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REVIEW ARTICLE

Surgical management of bisphosphonate-related osteonecrosis of the jaws: literature review

Larissa Fernandes Silva[1] · Cláudia Curra[2] · Marcelo Salles Munerato[2] · Carlos Cesar Deantoni[2] · Mariza Akemi Matsumoto[3] · Camila Lopes Cardoso[1,4] · Marcos Martins Curi[1,4]

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Abstract
Purpose Surgical management of bisphosphonate-related osteonecrosis of the jaws (BRONJ) has been performed in an attempt to increase healing rates of the affected cases. This literature review aimed to identify clinical studies of surgical management of bisphosphonate-related osteonecrosis of the jaws (BRONJ) in order to assess their surgical treatment modalities, outcome and the follow-up.
Methods A search in the PubMed (Medline) database using specific terms and/or phrases as "bisphosphonate-related osteonecrosis" or "jaw osteonecrosis", and "surgical treatment" or "surgical management" was conducted in order to identify clinical trials and cases of surgical treatment of BRONJ. The review search covered the time period from 2004 to 2014. All studies identified in the search were selected according to the inclusion criteria. Relevant information was recorded according to the following items: author, year, number of patients, BRONJ clinical stage, surgical treatment modality, clinical success, and follow-up.
Results The initial database search yielded 345 titles. After filtering, 67 abstracts were selected culminating in 67 full text articles. A variety of surgical approach was found in this review: debridement, sequestrectomy bone resection, and bone reconstruction. Adjunctive therapies included hyperbaric oxygen, laser therapy, growth factors, and ozone.
Conclusion Although there are many indexed studies about BRONJ, well-documented reports concerning surgical therapeutically techniques are scarce, resulting from a lack of well-established protocols. Considerable differences were found regarding sample size, surgical treatment modalities and outcomes. Clinical studies with larger number of patients and longer follow-up are required to provide best information for each surgical treatment modality and its outcomes.

Keywords Bisphosphonate-related osteonecrosis of the jaws · Surgical approach · Surgical treatment · Surgical management

✉ Marcelo Salles Munerato
marcelo@munerato.com.br

[1] Universidade do Sagrado Coração, Bauru, SP, Brazil

[2] Department of Oral and Maxillofacial Surgery, Universidade do Sagrado Coração, Rua Irmã Arminda 10-50, CEP: 17011-160 Bauru, São Paulo, Brazil

[3] Faculdade de Odontologia, Universidade Estadual Paulista, Araçatuba, São Paulo, Brazil

[4] Department of Stomatology, Hospital Santa Catarina, Sao Paulo, Brazil

Introduction

Bisphosphonates (BP) comprise a group of drugs commonly administered to modulate bone remodeling cycle of benign bone disorders, such as: osteoporosis, *osteogenesis imperfecta*, and Paget's disease, as well as to prevent malignancy induced osteoclastic activity in malignant neoplasias, as multiple-myeloma [1, 2].

BP mechanisms of action are not completely known, but some of the effects observed on bone metabolism are the following: inhibition of bone resorption; interference in the osteoclasts metabolic activity (inhibition of differentiation of new precursor cells, maturation and osteoclast activity and apoptosis) and anti-angiogenic activity [1–5]. All these effects result in inhibition of bone resorption, reducing hypercalcemia levels caused by tumors and/or bone metastases. Therefore, the administration of BP in pathological conditions described above, aims to obtain bone mass, to reduce bone fractures and

decrease pain symptoms. According to their specific mechanism of action, they are divided into two main classes: nitrogenous BP and non-nitrogenous BP, which may be administered orally or parentally [1–5].

Despite the great benefits of using BP in patients with these benign and malignant conditions, the identification of oral complications arising from the use of this drug, bisphosphonate-related osteonecrosis of the jaw. (BRONJ), called the attention of clinicians. Only nitrogenous BP has been associated with BRONJ [6–8]. BRONJ diagnostic criterion constitutes on the exposed bone for 8 weeks, at least, prior treatment history and/or recent with BP and absence of cervical facial radiotherapy [6–8]. In 2014, the American Association of Oral and Maxillofacial Surgeons (AAOMS) recommended changing the nomenclature BRONJ by medication-related osteonecrosis of the jaw (MRONJ) because other antiresorptive drugs, like denosunab, are also related to the onset of this disease [2].

