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DENTAL EXTRACTIONS IN PATIENTS ON ORAL OR INTRAVENOUS BISPHOSPHONATE THERAPY: A CLINICAL DILEMMA

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ABSTRACT

Dental extraction has been touted to be a potential trigger for the onset of bisphosphonate-related osteonecrosis of the jaw (BRONJ). In this article, we carry out a comprehensive discussion on the pharmacology of bisphosphonates. This article also aims to assess and outline the pathogenesis of BRONJ, the outcome of dental extractions on patients receiving bisphosphonate therapy, and to draw a protocol for its prevention and management.

REVIEW ARTICLE

INTRODUCTION:

Since the first description of bone necrosis in patients receiving bisphosphonate therapy in 2004, there have been numerous retrospective, prospective, and case-control studies that have served to characterize the diagnosis, associated risk factors, and treatment of this complication. Although bisphosphonate-related ONJ was not well recognized until 15 years ago, it is at present associated with several risk factors that are identified across several disciplines in medicine and dentistry. With this level of broad-based recognition, a lot of clinical and basic science research has been done to elucidate the etiopathogenesis of this disease process, significantly improving the level of disease management and prevention.

Osteoporosis can be considered a serious public health problem since it can result in bone fractures.[1] It is estimated that 30-50% of postmenopausal women suffer from a fragility fracture and its associated lifelong morbidity.[2] Therapeutical use of bisphosphonates has increased dramatically worldwide, particularly in the treatment of bone diseases such as osteoporosis, but are also used in the management of many other non-malignant and malignant conditions.[3,4]

BISPHOSPHONATES:

Bisphosphonates are a group of drugs that prevent the loss of bone density. The main biological action of bisphosphonates is to reduce bone resorption both by inhibiting osteoclast function, as well as by inducing apoptosis in osteoclasts.[5] They are analogs of pyrophosphates: carbon atom replacing oxygen in P-O-P skeleton (Figure 1).

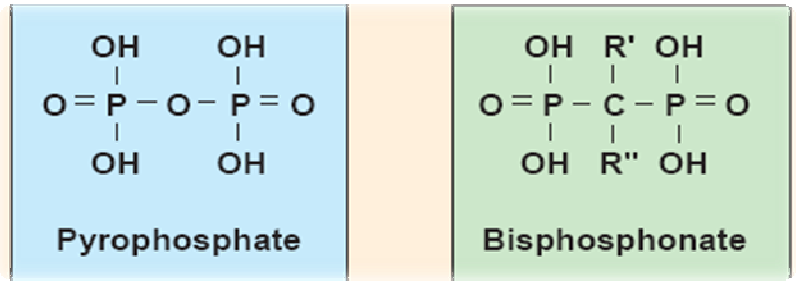


Figure 1: Chemical structure of bisphosphonates

They were first used for industrial purposes in the 19th century to prevent corrosion in the textile, fertilizer, and oil industries. It was only in 1968 that the first article describing the use of bisphosphonates in medicine was published.

Indications of bisphosphonate usage include 1) post-menopausal osteoporosis, 2) Paget's disease, 3) bone metastasis associated with solid malignant tumors and multiple myeloma, 4) hypercalcemia of malignancy.

Bisphosphonate administration serves to improve bone morphology, to prevent bone destruction and pathological fractures, and to reduce the pain associated with metastatic bone disease whilst decelerating bone resorption.

They have been previously classified into three generations depending on their relative potency (Table 1). However, a newer classification system classifies bisphosphonates according to their chemical structure into nitrogen-containing and non-nitrogen containing groups (Table 2). Nitrogen-containing groups are more widely used as they are extremely bone selective. For this reason, the non-nitrogen containing bisphosphonates are now rarely used.[6]

Table 1: Classification of bisphosphonates (generation based)

Bisphosphonate	Relative Potency
FIRST GENERATION	
Etidronate	1
Tiludronate	10
SECOND GENERATION	
Pamidronate	100
Alendronate	100-500
Ibandronate	500-1000
THIRD GENERATION	
Risedronate	1000
Zoledronate	5000

Table 2: Classification of bisphosphonates based on chemical structure (ATP: Adenosine Triphosphate; FPPS: farnesyl pyrophosphate synthase)

Group	Drugs in group	Effect
Non-nitrogen bisphosphonates	Tiludronate	Incorporation into ATP results in osteoclast apoptosis
	Clodronate	
	Etidronate	
Alkyl-amino bisphosphonates	Pamidronate	Inhibit the enzyme FPPS
	Alendronate	
	Ibandronate	
Heterocyclic nitrogen bisphosphonates	Risedronate	Inhibit the enzyme FPPS
	Zoledronate	

Bisphosphonates may be administered either via the oral or intravenous route. The bioavailability of both the routes is strikingly different and hence, it presents different adverse effects in both the routes.

