Review Article

The role of bisphosphonates in orthodontic tooth movement—A review

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Abstract

The present study has reviewed and put insights on the reports and recent literatures confined to the effects of bisphosphonate (BP) medication on orthodontic tooth movement (OTM). Pharmacological anchorage control plays a vital role in orthodontic treatment planning to the required patients. BPs inhibit bone resorption by involving increased activity of mineral adsorption on the bone surfaces where BPs tend to target osteoclasts. The present study reviewed on the latest report and examined cases relating to the impact of BPs in OTM. Clinical implication, chemical formulation, and mode of action of BPs have been discussed. This reviewspecifically focused on various kinds of BPs used in medication for bone adsorption in OTM therapy. Furthermore, it tries to explore the rare adverse and side effects of BPs observed based on the literatures. A systematic literature search was attempted in the Medline database (PubMed) using appropriate keywords, such as orthodontic tooth movement, bisphosphonates, and manual hand look was more overdone. On the basis of reports examined, BP treatments in OTM have posed an increased trend toward the benefit and interfere with osteoclastic resorption. In many cases, they may be advantageous for mooring strategies and encourage long-term planned randomized controlled trials to evaluate conceivable benefits and antagonistic impacts of BP treatments for OTM, before initiating remedial use.

Keywords: Bisphosphonate, bone resorption, orthodontic tooth movement

Introduction

Orthodontic tooth movement (OTM) relies on periodontal cells and the affinity between osteoblasts and osteoclasts. OTM is basic to the bone remodeling. While osteoclastic resorption occurs in the old bone, osteoblasts operate to synthesize new bone and are controlled by appropriate factors.[1] The use of bisphosphonates (BPs) has been regarded as crucial and uncontraindicate treatment in "pharmacological anchorage." Clinically, the capacity or potential to suppress activity on bone resorption, there are two significant attentions to be given both on anchorage loss and posttreatment relapse. Recent literature survey revealed that few studies were reported on use of BPs in human and specifically in orthodontic patient.[2] Nowadays, the transition of bone metabolism is followed by the impacts to the orthodontic treatment, possibly, updated indication is still not clear. Due to the missing of scientific authentication, OTM users subjected to BPs is still unpredictable.[3] BPs are comprehensive drugs used to prevent the loss of bone mass, care for malignant bone diseases involving bone (multiple myeloma, hypercalcemia), non-malignant bone diseases (osteoporosis, Paget's disease), and bone metastases from cancer (prostate, breast, lung, and kidney).[4-6] BPs play a role in adsorption on bone surfaces selectively and pre-persist covering at areas of high bone resorption activities if BPs administered systemically and involved in different kinds of intracellular biochemical process.[7] BPs are perpetuated in bone for different prolonged time intervals and lead to remarkable positive impact to an extent after undergoing therapy. It implies that benefit of this efforts is effective while under therapeutics condition and it required a review if any gap persists during medication.[8]

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Recent studies of BPs effects on dental diseases as proposed by NICE's technology appraisal committee guidance on primary prevention of osteoporotic fragility reported that BPs are an important treatment option for the people at the highest risk of osteoporotic fracture (nice.org UK/guidance/ta 464,2017).

The basic fact in orthodontics is that teeth movement is caused when adequate forces are delivered by alveolar bone. Several important criteria such as age, diet, consumption of medicine, etc., believed to affect orthodontic tooth movement. BPs exerts a mode of action that interferes with the bone resorption but caused unpredictable side effects in dental therapy, including inhibited OTM, impaired bone healing, and stimulated osteonecrosis in the maxilla and the mandible.[2] In 1995, the BPs was initially used as Fosamax or alendronate sodium, produced by Merck and Co. for osteoporosis.[9] Further developments led- to the introduction of new generations of BPs, which are characterized by their long-acting effects that improve patient compliance.[10] Currently, BP is an essential component in the treatment of osteoporosis also.[11] As with any other medication, BPs have side effects; osteonecrosis of the jaw (BRONJ) related to BPs use has important medical and dental implications.[12] Therefore, the present study has reviewed to identify and analyze the recent literatures reporting OTM and BPs medication in humans and to know the current state of scientific research regarding orthodontic therapy and BPs benefits with adverse effects are being debated.

