Review Article

Clinical impact of bisphosphonates in root canal therapy

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ABSTRACT

البايفوسفونيت نظير الهيكلة المستقرة من بيروفسفات التي تقمع نشاط الأوستيوكلاست مما أدى إلى انخفاض ارتشاف العظم. فهي أدوية أساسية في علاج هشاشة العظام. يعتبر نخر عظم الفك تأثير سلبي من علاج البايفوسفونيت. حيث أنه تختلف نسبة انتشار تنخر عظم الفك من البايفوسفونيت من 0% إلى 28% ومن الممكن أن يسببها قلع الاسنان والرضح (صدمة نفسية). يمكن تأخير علاج قناة الجذر أو حتى القضاء على الحاجة لقلع السن. وبالتالي يقلل من خطر تنخر عظم الفك المرتبط بالبايفوسفونيت. ونقترح قد يكون أفضل علاج للأسنان من مرض لبي أو محيط الذروة.

Bisphosphonates are stable structural analogs of pyrophosphate, which suppress the activity of osteoclasts, leading to decreased bone resorption. They are essential medications in the treatment of osteoporosis. Osteonecrosis of the jaw is a serious adverse effect of bisphosphonate therapy. The prevalence of bisphosphonate-related osteonecrosis of the jaw varies from 0% to 28%, and it can be triggered by dental extraction and trauma. Root canal therapy can delay, or even eliminate, the need for tooth extraction, and therefore, may reduce the risk of bisphosphonate-related osteonecrosis of the jaw. We suggest that this might be the best treatment for teeth with pulpal and/or periapical disease.

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Bisphosphonates (BPs) are an essential medication in the treatment of osteoporosis, and are also used in the treatment of certain cancers.[1] In 1995, the United States approved the first BP, fosamax or alendronate sodium, produced by Merck & Co for use in the treatment of osteoporosis.[2] Further developments led to the introduction of new generations of BPs, which are characterized by their long-acting effects that improve patient compliance.[2] Currently, BPs are an essential component in the treatment of osteoporosis.[1] Bisphosphonate is broadly described worldwide.[2] In the European Union countries, approximately 5% of the population aged 50 years or older has osteoporosis, and receives treatment with BPs frequently.[3] As with any other medication, BPs have side effects; osteonecrosis of the jaw (BRONJ) related to BP use has important medical and dental implications.[4]

The purpose of this review is to provide an overview of BPs, highlight their implications in endodontic treatment, and provide guidelines to promote oral care in all patients receiving BP therapy during root canal treatment, to prevent BRONJ.

Bisphosphonate properties and effects. Bisphosphonates are stable structural analogs of pyrophosphate, which are deposited on the bone surface in the first few minutes or hours after uptake, with unbound BP swiftly removed renally.[1,4] Bisphosphonates suppress the activity of osteoclasts, which leads to decreased bone resorption.[5] The effects of BPs vary according to the generation they belong to (first, second, or third generation). The first generation (non-nitrogen containing) BPs induce apoptosis by the formation of a toxic analog of adenosine triphosphate, whereas the second and third generations (nitrogen-containing BPs) inhibit osteoclast function by targeting the enzyme farnesyl diphosphate synthase, which is necessary for post-translational modification of small Guanosine Triphosphate(GTP)-binding proteins.[1] Both the potency and strength of binding to hydroxyapatite differ greatly between individual compounds.[6] **Table 1** shows the types of BPs, their modes of action, and examples of commercially available BPs.

Table 1 - Types and mode of action of bisphosphonates (BPs).

Generation	Type	Examples	Mode of action
First generation	Non-nitrogen containing BPs	Etidronate (Didronel® Norwich Pharmaceuticals, Inc. North Norwich) Clodronate (Bonefos® Bayer PLC, UK)	Formation of an ATP derivative that diminishes osteoclast function and encourages osteoclastic, programmed cell death by apoptosis.
Second generation	Alkyl-amino non-nitrogen containing BPs	Tiludronate (Skelid® Sanofi-Aventis Australia Pty Ltd) Pamidronate (Aredia®, Novartis International AG, Basel, Switzerland) Alendronate (Fosamax®, Merck & Co., Inc. Kenilworth, New Jersey, USA) Ibandronate (Boniva®Roche and GlaxoSmithKline Brentford, London,UK)	Prevents sterol formation by the isoprenoid pathway through prohibiting its farnesyl pyrophosphate synthase enzyme
Third generation	Heterocyclic nitrogen containing BPs	Olpadronate (Olpadronate Sodium®, PharmaChem USA) Risedronate (Actonel®, Sanofi S.A. Gentilly, France) Zoledronate (Reclast® Novartis Pharma AG, Switzerland)	Prevents farnesyl pyrophosphate synthase FPPS enzyme and stabilizes conformational changes.

