

REVIEW ARTICLE

Biphosphonates Related Osteonecrosis: Prevention and Treatment Possibilities

Henrikas Rusilas¹, Andrius Gegužis², Albinas Gervickas³

1- Dept. of Oral & Maxillofacial Surgery, Lithuanian University of Health Sciences, Faculty of Dentistry, Lithuania

2- Dept. of Oral & Maxillofacial Surgery, Lithuanian University of Health Sciences, Faculty of Dentistry, Lithuania

3- Associate Professor, Dept. of Oral & Maxillofacial Surgery, Lithuanian University of Health Sciences, Lithuania

Abstract

Background: Bisphosphonates are a group of antiresorptive drugs used mainly for patients with osteoporosis, multiple myeloma, Paget's disease. Their high affinity to bone mineral and ability to inhibit bone turnover sometimes lead to bisphosphonates related osteonecrosis of the jaw (BRONJ). Due to the complexity of treatment, the prophylaxis of BRONJ is the key. **Objectives:** The objective of this review was to find most successful prevention methods and new approaches to treat BRONJ. **Methods:** A systematic review was carried out in the PubMed and Google Scholar databases using these keywords: bisphosphonates, BRONJ, prevention. All publications were published in English language. The review was registered on PROSPERO International Prospective register of systematic reviews [Reg.Nr. CRD42017068582]. **Results:** 20 of 534 publications were included in the analysis, study results on prevention of BRONJ were gathered. Several prevention methods were found: mouth sanitation, alternative surgery techniques, antibiotic prophylaxis, CTX testing and teriparatide hormone therapy. **Conclusions:** Any patient should get mouth sanitized before starting bisphosphonates therapy, atraumatic extraction techniques should be used to extract teeth, antibiotic prophylaxis is necessary, CTX testing and teriparatide hormone therapy are still debatable prevention methods. A Prospective randomized study is required to compare these BRONJ prevention methods.

Keywords: bisphosphonates, BRONJ, prevention

Address for correspondence: Henrikas Rusilas. Lithuanian University of Health Sciences V. Kudirkos 19, Kaunas, Lithuania 50276. Mobile Number: +370 64142041 E-Mail: henrikas.h@gmail.com

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Introduction

Bisphosphonates are a group of antiresorptive drugs used mainly for patients with osteoporosis, multiple myeloma, Paget's disease or underlying malignant diseases resulting in bone metastases. The potency of these drugs is very different: while oral BPs have low potency and are used for treatment of osteoporosis, intravenous BPs have much higher potency and are usually used for cancer patients. The first generation of BPs (clodronate, etidronate) possesses alkyl or halide side groups. The second generation (pamidronate) is characterized by an amino-terminal moiety and has 10 to 100 times greater antiresorptive potency than first generation BPs. Zoledronate is a representative of third generation BPs that possess an imidazole ring in the side chain.

Zoledronate is about 100 times more potent than pamidronate (Table 1).^(1,32)

Table 1: Bisphosphonates: Groups of substances, effective substances, potency

Bisphosphonate group	Substance	Potency
Oral bisphosphonates	Etidronate	1
	Clodronate	10
	Pamidronate	100
	Ibandronate	1000–10000
	Risedronate	1000–10000
Intravenous bisphosphonates	Pamidronate	100
	Ibandronate	1000–10000
	Zoledronate	>10 000

Bisphosphonates possess a strong affinity for bone mineral – approximately 50% of absorbed dose is excreted with urine and the remaining half binds to bone with a half-life of greater than

10 years ⁽⁶⁾. Bisphosphonates can easily bind covalently to hydroxyapatite and are quickly absorbed by osteoclasts, bone resorption is inhibited while bone turnover is stopped. Their tight binding and the release and re-deposition in the context of bone remodeling mean that they often remain in the bone for many years ^(2,3). In 2003, Marx et al. Were the first to describe occurrence of osteonecrosis of the jaw between the patients with intravenous administration of zoledronate and pamidronate ⁽⁴⁾. After Ruggiero et al. Reviewed 63 cases in 2004, it was suggested to assess use of bisphosphonates as risk factor for BRONJ to develop after various dental procedures. ⁽⁵⁾