Its incidence has been estimated as 1:143,000 patients/year, undergoing dental procedures [2, 9] 0.8 to 12 % in patients who have received intravenous administration, for malignant neoplasia [10] and 0.00038 to 0.06 % [11] in patients who have administered BP orally. MRONJ pathogenesis has been extensively investigated and is not yet fully understood. Currently, the interaction between bone metabolism, infection, local trauma and theories, as suppression of bone remodeling, anti-angiogenic effect and mucosal toxicity, constitute the main study fields, in order to clarify its etiopathogenesis [2, 12–14].

A clinical staging classification system of the disease was proposed in an attempt to guide the type of appropriate therapeutic approach in each case [6–8]. It is essential to emphasize that MRONJ development depends on systemic and local factors of the individual, type of BP, dose, time and administration via.

There is no standard approach for treating MRONJ in the literature. There is a great debate and no agreement in relation to a conservative approach versus surgical approach in the treatment of BRONJ. Despite the lack of consensus for treating MRONJ, there is a tendency for conservative treatment, in cases of clinical stage 1 (asymptomatic), characterized by the use of topical 0.12 % chlorhexidine antiseptics intermittent use of systemic antibiotics and small surgical local debridement [6–8, 15–17]. Some authors have recommended conservative approach to MRONJ [6–8, 15–18]. This conservative approach has been widely recommended for all MRONJ patients, at initial identification of this clinical entity in 2003. However, most MRONJ cases comprise major symptoms, associated with major infection (stages 2 and 3), which do not respond satisfactorily to conservative treatment, requiring surgical treatment [6–8, 15–19]. The surgical treatment modality vary from marginal bone resection (without loss of mandible continuity) to segmental bone resection (mandibular continuity is broken) when the mandible is affected, and partial or total maxillectomies when the maxilla is involved and all these surgical procedures can be followed by reconstruction. Considering the failures of the conservative approach, the surgical approach has been widely recommended for treating these cases, due to bacteremia and sepsis risks, in immunocompromised patients (cancer) as well as impaired quality of life [6–8, 15–19].

Studies have shown MRONJ cases that do not respond to a conservative approach result in debilitated patients with oral complications, such as: exposed bone, infection, pain and discomfort, requiring extreme care, in order to restore the quality of life of the patient [20–24]. It is important to consider that this condition facilitates infection. Conservative treatment was reported to be partially successful, with resolution reported in only 50 % of cases, particularly concerning MRONJ at clinical stages 2 and 3 [25–31]. Therefore, there is a tendency in the literature to therapeutically surgeries [32–38].

Based on this context, treatment options are being used in order to improve the resolution indexes of MRONJ cases. The absence of a well-established surgical treatment protocol in the scientific literature, makes it difficult to conduct therapy in advanced cases. Therefore, the present study aims to review the literature on surgically treated cases, in order to analyze how surgical treatment has been performed, success rates and to follow-up the cases.

Materials and methods

Two investigators searched the English language literature using the PubMed database. The search was performed using the following keywords: “bisphosphonate-related osteonecrosis of the jaw”; “surgical approach”; “surgical treatment”; and “surgical management” accessing the Medline database (PubMed), from 2004 to 2014. The survey included only surgically treated MRONJ cases (only BRONJ). The process of selection involved a list of titles obtained from the electronic database, and followed by an evaluation of the abstracts of all selected titles analyzed pertinent titles based on predetermined inclusion criteria. The inclusion criteria were: English language article in a peer-reviewed journal; and any clinical study of surgical management of BRONJ. The exclusion criteria were: articles that did not mention the surgical treatment modality; review/technique articles without associated clinical trial and data; article description that did not allow extraction of the required data. The next step involved a carefully studied of the full text of all included articles. Relevant data were included considering the following items: author, year, number of clinical cases, clinical stage, type of surgical approach, clinical success, and follow-up period.

Results

The electronic search from the database yielded 345 titles. Of these, only 67 studies were relevant to the study, which culminated in a total of 67 full text articles after application of the predetermined exclusion criteria. Application of exclusion criteria eventually resulted in 67 articles that were considered for final analysis (Table 1). Most studies reported surgical management of MRONJ since 2007. The following surgical treatment modalities were found in this review: debridement, sequestrectomy, marginal resection (bone resection without bone defect), bone reconstruction (free flaps), and laser therapy and hyperbaric oxygenation, as adjunctive therapy after surgery.