Adverse effects of the oral route include 1) recurrent ulcers, 2) erosive oesophagitis, 3) esophageal stenosis, 4) uveitis, 5) gastric ulceration.

The adverse effect of the intravenous route includes the much more serious and daunting problem of bisphosphonate-related osteonecrosis of the jaws (BRONJ).

The mode of action of bisphosphonates is now more clearly understood. They work by suppressing and reducing bone resorption by osteoclasts. This is accomplished by preventing the recruitment and function of osteoclasts. They also indirectly stimulate osteoblasts to produce inhibitors of osteoclast formation.[7] This results in suppression of bone resorption and thereby is very effective in treating diseases such as Paget's disease of bone, fibrous dysplasia, and metastatic bone cancer.

The blood level half-life of bisphosphonates is very short ranging from 30 minutes to 2 hours.[8] However, bisphosphonates have a high affinity for calcium ions and thus, they are strongly attracted to the bone. They can persist for up to 10 years in the skeletal tissues, depending on skeletal turnover time.[9,10] After jaw bone surgery, a radiolucent lesion or bone exposure may develop rather than a typical healing mechanism.

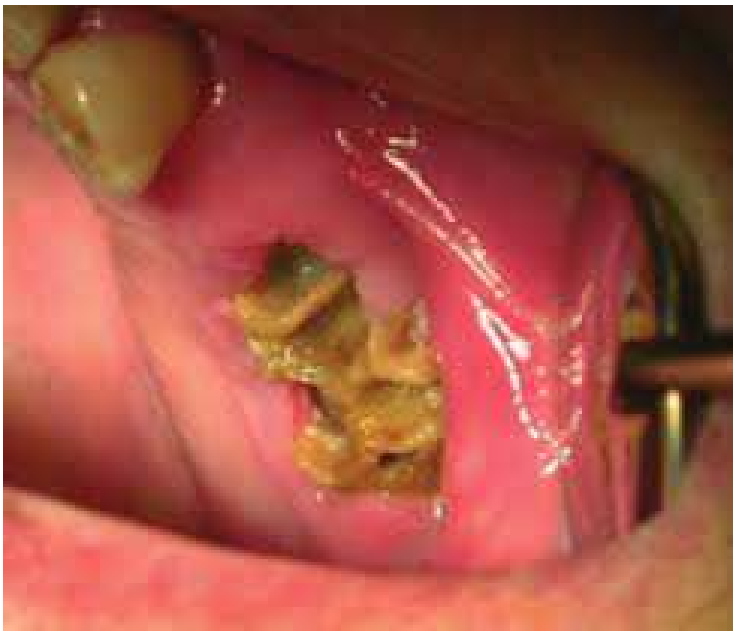
Bisphosphonate-related osteonecrosis of the jaws (BRONJ):

Ischemic osteonecrosis refers to avascular necrosis that can affect any bone of the skeleton. It was first described in the eighteenth century in the femoral head.[11] Osteonecrosis of the jaw (ONJ) was an extremely rare condition, secondary to local and systemic factors, from rheumatological to thrombophilic disorders. In the oncological setting, it was mainly consequent to radiation therapy of head and neck and it was defined osteoradionecrosis.[12]

In 2003, Marx and colleagues described an increasing number of cases of ONJ in patients affected by cancers, mainly multiple myeloma and breast cancer, not undergoing radiation therapy.[13] All the 36 cases described by Marx received treatment with I.V. bisphosphonates (BP), mainly pamidronate and zoledronic acid. Soon after Marx, several other authors confirmed the observation in retrospective epidemiologic surveys in dental clinics and cancer centers worldwide confirming the association between ONJ and BP administration. The almost

constant association with BP resulted in this condition being named bisphosphonate-related osteonecrosis of the jaw (BRONJ).