ATP - adenosine triphosphate, NBPs - nitrogen containing bisphosphonates, FPPS - farnesyl pyrophosphate synthase enzyme

Side effects of bisphosphonates. As with any other drug, BPs have their own side effects. Oral BPs can cause nausea, epigastric pain, esophagitis, and gastric ulcer.[7,8] Myalgia, arthralgia, low-grade fever, headache, and bone pain due to a temporary acute-phase response could occur during the first 24 to 72 hours following intravenous (IV) administration of BPs.[9] Some reports mention an association between atrial fibrillation and the use of BPs.[7,10,11] There is no definitive evidence of the increased risk of esophageal cancer or gastric cancer in male and female patients taking BPs.[12] A case series study that extracted data from 2 main primary care centers in the United Kingdom showed that there was no relationship between BPs and esophageal cancer, but that using alendronate for a short duration might increase the possibility of gastric cancer.[13] Bisphosphonates may rarely cause uveitis, scleritis, and orbital inflammatory disease.[14-16] Atypical proximal femoral fractures could occur with long-term use of BP.[17,18]

Bisphosphonate-related osteonecrosis of the jaw (BRONJ). Bisphosphonate-related osteonecrosis of the jaw is one of the serious adverse effects of BP therapy.[19,20] The first cases of BRONJ related to BPs were reported over a decade ago.[21] The American Society for Bone and Mineral Research (ASBMR) defines BRONJ as an exposed area of the bone in the upper or lower jaw, in the maxillofacial region, which does not recover within 8 weeks after diagnosis in a patient taking a BP, who has not received radiation therapy in the maxillofacial region.[22]

The occurrence of BRONJ has been correlated with 2 hypotheses: firstly, BPs tend to be highly concentrated in the jaw because of high vascularity, causing an anti-angiogenic effect, and secondly, its cytotoxic effect on osteoclasts and periodontal ligament cells suppresses bone turnover.[23,24]

The prevalence of BRONJ varies from 0% to 28%, with a higher incidence associated with the use of IV nitrogen-containing BP.[25] The type of BP, frequency of use, and therapy duration are all factors that have effects on BRONJ. Moreover, oral BP use is associated with not more than a 4% incidence of BRONJ.[26] Dental extractions and trauma trigger 64% of BRONJ cases;[27] periodontitis accompanies 84% of BRONJ cases.[28] The differential diagnoses of BRONJ include sinusitis, alveolar osteitis, periapical pathosis, gingivitis/periodontitis, and some types of cemento-osseous dysplasias with secondary resorption.[29] The exposed necrotic bone may continue to be asymptomatic for a long duration.[27] Inflammation of tissues surrounding these lesions will cause signs and symptoms such as tooth mobility, soft tissue swelling, erythema, ulcers in the mucosa and soft tissues,[25,30] paresthesia, or even numbness of the associated branch of the trigeminal nerve.[31] Signs and symptoms may appear before osteonecrosis becomes clinically noticeable.[25,32]

Table 2 - Clinical signs and symptoms of Bisphosphonate-related osteonecrosis of the jaw (BRONJ).

Traditional signs of BRONJ	Possible clinical signs and symptoms associated with Bisphosphonate-related osteonecrosis of the jaw BRONJ
Exposed necrotic mandibular bone	Pain in the tooth or bone purulence
	Swelling
	Fistula and sinus in the affected jaw
	Teeth mobility
	Trismus
	Non-healing extraction sockets
	Ulcers in soft tissue
	Gross deformation in lower jaw
	Bone resorption

Table 2 shows the clinical signs and symptoms of Bisphosphonate-related osteonecrosis of the jaw (BRONJ). Most cases of BRONJ undergo conservative treatment; the treatment regimen includes improving and maintaining oral hygiene, removing dental and periodontal disease, mouthwashes with local antibiotics, and systemic antibiotics.[29] In unresponsive cases, surgical management should be considered; ostectomy of the affected bone should be continued until normal bone is observed.[29]

Table 3 shows BRONJ staging systems and suggested treatments, according to the American Association of Oral and Maxillofacial Surgeons.[33]

Endodontic clinical implications of bisphosphonates.

