, as atraumatic surgery is more comfortable for patients, the authors suggest the adoption of this protocol, which limits trauma to both the soft and hard tissues [9, 12].On the other hand, Mozzati *et al.* proposed a clinical protocol based on the filling of the extraction site with Plasma Rich in Growth Factors (PRGF). Thus, the healing process is accelerated by promoting angiogenesis as well as bone and mucosal wound healing which may reduce the risk of BRONJ [11].

In 2014, the American Association of Oral and Maxillofacial Surgeons recommended changing the nomenclature of bisphosphonate-related osteonecrosis of the jaw (BRONJ) in favor to the term medication-related osteonecrosis of the jaw (MRONJ, owing to the growing number of osteonecrosis patients involving the jaw associated with other antiresorptive (denosumab) and antiangiogenic therapies [21].

CONCLUSION

This study showed a highly significant risk of developing a BRONJ for patients on IV BPs undergoing dental extractions. It is also important to note that the risk may be present for oral BPs. However, the incidence of BRONJ is much lower than for IV BPs. Thus, further studies are required to identify the other significant factors that, together, can contribute to developing a BRONJ. Therefore, in order to reduce the risk of BRONJ, patients should receive a detailed dental examination and, if necessary, dental treatment before starting BP therapy.

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