It is defined by the American Association of Oral and Maxillofacial Surgeons (AAOMS) as "an avascular area of necrotic bone in the maxillofacial area, with or without exposed bone, that has been evolving for longer than 8 weeks in patients without a history of irradiation in the maxillofacial region".



Even though ONJ has been well described in the literature, the pathogenesis of this disease process remains poorly understood.

Four major hypotheses have been proposed to explain the etiology of the disease process

1. Bone remodeling suppression (osteoclast-mediated)
2. Disturbances in bone vascularity (anti-angiogenesis)
3. Local mucosal toxicity
4. Genetic factors

The most popular and researched hypothesis focuses on the profound inhibition of osteoclast function associated with these drugs. Bisphosphonate-mediated suppression of bone remodeling is thought to have a greater effect in the jaw, where baseline bone turnover rates are typically much higher than at other skeletal sites.[14]

Defects of angiogenesis have also been considered as a mechanism for ONJ. This idea has been fuelled by reports of bisphosphonate-induced inhibition of angiogenesis in culture and animal tumor models.[15,16] These findings, however, are tempered by other animal studies in which bisphosphonates had no effect on angiogenesis associated with endochondral ossification[17] and findings of normal vasculature in regions of bisphosphonate-induced matrix necrosis.

Direct mucosal toxicity from high bisphosphonate concentrations in the bone has been considered as the primary event for jawbone exposure and necrosis.[18] This idea is based on culture data in which high concentrations of bisphosphonates were found to be toxic to oral mucosal cells. The clinical scenario where ONJ presents spontaneously in the non dentate region of the jaw, however, does not fit this hypothesis well.

The fact that only a small subset of patients exposed to bisphosphonates develop jaw necrosis has led some investigators to

consider certain pharmacogenetic factors as well.[19,20] In particular, Sarasquette[21] noted certain genetic irregularities (ie, single nucleotide polymorphisms) in the cytochrome P450-2C gene in patients with multiple myeloma and ONJ. Patients who were homozygous for the T allele had a 12.7-fold increased risk of developing ONJ. The link to ONJ formation is thought to be related to alterations in bone vascularity and arachidonic acid metabolism, both of which are controlled by this gene.

All these studies provide a much greater understanding of this disease process and certainly provide a clearer direction to which future research should be directed. Considering the aforementioned studies, ONJ can be accurately predicted based on specific risk factors such as the presence of jaw inflammation (trauma or infection), a genetic marker, and antiresorptive bone therapy.

Clinical presentation and diagnosis:

Standardization of diagnostic criteria and nomenclature for this clinical entity is important to facilitate future clinical and epidemiologic research. Also, a uniform definition for ONJ serves to distinguish this new clinical entity from other delayed intraoral healing conditions.

The American Association of Oral and Maxillofacial Surgeons (AAOMS) established a working definition for BRONJ, which has remained unchanged since it was first defined in 2006. The tenets of the diagnosis include
(1) an exposure history to bisphosphonates
(2) exposed bone within the oral cavity, and
(3) no history of prior radiation therapy to the jaws

The ADA later introduced the more generic term ARAONJ (antiresorptive associated osteonecrosis of the jaw) to include those new cases of necrosis associated with monoclonal therapy.

Despite the variations in nomenclature, the clinical finding of exposed, necrotic bone remains the consistent hallmark of the diagnosis, and therefore patient history and physical examination are the most sensitive diagnostic tools for this condition. Areas of exposed and necrotic bone may remain asymptomatic for weeks, months, or even years. These lesions are most frequently symptomatic when the surrounding tissues become inflamed or there is clinical evidence of exposed bone. Signs and symptoms that may occur before the development of clinically detectable osteonecrosis include pain, tooth mobility, mucosal swelling, erythema, and ulceration. These symptoms may occur spontaneously or, more commonly, at the site of prior dentoalveolar surgery. Most case series have described this complication at regions of previous dental surgery (i.e., extraction sites); exposed bone, however, has also been reported in patients with no history of trauma or edentulous regions of the jaw. Intraoral and extraoral fistulae may develop when the necrotic jawbone becomes secondarily infected. Some patients may also present with complaints of altered sensation in the affected area as the neurovascular bundle becomes compressed from the inflamed surrounding bone. Chronic maxillary sinusitis secondary to osteonecrosis with or without an oral-antral fistula can be the presenting symptom in patients with maxillary bone involvement.