While it the mechanism of resorption inhibition is well known, the pathomechanism of ONJ development remains ultimately unexplained. It is thought that the pH value, which is lowered as a result of the inflammatory response, triggers and biologically activates the bisphosphonate and results in a raised, locally toxic molecule

concentration. ONJ usually develops after surgical interventions (mostly teeth extractions) but spontaneous occurrence is also possible. ⁽⁸⁾

The incidence of ONJ in patients taking oral bisphosphonates for the management of osteoporosis is low (between 0.001% and 0.01%), whereas it is higher (~1-10%) in patients taking intravenous bisphosphonates for the treatment of metastatic bone diseases. ⁽⁶⁾

According to AAOMS (AAOMS, American Association of Oral and Maxillofacial Surgeons) patient is diagnosed with BRONJ if all the following clinical findings are detected:

- Ongoing or antecedent treatment with antiangiogenic or antiresorptive drugs
- No patient history of radiation therapy or manifest metastasis to the jaw
- Exposed bone or presence of an intraoral or extraoral fistula in the maxillofacial region persisting for more than 8 weeks ⁽⁷⁾

Table 2: BRONJ staging according to AAOMS ⁽⁷⁾

BRONJ	Description	Treatment strategies
At risk	No apparent necrotic bone in patients who have been treated with either oral or intravenous antiresorptives, asymptomatic	<ul style="list-style-type: none"> • No treatment indicated • Patient education
Stage 0	No clinical evidence of necrotic bone, but nonspecific clinical findings and symptoms	<ul style="list-style-type: none"> • Systematic management, including the use of pain medication and antibiotics
Stage 1	Exposed and necrotic bone in asymptomatic patients without evidence of infection	<ul style="list-style-type: none"> • Antibacterial mouth rinse • Clinical follow-up on a quarterly basis • Patient education and review of indications for continued bisphosphonate therapy
Stage 2	Exposed and necrotic bone associated with infection as evidenced by pain and erythema in region of exposed bone with or without purulent drainage	<ul style="list-style-type: none"> • Symptomatic treatment with oral antibiotics • Oral antibacterial mouth rinse • Pain control • Debridement to relieve soft tissue irritation and infection control
Stage 3	Exposed and necrotic bone in patients with pain, infection, and one or more of the following: exposed and necrotic bone extending beyond the region of alveolar bone (ie., inferior border and ramus in the mandible, maxillary sinus and zygoma in the maxilla) resulting in pathologic fracture, extraoral fistula, oral antral/oral nasal communication, or osteolysis extending to the inferior border of the mandible or the sinus floor	<ul style="list-style-type: none"> • Antibacterial mouth rinse • Antibiotic therapy and pain control • Surgical debridement/resection for longer term palliation of infection and pain

The purpose of this review was to find out what approaches of BRONJ prevention exist.

Methods

A systematic literature review was conducted according to PRISMA criteria: out of 534 articles we included 32 after removing duplicates, single case reports and systematic reviews. Evaluated studies were published between January 2006 and 2016 December. We searched for these keywords in articles abstracts and titles: bisphosphonates, BRONJ, prevention,

Articles in other languages than English were excluded. A table of study quality was created including these parameters: method of prevention, year of publication and author, number of patients, study design, follow up time and success rate. The review was registered on PROSPERO International Prospective register of systematic reviews [Reg.Nr. CRD42017068582]