Regarding the clinical staging of cases, most reported the presence of stages 0, 1, 2, and 3. However, stages 2 and 3 prevailed. Clinical success was obtained in most cases. The follow-up period was informed in most of them, and the shortest period comprised three months, and the longest, eighty-two months.

Discussion

Treatment of MRONJ is a challenging task, and numerous studies have discussed about the best procedure for this condition [6, 8, 10, 16–19, 36–39, 100, 101]. Most studies found in the literature support the conservative approach and claim that MRONJ surgical treatment should be designated for patients in advanced stages, which have not responded to other conservative approaches [6, 16, 19, 101]. However, relevant studies have demonstrated that MRONJ cases do not respond to conservative treatment, and this condition leads the patient to a poor health condition, especially concerned to oral complications, such as: bone exposure, infection, pain and discomfort. These cases may require a more radical treatment to restore their quality of life [1, 3, 4, 9, 10]. In addition to this, it becomes very important to consider the risk of a necrotic bone exposure as a via for bacteria entrance, regarding cancer patients who need hematopoietic stem cells transplantation, or patients who have undergone high-dose chemotherapy, because of immunosuppression condition. *Actinomyces* have been considered to play a role for MRONJ pathophysiology, although not fully comprehended [39, 102]. Some studies have questioned whether the presence of such microorganisms contribute to the development of MRONJ, or if it represents a secondary opportunistic infection of the exposed necrotic bone [39, 102]. There are reports of *actinomyces* present in most of the samples, taken from MRONJ patients, and those with osteoradionecrosis facing the above context, treatment options are being used in order to improve the MRONJ rates resolution cases. Among those therapies, bone resection treatment, combined with growth factors, have shown satisfactory and promising results for curing this complication [19, 73].

Surgical treatment has been increasingly reported in literature [33, 35–38, 103] and is considered a success when oral mucosa healing is maintained without bone exposure or infection, and presents an acceptable radiographic healing for a period of 12 months, after surgery. Thus, it is important to follow-up patients for at least 1 year after surgery, in order to monitor the possibility of disease recurrence.

In the literature, the conservative MRONJ treatment has demonstrated to be partially successful, with resolution reported in only 50 % of cases, particularly in stages 2 and 3 of this condition [25–31]. Treatment with intravenous BF generally results into more advanced and extensive BRONJ, and is less sensitive to conservative treatment, compared with the clinical outcome of treatment with bisphosphonates, administered orally. In contrast, surgical therapies have proven effective results, for more than 80 % of the patients [33, 35–38, 103]. However, the comparison between the results of different therapies is complicated, due to the inclusion of patients taking different bisphosphonates and doing it in an uncontrolled clinical way.

The success of surgical management of MRONJ depends mainly on the systemic conditions of patients. However, the literature does not show the individual patient status, only considerations of the surgical technique. The success of MRONJ surgical treatment seems to be related to the determination of the extension of marginal bone resection, which is still difficult to quantify, and has been identified as a crucial and uncertain factor [33, 35–38, 103]. The boundary of the marginal bone resection has been based on intraoperative findings, such as bone color and bleeding in the remaining bones as a sign of vitality, and does not always correlate positively with the vitality of bones. Marginal resections are not always easy to be performed by less experienced maxillofacial surgeons, particularly for BRONJ cases with advanced bone sclerosis in the jaw. Authors [25] have performed bone resection after the fluorescence-guided application, based on the tetracycline absorption in bone, administered before surgery to select the necrotic bone resection. This technique can help in distinguishing the necrotic bone, from the viable bone, and hence, to standardize surgical treatment. It is believed that an experienced maxillofacial surgeon is able to perform a successful treatment through bone resection of the affected region. During surgery planning, a good relationship between the dentist and the oncologist is important to decide whether treatment with BFs will be interrupted, taking into consideration the risk of bone complications, in relation to more MRONJ risks.