It has been observed that lesions are found more commonly in the mandible than in the maxilla (2:1 ratio). They are also more prevalent in areas with thin mucosa overlying bone prominences such as tori, exostoses, and the mylohyoid ridge.[22-24] The area of the exposed bone is typically surrounded by inflamed erythematous soft tissue. Purulent discharge at the site of the exposed bone is present when these sites become secondarily infected. Microbial cultures from areas of exposed bone usually show normal oral microbes and therefore are not always helpful. In cases in which there is extensive soft-tissue involvement, however, microbial culture data

may define co-morbid oral infections that may facilitate the selection of an appropriate antibiotic regimen.

A clinical staging system developed by Ruggiero and colleagues[23] and adopted by the AAOMS in 2006[25] and updated in 2009[26] has served to categorize patients with ONJ, direct rational treatment guidelines, and collect data to assess the prognosis and treatment outcome in patients who have used either intravenous (IV) or oral bisphosphonates (Table 3).

Table 3: Staging of BRONJ

Stage	Findings
At-risk category	No apparent exposed/necrotic bone in patients who have been treated with either oral or IV bisphosphonates
Stage 0	Nonspecific clinical findings and symptoms such as jaw pain or osteosclerosis but no clinical evidence of exposed bone
Stage 1	Exposed/necrotic bone in patients who are asymptomatic and have no evidence of infection
Stage 2	Exposed/necrotic bone associated with infection as evidenced by pain and erythema in the region of the exposed bone with or without purulent drainage
Stage 3	Exposed/necrotic bone in patients with pain, infection, and one or more of the following: pathologic fracture, extraoral fistula, or osteolysis extending to the inferior border or sinus floor

The radiographic features of ONJ are nonspecific. Plain film radiography does not typically demonstrate any abnormality in the early stages of the disease because of the limited degree of decalcification that is present. Findings on plain film imaging, however, such as localized or diffuse osteosclerosis or thickening of the lamina dura (components of stage 0), maybe predictors for future sites of exposed, necrotic bone. Little or no ossification at a previous extraction site may also represent an early radiographic sign. The findings on computed tomography (CT) are also nonspecific, but this modality is significantly more sensitive to changes in bone mineralization and is, therefore, more likely to demonstrate areas of focal sclerosis, thickened lamina dura, early sequestrum formation, and presence of reactive periosteal bone (figure 3). The CT images have also proved to be more accurate in delineating the extent of disease, which is helpful for surgical treatment planning.[27, 28]

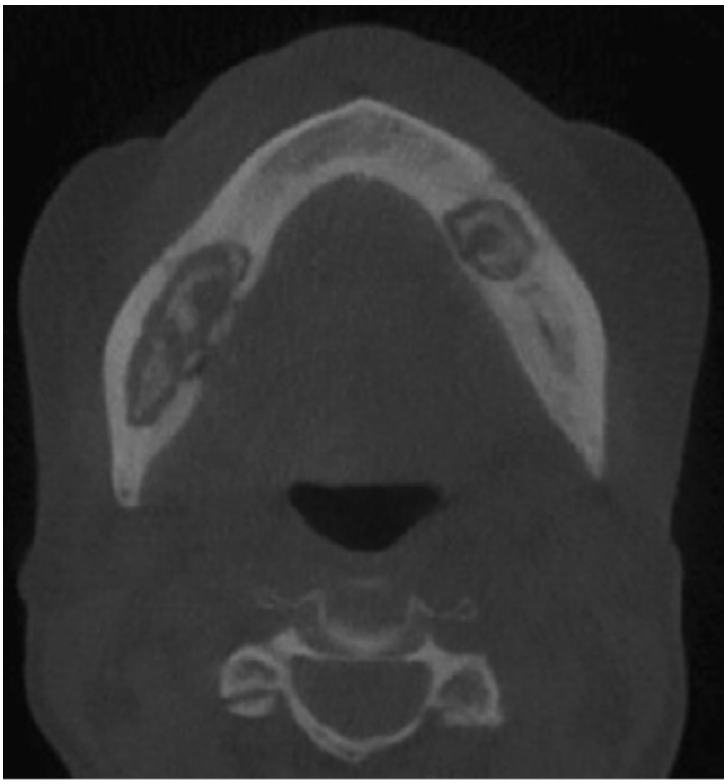


Figure 3: Axial CT scan demonstrating bone sequestration and extensive osteosclerosis in a patient with breast cancer receiving IV bisphosphonate therapy

Dental extractions and BRONJ:

Dental extractions and dentoalveolar surgical procedures in patients receiving bisphosphonates and other antiresorptive drugs are of rising clinical importance in the field of dentistry as well as oral and maxillofacial surgery. Based on clinical and epidemiological findings, dental extraction often precedes the manifestation of BRONJ. Therefore, it is sometimes called a precipitating or trigger event. Furthermore, dental extractions and dentoalveolar surgical procedures have also been regarded as risk factors for the onset of BRONJ. As a result, some of the guidelines even recommend avoiding extractions and dentoalveolar surgery under bisphosphonate intake whenever possible.