Table 3. Study results on preventing BRONJ

Method	Author/year	Patients, design	Study period (months)	Measure	Results
Teriparatide hormone (TPD) therapy	Y.-D. Kwon 2012	6, Prospective	3	BP suspended, TPD prescribed.	All 6 patients healed BRONJ lesions. S-CTX elevated in 4/6.
	K. M. Kim 2014	24, Retrospective	6	Calcium and vitamin D supplementation, experimental group: TPTD injections of 20µg daily.	Non-TPTD group: 60% 1 stage improvement, 40% no improvement. TPTD group: 62,5% one stage improvement, 37,5% two stages or complete healing. (p<0.05)
	Keskinruzgar 2016	80, Experiment	3,5	TPTD injection pre, post extraction and after ONJ developed	Numbers of osteoblasts and osteoclasts reduced in pre and post TPD groups after 10 weeks. (p=.037) No positive effect of TPD after ONJ developed.
	Zandi, 2016	100, Experiment	2	TPD pre and post groups; Control group Bone exposure/fistula and number of osteocytes per 25mm ² measured	AT group: 20%, 15.36, and 2.63 AC: 78%, 5.78, and 6.81 BT: 14%, 16.94, and 2.08 BC: 78%, 7.54, and 5.95 (P < 0.001)
	Ersan N, 2014	30, Experiment	2,5 months	Zoledronic acid (ZA) injection; ZA and TPD injection; Control group	Control:no ONJ ZA: osteonecrotic area 88%, vBMD of the newly formed bone lower than ZA+TP ZA+TP: osteonecrotic area 62%

Alternative surgical techniques	Lodi, 2009	23, Prospective	12	Extractions performed atraumatically with antibiotic treatment starting 3 before, wound closure with mucoperiosteal flap.	38 teeth extractions without occurrence of ONJ.
	Montefusco, 2008	178 Retrospective	35	Dental treatment ant antibiotic prophylaxis in intervention group.	Without antibiotics: 25% ONJ With antibiotics: 0% ONJ.
	Ferlito, 2011	43, Prospective	12	Antibiotic prophylaxis before surgical dental extraction, alveolectomy and wound closure.	102 extractions without occurrence of ONJ.
	Regev, 2008	10, Prospective	9	Atraumatic extraction using orthodontic rubber ligatures	No occurrence of necroses, time to exfoliation circa 6 weeks, no control group.
	Pautke, 2011	15, Prospective	1	Fluorescence-guided resection of necrotic bone was performed by means of a certified fluorescence lamp	85% lesions showed mucosal closure. 15% lesions showed mucosal dehiscence.
Mandatory dental check ups	Ripamonti, 2009	966, pro- and Retrospective	10	Dental check-up + OPG, treatment	Control group: 3,2% ONJ Intervention group: 1,3% ONJ Incidence ratio: 0.30 (95% CI: [0.03; 1.26]; p = 0.048)
	Bonacina, 2011	282, Prospective	18	Dental check-up + OPG, treatment	Control group: 10.8% ONJ Intervention group: no ONJ.
	Vandone, 2012	269, pro- and Retrospective	47	Dental check-up + OPG, treatment	Control group: ONJ 5,5% Intervention group: 2.8%

	Dimopoulos, 2009	128, Retrospective	17	Dental check-up, treatment before starting ZOL therapy in patients with multiple myeloma	16 of 128 patients developed necroses, Control group: 23%, intervention group: 7% Incidence ratio: 2.92 (95% CI [1.06; 8.03]; p = 0.0296)
Other	Kunchur, 2009	348, Prospective	14	CTX test was performed before extractions	102 out of 222 patients had CTX mean <200pg/ml. 1 developed ONJ
	Marx, 2007	30, Prospective	6	Drug holiday (DH) – CTX test performed	17 of 30 patients: Before DH CTX mean: 72.9 pg/ml After DH CTX mean: 228.2 pg/ml
	Bagan, 2008	25, Prospective	-	Relationship between CTX value and ONJ lesions size and number evaluated	No significant relationships between CTX and size/number of ONJ areas.
	Cameron, 2010	163, Prospective	2	CTX tests performed and drug holiday introduced	No ONJ developed in both CTX and non CTX groups. The mean gain for each month of a drug holiday was 66.2 pg/mL.
	Wutzl, 2011	58, Retrospective	6	Drug holiday before surgery and 6months follow-up.	Median stage improvement in Control group: +1 Drug holiday group: +1,5
	Kwon, 2009	18, Prospective	-	CTX test performed, BRONJ risk assessed	CTX mean: 112±76.1 All patients were in risk. Significant correlation between the disease severity and the risk assessment using serum CTX.