Pulpal necrosis is the result of microorganism invasion into the root canal system, leading to infiltration and inflammation through the apical foramen, into the periapical tissues, causing an increase in osteoclastic activity and bone resorption.[34,35]

The activated inflammatory cells secrete multiple proteins, including cytokines (namely, interleukin 6 or TNF-a) and degrading proteins (namely, collagenase or proteinases) that interfere with healing.[36] Bacterial endotoxins will activate the complement system, all these factors provoke the differentiation of macrophages into osteoclasts.[37]

The BPs target osteoclast-mediated bone resorption, and ultimately inhibit bone remodeling. This process can interfere with healing of periapical lesions following root canal treatment.[38] The periapical lesions can be considered as predisposing factors that may aggravate the development of BRONJ, following tooth extraction.[39]

A recent animal study evaluated the role of periapical lesions in exacerbation of BP-related osteonecrosis of the jaw (BRONJ) following tooth extraction. This revealed the increasing occurrence of BP-related osteonecrosis following the extraction of teeth with periapical lesions, and pointed out that periapical lesions should be controlled before tooth extraction, to minimize the risk of BRONJ.[39]

Table 3 - Bisphosphonate-related osteonecrosis of the jaw staging systems according to the American Association of Oral and Maxillofacial Surgeons and suggested treatments.[21]

Stage	Specification	Treatment
At-risk category	No evidence of exposed or necrotic bone in patients treated with bisphosphonates	These patients do not require treatment.[21] However, patients should be educated regarding the risk of developing Bisphosphonate-related osteonecrosis of the jaw (BRONJ), including, quickly reporting each sign and symptom. Perform local risk factor management and periodic clinical and radiological check-ups.
Stage 0	Non-specific clinical findings and symptoms such as mandibular pain or osteosclerosis, but no clinical evidence of exposed bone.	Perform medical treatment (antiseptic, analgesic, antibiotic, and antiphlogistic therapy) and management of local risk factors.[21] Low-level laser therapy is a possible choice for the treatment of osteonecrosis by aiding the reparative process, improving the osteoblastic index, and stimulating growth of the lymphatic system and blood capillaries.[65] A careful follow-up for evolution to a higher stage is necessary.
Stage 1	Exposed/necrotic bone in asymptomatic patients with no proof of infection	If exposed/necrotic bone or fistulae are present, rinse them with antiseptic fluids and cover them with an adhesive paste 3 times a day. In the absence of a healing development, after 8 weeks, a surgical debridement approach is possible.[66]
Stage 2	Exposed/necrotic bone associated with proof of infection such as pain and erythema in the area of the exposed bone, with or without pus drainage	Conservative surgical debridement after 2 weeks of medical therapy, to minimize inflammation., removing all the affected bone.[67] Administer antibiotic and antiphlogistic treatments. Follow-up examinations are necessary.
Stage 3	Exposed/necrotic bone with pain, infection. This stage is associated with one or more of the following: pathologic fracture, extraoral fistula, or osteolysis extending to the inferior border or sinus floor.	Perform marginal or segmental osteotomies for severe cases.[67,68] Perform invasive surgery only if it could improve the patient's quality of life. In other cases, or if the patient rejects surgery, perform a conservative approach to control symptoms and prevent osteonecrosis progression.[67]

Patients undergoing BP therapy are at a higher risk of developing BRONJ.[40] Extraction of the affected teeth may trigger BRONJ. Dental extraction could be delayed or even avoided by performing root canal therapy in the affected teeth.[41] Non-surgical root canal treatment, as an alternative to extraction, will decrease the risk of BRONJ incidence.[38] The purpose of root canal therapy is to eliminate infection and prevent it from infiltrating into the periapical tissues.[38] In a study, it was found that the healing rate of periapical lesions following root canal treatment in patients taking oral BPs for long time was 73.5%; and was not significantly difference than the healing rate of periapical lesions after root canal treatment in patients who did not use oral BPs (81.6%).[38]

The major limitation of the study was the small size of the sample. The evidence-quality of that study was moderate. Therefore, this subject requires further research to explain the relationship between endodontic treatment and the effects on patients undergoing BP therapy.[42] A recent study evaluated the effect of IV zolendronate on the clinical and radiographic success of non-surgical root canal treatment. The results of this study revealed a strong relationship between the duration of BP treatment and the success of root canal treatment, where the success rate increased in patients with shorter BP treatment durations (less than 1 year).[43] Also, the major limitation of the study was a small sample size, and observation period was only 12 months. Further studies are needed on this subject. Most patients reported to have BRONJ have had a history of chemotherapy or dexamethasone use.[44] The other risk factors of BRONJ are intraoral trauma, alcohol/tobacco use, and preexisting periodontal disease.[44]