The prevention of BRONJ is fundamental and is relatively simple in patients who are about to begin bisphosphonate treatment. It is generally recommended to adopt an aggressive approach directed towards the extraction of any unsalvageable tooth followed by completion of all other invasive dental procedures. Maintenance of good oral hygiene is paramount to avoid future infections, inflammation, and dentoalveolar surgery.

Dental extractions and other dentoalveolar surgeries should be avoided in patients on bisphosphonate therapy as much as possible. However, in cases where it is indicated, one should proceed with caution.

LABORATORY TESTS:

It has been proposed that assays to monitor markers of bone turnover may help in the diagnosis and risk of developing BRONJ.[29] C-telopeptides (CTx) are fragments of

collagen that are released during bone remodeling and turnover. Because bisphosphonates reduce CTx levels, it is believed that evaluating serum CTx levels can be a reliable indicator of the risk level. The CTx test (also called C-terminal telopeptide and collagen type 1 C telopeptide) is a serum blood test obtained by laboratories or hospitals.

Marx has suggested a preoperative protocol for administering bisphosphonates to patients who are undergoing oral surgical procedures.[30] His protocol considers the type and duration of bisphosphonate use as well as radiographic and clinical risk factors. Depending upon the laboratory values obtained, a "drug holiday" may be indicated, which includes temporary interruption of bisphosphonate treatment. However, improvement of bisphosphonate levels may not be observed, because measurable levels have been shown to persist in bone for up to a decade after cessation of therapy.

PROTOCOL AND SUGGESTIONS:

Oral bisphosphonate use > 3 years

1. Physician approval to discontinue bisphosphonates 3 months before surgery and 3 months after surgery ("drug holiday").
2. Determine serum CTx levels during the initial consultation and immediately before surgery; CTx levels must be >150 pg/mL before proceeding with surgery.
3. Detailed informed consent for bisphosphonate-associated osteonecrosis.

Oral bisphosphonate use < 3 years without clinical or radiographic risk factors

1. Serum CTx level must be > 150 pg/mL.
2. Proceed with surgery with detailed informed consent for bisphosphonate-associated osteonecrosis.
3. If serum CTx level < 150 pg/mL, institute a physician-approved "drug holiday"; continue monitoring every 3 months until CTx levels > 150 pg/mL.

Oral bisphosphonate use < 3 years with clinical or radiographic risk factors

1. Physician-approved "drug holiday" for 3 months.
2. Serum CTx level must be > 150 pg/mL to proceed with detailed informed consent for bisphosphonate-associated osteonecrosis.
3. If serum CTx level < 150 pg/mL, continue monitoring every 3 months until CTx level > 150 pg/mL.

Table 4: Laboratory risk assessment of serum CTx levels

CTx Value (pg/mL)	Risk for Osteonecrosis
300 – 600 (normal)	None
150 – 299	None to minimal
101 – 149	Moderate
< 100	High

One of the major drawbacks of the serum CTx test is that this test is not valid in patients with underlying malignant diseases and skeletal metastases and can only be used for osteoporotic patients.