Results

25 publications were included from PubMed search and 7 publications were additionally included after conducting a search using Google Scholar search engine. We divided results into several prevention groups in order to compare them.

Mandatory dental checkups

While the influence of oral hygiene and oral health to BRONJ remains unexplained, it seems rather common sense to recommend patients taking bisphosphonates get checked by oral health professionals every 6 to 12 months. Up to this day to the best of our knowledge dental checkups are not mandatory for patients in risk of BRONJ.

According to most of the studies found – regular clinical mouth assessments with OPG analysis and detection of teeth and periodontal tissue diseases can really help to prevent BRONJ. Ripamonti and others⁽⁹⁾ suggested screening of the oral cavity and dental care as mandatory preventive measures of BRONJ in patients receiving BPs. In a retro- and Prospective study of 966 patients they managed to lower ONJ ratio from 3,2% (control group) to 1,3% (intervention group) after implementing preventive measures programme. All the patients who candidated to BP therapy were referred to hospital dentists to evaluate any possible infection and (or) inflammation. After clinical inspection and OPG dental procedures were prescribed: extraction of teeth with grade 3-4 mobility, correction of periodontal conditions, oral hygiene treatments with professional root scaling.

Similar results are obtained in other publications: Bonacina et al.⁽¹⁰⁾ (control group – 10,8% ONJ, intervention group – no ONJ;282 patients), Vandone et al.⁽¹¹⁾ (control group – 5,5% ONJ, intervention group – 2,8%; 269 patients), Dimopoulos et al.⁽¹²⁾ (control group – 23% ONJ, intervention group – 7% ONJ;128 patients). On the basis of these results it is highly recommended for the patient to receive an oral sanitation before starting therapy of BPs and have regular dental checkups every 6 months.

Alternative surgery techniques

In most of the cases teeth extractions remain the main trigger for BRONJ to develop^(7,13) which gives us the idea to use new approaches of extractions, minimizing the trauma to the jaw resulting in reduced inflammatory process.

Several dental extraction protocols have been described in the literature related to BRONJ. In a case series of 23 patients (38 extractions) Lodi and others⁽¹⁴⁾ used a set of preventive measures: mouth rinsing with 0,2% chlorhexidine once a day, professional oral hygiene treatment 2-3 weeks before extraction, amoxicillin for 17 days, full-thickness mucoperiosteal flap was reflected, socket debrided and the flap was sutured. Sutures were released after 1 week. After 38 extractions no ONJ was observed.

Similar study was performed by Ferlitto and others⁽¹⁵⁾ with 43 patients, in addition removing adjacent alveolar bone after extraction and using amoxicillin with clavulanate. 102 extractions

were made without occurrence of ONJ. A rather controversial atraumatic method of extraction has been described using orthodontic elastic bands in order to reduce pathogen load. The force of ligatures results in exfoliation of teeth but the downside of this method is mean treatment duration – 6 weeks, although no occurrence of ONJ was found.⁽¹⁶⁾

If BRONJ is not prevented, then surgical debridement is therapy of choice – especially for advanced stages. The classical surgical approach is flawed due to lack of suitable imaging modalities. Pautke and others⁽¹⁸⁾ described a modern approach - Fluorescence-Guided bone resection with some promising results – 17 out of 20 lesions showed mucosal closure 4 weeks after surgery.

Antibiotic prophylaxis

After teeth extraction the bone exposure can lead to bacterial colonization of the socket. In order to prevent this 57% patients have received amoxicillin – clavulanate 1g *per os* one day before surgical intervention. In these patients no ONJ was observed while 25% of patients who didn't get antibiotic prophylaxis developed BRONJ.⁽¹⁷⁾

We have already mentioned a few case series which included antibiotic prophylaxis prior to surgical procedures and after them. The problem with the case series is that antibiotic prophylaxis is used together with atraumatic procedures / wound closure and etc. We found that there is a lack of studies which concentrated not on treatment of BRONJ but prevention. A duration, dosage and type of antibiotics remain a debatable matter.