Experimental and clinical studies have demonstrated the efficacy of various cell mediators (Bone morphogenetic proteins, interleukins and angiogenic growth factors) for healing

Table 1 Number of patients, BRONJ clinical stage, and outcome of surgical management of each selected study

Author, year	Number cases	BRONJ stage	Surgical treatment	Success (%)	Follow-up (months)
Franco et al., 2014 [39]	203	0, 1, 2, 3	Debridement/bone resection	84.96	>12
Spinelli et al., 2014 [40]	8	2 e 3	Bone resection/reconstruction	100	28, 9
Lee et al., 2014 [41]	40	1, 2, 3	Debridement/bone resection	100	NI
Rupel et al., 2014 [42]	745	1, 2, 3	Debridement/bone resection/laser therapy	>80	Average 7.2
Longo et al., 2014 [43]	49	1, 2, 3	Bone resection with or without PRP	With PRP 53 %, no PRP 94 %	6–94
Zavalishina et al., 2014 [44]	17	NI	Bone resection	NI	NI
Vescovi et al., 2014 [45]	63	1	Bone resection/laser therapy	92.6	6
Carlson, 2014 [46]	540	NI	Bone resection	>50	NI
Sadiq et al., 2014 [47]	3	3	Bone resection	100	3
Soydan et al., 2014 [48]	1	N.I	Bone resection/PRF	100	6
Stockmann et al., 2014 [49]	80	1, 2, 3	Bone resection	84.2	20
Nomura et al., 2013 [50]	5	1, 2, 3	Bone resection	23.1	Average 16.2
Holzinger et al., 2013 [51]	108	1, 2, 3	Bone resection	59	11
Hanasono et al., 2013 [52]	13	2, 3	Bone resection	53.6	Average 15.3
Janovska et al., 2013 [53]	11	1, 2, 3	Debridement/sequestrectomy	100	82
Blus et al., 2013 [54]	8	2, 3	Bone resection	100	12–38
Beninati et al., 2013 [55]	51	NI	Curetage	31	Average 19
Freiberger et al., 2012 [56]	46	NI	Bone resection/HBO	NI	24
Graziani et al., 2012 [57]	347	NI	Debridement/bone resection	59	NI
Vescovi et al., 2012 [58]	128	1, 2, 3	Surgical treatment/laser therapy	89	16–44, 10–95
Vescovi et al., 2012 [59]	151	1, 2, 3	Debridement/sequestrectomy/laser therapy	100	NI
Ferlito et al., 2012 [60]	94	1, 2	Debridement	100	6
Andriani et al., 2012 [61]	34	NI	Debridement/sequestrectomy	50	26
Jabbour et al., 2012 [62]	8	2	Bone resection	62.5	12.6
Anitua et al., 2012 [63]	1	N.I	Surgical/PRGF	100	12
Hewson et al., 2012 [64]	1	3	Bone resection	100	6
Cicciu et al., 2012 [65]	20	NI	Resection/rhBMP-2	100	12
Galesio et al., 2012 [66]	32	NI	Surgery/PRGF	100	Average 52.5
Galego et al., 2012 [67]	3	3	Sequestrectomy/reconstruction pedicled buccal fat pad flap	100	Average 12.3
Voss et al., 2012 [68]	21	2,3	Debridement	95.2	16
Schubert et al., 2012 [69]	54	0-3	Bone resection	98.5	6
Martins et al., 2012 [70]	22	1, 2, 3	Bone resection/PRP/laser therapy	73	1 and 6
Lemound et al., 2012 [71]	20	1, 2	Bone resection	90	19
Faloni et al., 2011 [72]	1	2	Debridement/curetage	100	8
Curi et al., 2011 [73]	25	1, 2, 3	Bone resection/PRP	80	36
Lee et al., 2011 [74]	13	0-3	Bone resection/PRP/HBO	100	12–18
Cella et al., 2011 [75]	1	3	Bone resection/laser/PRP	100	30
Atalay et al., 2011 [76]	10	1, 2	Bone resection/laser	55	3–28
Wilde et al., 2011 [77]	1	3	Bone resection	100	48
Eckardt et al., 2011 [78]	122	NI	Sequestrectomy and bone resection	60	37.1
Bedogni et al., 2011 [79]	30	0-3	Bone resection	73	6–24
Hoefer et al., 2011 [80]	46	1, 2	Sequestrectomy	70	Average 11.5
Manfredi et al., 2011 [81]	10	0	Bone resection/laser therapy	100	Average 16.6
Pautke et al., 2011 [25]	15	2, 3	Bone resection	85	Every 3
Mucke et al., 2011 [82]	108	1, 2, 3	Debridement/bone resection/reconstruction	71.3	NI
Wilde et al., 2011 [37]	24	1, 2, 3	Bone resection	88	15
Scoleta et al., 2010 [83]	NI	1, 2, 3	Debridement	NI	NI