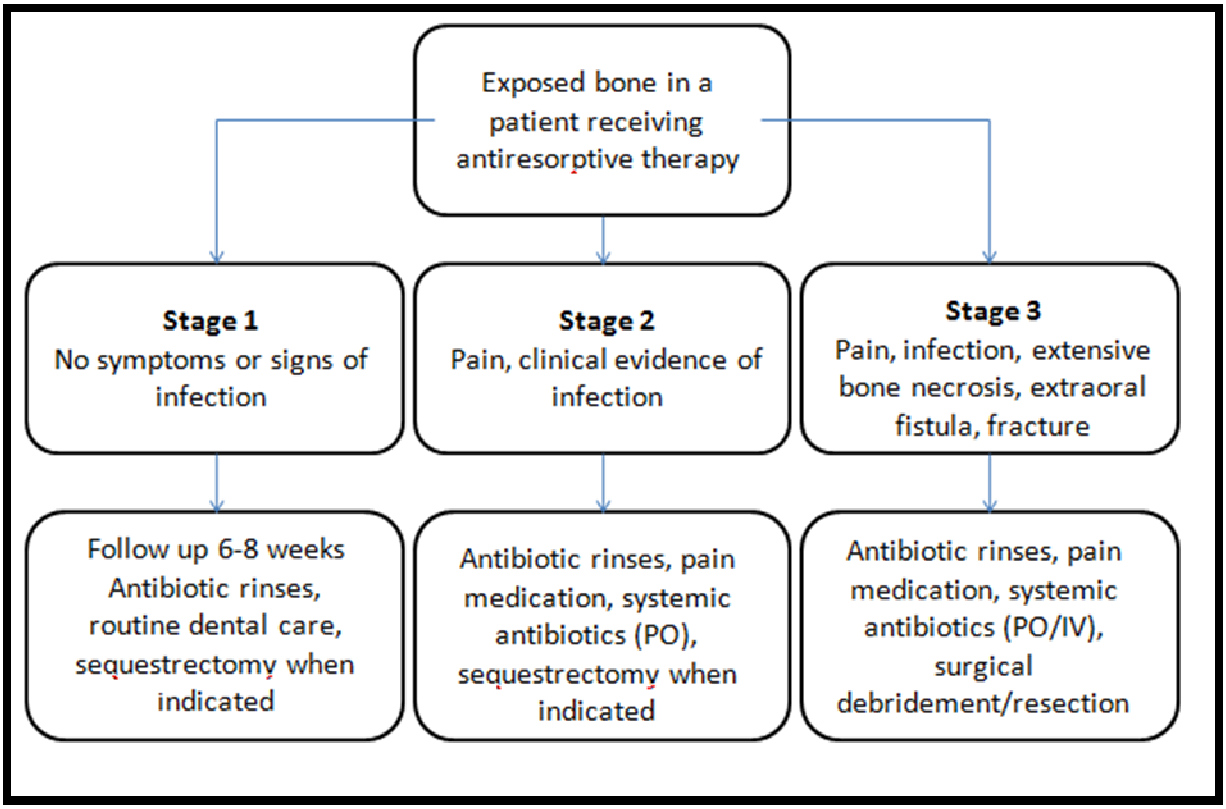
Recently, there has been a shift of paradigms in the sense that tooth extraction and dentoalveolar surgical procedures are not necessarily avoided in patients receiving bisphosphonates, especially when the main intention of these procedures is the eradication of a local infection which cannot be cured by conservative measures. Tooth extraction and dentoalveolar surgical procedures aiming at treating and curing local infections (e.g. apical or marginal periodontitis) could lead to a decreased risk for the development of ONJ.[31]

The latter needs to be proven by further prospective studies.

It is recommended that all local infections should be treated and overcome by the removal of infected teeth and suspicious bony lesions, and by antibiotic treatment and mucosal coverage of the extraction wounds, protecting the extraction sockets from bacterial ingrowth after extraction.[31]

Management of BRONJ:

The management of patients with ONJ remains challenging because surgical and medical interventions may not eradicate this process. The goal of treatment of patients at risk of developing ONJ, or for those who have active disease, is the preservation of quality of life by controlling pain, managing infection, and preventing the development of new areas of necrosis. This treatment has to be balanced with the oncologic management of the patient with osteolytic metastases and the risk of pathologic fracture in the patient with osteoporosis.



CONCLUSION:

It is a fact that dental extractions and other dentoalveolar procedures in patients on bisphosphonate therapy are a trigger factor for BRONJ. However, when these procedures are inevitable, it is important to follow an evidence-based approach to prevent undesirable outcomes.

The combination of perioperative antibiotic prophylaxis, atraumatic surgery, smoothening of sharp bony edges, and plastic wound closure, offers a safe and reliable strategy for tooth extraction in patients receiving oral and intravenous bisphosphonate treatment.

Serum CTx is a laboratory test that provides a rather reliable tool for evaluating the status of the turnover ability of the bone. It thus aids in forming a treatment plan, as stated in the Marx protocol.

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