CTX testing and drug holiday

In order to evaluate risk of BRONJ systemic markers of bone turnover might be assessed - the measurement of biochemical markers from either urine or blood tests is sensitive and rapid indicator of change in bone resorption. During bone resorption, the dominant type 1 collagen is degraded, releasing the C-terminal telopeptide (CTX). It is recommended to evaluate CTX test values before starting any surgical manipulations.

Values lower than 150 pg/mL represent increasing risk of BRONJ – risk increases as the values get lower. While the test seems favorable because of the low invasiveness, studies show

little reliability. There is only 1 study which found a significant correlation between the disease severity and the risk assessment using serum CTX.⁽¹⁹⁾

Other studies seem to indicate that CTX testing is not so reliable – Bagan et al.⁽²⁰⁾ didn't find any statistically significant relationships between the values of serum CTX and the number of areas of exposed bone. 102 out of 222 patients had CTX value <200 pg/mL and only 1 developed ONJ in Kunchurs study⁽²¹⁾ It is noted that CTX test was not predictive of the development of ONJ for an individual patient but does identify those in the "risk zone" and bisphosphonates can be ceased in order to bring the patient out of the risk zone.

Drug holiday increases CTX values anywhere from 26.4 pg/mL to 66.4 pg/mL per month^(22,23) and improves surgical outcomes compared to control groups.⁽²⁴⁾

Teriparatide hormone therapy

Teriparatide (TPD) is a biosynthetic hormone composed of 34 amino acids of parathyroid hormone. Usage of TPD stimulates bone turnover through activation of osteoblasts and osteoclasts – these anabolic properties neutralize the negative effect of BPs.

The hormone is used either as an adjunctive modality for treatment or as preventive measure. Kwon et al.⁽²⁵⁾ described TPD as a drug for BRONJ treatment in when BPs were suspended and TPD prescribed – all 6 patients healed ONJ lesions and serum CTX values elevated in 4 out of 6 patients. Significant results were achieved in Kims et al.⁽²⁶⁾ when all patients in TPD group improved one or more BRONJ stages.

There is a lack of Prospective studies with humans yet there are some studies showing significant role of TPD in prevention of BRONJ between rats^(27,28) and showing no positive effect of TPD after ONJ has developed.⁽²⁹⁾

Discussion

Bisphosphonates have several positive effects for patients: the rate of spontaneous bone fractures between patients with osteoporosis is reduced⁽³⁰⁾, survival of breast cancer is increased⁽³¹⁾ and etc. – improving quality of life.

Since 2003, when Marx et al., described reported first BRONJ cases, many prevention

strategies were introduced but the effectiveness of these strategies seemed unclear. After reviewing the existing literature maintaining good oral health appears to most effective and most investigated prevention method. Before starting bisphosphonates therapy, an examination of the oral cavity should be compulsory requirement. Any possible source of infection should be dealt before taking BPs – any teeth beyond saving must be extracted and periodontal infections should be treated. Patient should be always informed about the increased risk to develop BRONJ even spontaneously.

If any intervention is necessary during BP therapy, atraumatic extraction techniques should be used in conjunction with antibiotics – though the most effective dosage and type of antibiotics is still unknown. In most of the studies antibiotics are used in addition to other prevention methods.

Before performing a surgery of any type CTX test could be carried out to evaluate bone turnover rate - any patient with mean value of CTX lower than 150 pg/mL is considered to be in risk. The reliability of this test remains debatable – various studies show very different results and it are not clear if CTX test can predict development of ONJ and identify those patients in risk. If this test proves to be significantly useful – drug holiday should be indicated since it elevates values of CTX drastically.

One of the most promising and newest prevention methods is teriparatide hormone – it might even be used for treatment of BRONJ. Though the hormone seems to give significant results in preventing osteonecrosis there is a great lack of Prospective studies with humans.

The antiresorptive medications such as bisphosphonates improve quality of life for many patients by reducing possible complications but have negative effect on jaws, especially on the lower jaw. Though BRONJ is a rare condition, having in mind that life expectancy of population is getting longer and that antiresorptive drugs therapy is spreading it is necessary to acknowledge the importance of prophylaxis and early detection of lesions in general practice in order to prevent BRONJ.

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