Root canal therapy can trigger the process of BRONJ through soft tissue damage, especially during application of a rubber dam and apical extrusion of debris during cleaning and shaping of the root canal system.[45] Patel and Saberi[46] described case series of external cervical resorption in patients taking BPs, where there was no other possible cause of resorption. Amino-containing BPs could cause an acute-phase response and release of proinflammatory cytokines, which appears to be associated with the release of tumor necrosis factor-alpha (TNF-α), Interleukin-1 (IL-1), and IL6;[46] this may initiate external cervical resorption in teeth.[46] In rats, the local application of BPs causes an increasing of IL-1 and TNF- α activity which lead to increasing of odontoclast numbers.[47] Animal studies revealed that the superficial application of zoledronate and alendronate decreased replacement root resorption in

intentional replanted teeth.[48,49] The low concentrations of alendronate could inhibit the receptor activator of nuclear factor kappa-ß ligand (RANKL) of generated osteoclasts without cytotoxic influences.[49] The clinical importance of these in vitro findings are not known; further studies must be conducted to prove its clinical capability as a therapeutic procedure for avulsion teeth.

Open apex teeth with pulpal necrosis provides a great challenge to dental practitioners; however, recent years have witnessed a new concept for management of these cases which is called "revascularization."[50] This concept, based on disinfecting the root canal system and inducing intracanal bleeding through the apical foramen creates a suitable atmosphere for endogenous mesenchymal stem cells (MSCs) to differentiate to several type of odontogenic cells and complete root maturity.[50] The root canal revascularization procedures include induction of intracanal bleeding through the apical foramen by over instrumentation, and this may trigger BRONJ. Therefore, the treatments of choice in these cases are apexification or apexogenesis.

Clinical recommendations. The following recommendations could reduce the risk of BRONJ during endodontic treatment.[51]

1. Informed consent and communication with the patient's treating physician are the first and most essential steps before any procedure.

2. A chlorhexidine mouthwash rinse for one minute, before starting treatment, reduces the number of microorganisms in the oral cavity,[52] and minimizes the possibility of bacteremia that may be present due to soft tissue trauma.

3. Avoid using anesthetic agents with vasoconstrictors[53] to reduce the risk of inadequate vascularization, as BPs already have anti-angiogenic effects.[54]

4. Minimize trauma, particularly to the soft tissues, during rubber dam clamp application.[45]

5. Perform the work in a strictly aseptic environment. Disinfect the tooth and the rubber dam by rubbing them with a suitable disinfecting solution for 2 minutes.[51] Tincture of iodine (5%) has proved to be one of the few reliable agents for disinfecting rubber dam and tooth surfaces during the preparation of an aseptic endodontic workfield.[55]

6. Avoid patency of the apical foramen, which can increase the possibility of bacteremia from extruded debris.[51] Electronic apex locators are used to determine the apical constriction. Therefore, it may be

recommended to use the electronic apex locators during cleaning and shaping to maintained the files at apical constriction and prevent it from apical extrusion.[56]

7. During root canal shaping, use Nickle Titanium (NiTi) rotary systems and avoid reciprocating systems, which may cause more extrusion of debris.[57]

8. Apply obturation techniques with minimum risks of overfilling and overextension, to increase the efficiency of root canal treatment[58] and reduce the possibility of periapical tissue irritation.[59] The cold lateral compaction technique minimizes the risk of apical overfilling of the root canal compared to warm root filling techniques.[60]

9. High-risk patients include those under IV or oral BP therapy for more than 3 years and patients presenting systemic issues (such as chronic kidney disease, diabetes, and corticosteroid therapy), who require care.[21,61]

10. Prophylactic antibiotic use in patients treated with BPs before a nonsurgical root canal has not achieved consensus.[62] We recommend prophylactic antibiotics in the following cases:[51,63,64] necrotic pulps in patients undergoing IV BPs treatment, patients treated with oral BPs more than 3 years, and patients with several teeth requiring root canal treatment. It is preferred to schedule all the treatments during a single visit, to limit the dosage of antibiotic prophylaxis to a single regime.

In conclusion, BPs are essential medications for osteoporosis treatment. As with any other drug, BPs have their own side effects. Patients on BP therapy are at a high risk of developing BRONJ. Extraction of the affected teeth may trigger BRONJ. Non-surgical root canal therapy, as an alternative to extraction, will decrease the risk of BRONJ incidence, eliminate the infection, and prevent it from infiltrating into periapical tissues. There are special preventive measures, which should be followed strictly to reduce the risk of BRONJ during endodontic treatment: the work should be performed in a strictly aseptic environment with minimum trauma, prophylactic antibiotics are recommended for necrotic pulp in patients undergoing IV BPs treatment, patients treated with oral BPs more than 3 years, and patients with several teeth requiring root canal treatment. It is preferred to schedule all the treatments during a single visit, to limit the dosage of antibiotic prophylaxis to a single regime.

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