Table 1 (continued)

Author, year	Number cases	BRONJ stage	Surgical treatment	Success (%)	Follow-up (months)
Rugani et al., 2010 [84]	5	2	Bone resection/laser	100	12
Sacco et al., 2010 [85]	22	3	Bone resection/reconstruction	100	12
Wultz et al., 2010 [86]	43	0, 1, 2, 3	Sequestrectomy/bone resection	58.5	6
Stockmann et al., 2010 [87]	50	1, 2, 3	Bone resection	89	12
Chiu et al., 2010 [88]	12	1, 2, 3	Debridement	NI	NI
Favia et al., 2009 [89]	102	1, 2, 3	Debridement	100	16.4
Junquera et al., 2009 [90]	21	1, 2, 3	Debridement	100	6–30
Thumbigere-Math et al., 2009 [91]	26	1, 2, 3	Debridement	100	>6
Carlson et al., 2009 [33]	82	1, 2, 3	Bone resection	100	13–22
Stanton et al., 2009 [36]	30	NI	Debridement	100	Average 10.7
Cetiner et al., 2009 [92]	32	2, 3	Debridement/sequestrectomy	NI	6
Allons et al., 2009 [93]	7	NI	Curettage	85.7	5–52
Saussez et al., 2009 [94]	34	1, 2, 3	Bone resection	20	NI
Engrof et al., 2008 [95]	1	3	Surgical treatment with immediate reconstruction	100	NI
Arabi et al., 2008 [96]	1	NI	Bone resection	100	24
Adornato et al., 2007 [97]	12	NI	Bone resection/PRP	83.33	NI
Diego et al., 2007 [98]	10	NI	Sequestrectomy/partial maxillectomy	100	NI
Borgioli et al., 2007 [99]	15	NI	Bone resection/partial maxillectomy	100	6–12
Lee et al., 2007 [100]	2	NI	Bone resection/PRP/HBO	100	>9
Curi et al., 2007 [19]	3	2, 3	Bone resection/PRP	100	6–8

BRONJ Bisphosphonate-related osteonecrosis of jaw, *PRP* Platelet-rich plasma, *NI* Not informed, *PRF* platelet-rich fibrin, *HBO* Hyperbaric Oxigen Therapy, *PRGF* platelet-rich growth factor, *rhBMP-2* recombinant human bone morphogenetic protein-2

bone defects [19, 104–118]. The platelet-rich plasma (PRP) is an autologous source of growth factors, obtained by a centrifugation process [116–118] which produces a very high concentration of human platelets containing various growth factors (growth factor derived from platelets of transforming growth factor-β, epidermal growth factor and vascular endothelial growth factor). These factors are actively secreted by platelets, on wounds and promote healing [116–118]. Several studies have reported success in bone regeneration and healing of soft tissues after using PRP [104–118]. Authors in 2007 reported three MRONJ clinical cases, refractory to conservative treatment, treated with marginal bone resection, associated to PRP, with complete resolution of all cases [19]. The same group of researchers, in 2011, published a series of 25 MRONJ patients; considering that 20 cases (80 %) had complete response resolution, with no bone exposed during the control period [73]. Further, other studies have been reported using the same surgical protocol, with satisfactory outcomes [19, 97, 100].

The current scientific literature on the subject, has presented since 2007, alternative treatments for advanced cases, but many details deemed important are missing, in most of the articles. Given the fact that MRONJ presents different clinical stages, it is difficult to compare the surgical treatment options. Regardless of the technique or type of surgical approach, it is essential that the treatment is performed by an experienced and skilled surgeon. Monitoring must be rigorous weekly at the beginning, monthly, after resolution, and every three months after resolution, monthly, and after three months establish proservation every 6 months. The works cited here [25, 33, 36, 37, 39–100], demonstrated great variability of follow-up period, revealing absence of a defined protocol, for monitoring the cases. In addition, the clinical success was not explicit in most of the articles, so this factor contributed for the non-conclusion about the best way for treating MRONJ.

Through this study, it was possible to conclude that, although there are many scientific articles on MRONJ, well-documented works are scarce on MRONJ surgical approach, particularly with respect to successful and clinical cases with long-term follow-up period. Therefore, it becomes difficult to conclude about best surgical technique for the treatment of MRONJ, due to the absence of well-established protocols.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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