History (A sudden turnover to medication)

BPs were first synthesized and throw a light on its usage as corrosion inhibitors, irrigated fertilizer, and in oil industries in 1865 was first discovered in Germany. BPs novelty was not identified until the 1960s, when BPs had turned to the field of medication. BPs played a remarkable inhibiting role such as *in vitro* synthesis and dissolution of calcium phosphate salts in the plasma and urine. It also acts as a regulatory mechanism in the physiological process of calcification and decalcification activities.[13] In 1969, BPs bloomed in the medical attribute. The following Table 1 shows types, mode of action, and commercial products of BPs, according to generation basis.

Pharmacology of bisphosphate

BPs are an analogous chemical compound that exhibits a P-C-P core molecular structure and inside chains are bound with a covalent bond to the central carbon atom and are usually designated as R1 and R2.[15,16] R1 and R2 side chains showed a stereochemistry with phosphate groups are bounded and to be attributed to the vital biological activities of BPS.[16] BPs used, such as etidronate and clodronate without nitrogen atom in the R2-chain increases the pharmaceutical efficacy of the molecule by 10100 folds. At present, the majority of the BPs are with a nitrogen atom. The interaction capability of BPs to hydroxyapatite in turn also elevated by attaching a hydroxyl group (-OH) in the R1-chain.[17] Such a whole structure of BPs molecules is believed to be responsible and potential in exhibiting an effect on bone resorption and their ferocious interaction with minerals. In clinical medication, however, BPs are recommended for the treatment to the postmenopausal osteoporosis, in such a way that increases the resorption process and bone turnover. And it also increases bone mass density (BMD), thereby controlling structural characteristics of bone.[18]

Bisphosphonates effects on Orthodontic Tooth Movement (OTM)

The outcome of the referred reports envisaged that OTM is minimized by the administration of BPs, providing a promising clinical application of augmenting anchorage. An observation found and reported by Liu *et al.*[19] stated that similar models and protocols were used in reducing OTM. A study demonstrated followed by subcutaneous injections[20] reported that a remarkable reduction in OTM, when expansion forces ranging 120 and 165 mN, were given. A comparative study concluded that risedronate acid found to be effective in minimizing OTM, subsequently with 4-amino-1- hydroxybutylidene-1,1-bisphosphonate (AHBuBP), followed by clodronate. In contrary, Keles *et al.*[21] stated that there was no significant reduction in orthodontic tooth movement after administration of pamidronate and contraction forces. However, 70% of osteoclast was remarkably minimized.

BPs are often medicated for osteoporosis in postmenopausal women. A retrospective cohort study relating orthodontic patients who underwent BP medication.[22] A sum of 113

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	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. Citation adopted Mothanna K. AlRahabi, *et al.*[14]

women patients below the age of <50 years was grouped into two, group one consisting of the number of patients n = 20; (19 were applied with oral BP, 1 with IV BP) and another group (n = 93) was separately maintained without BP treatment. As a result, it concluded that the BP-administered group showed a higher degree of opportunities of incomplete extraction space closure at the terminus of therapy and period of time was longer. However, in both the groups, the alignment of lower incisors was seen to be same. The reduction in tooth movement was reported by many studies[23,24] and revealed decrease in the orthodontic posttreatment relapse. The reason may be attributed by the reduction in osteoclasts[25] morphological changes in the cell which cover undulating margins, and cytoplasmic polarity. BPs remarkably minimize the subcellular localization and incorporation of H (+)-ATPase and cathepsin K during orthodontic movement.[26] In an observation of *in vitro* study by Liu *et al.*[27] they demonstrated that effects were attributed to minimize in the tooth movement and decreased stress on the periodontal ligament. The metabolic pathway components included prostaglandin E2 levels, decreasing trend of cyclooxygenase 2. The low level activity of nuclear factor kappa B ligand was the profound indicator of suppressed resorption of bone minerals.

BPs recommended for rapid palatal expansion in orthodontics

An early study by majority of the authors demonstrated the proper procedure for rapid palatal expansion in orthodontics specifically to the constricted maxillary arches. An orthopedic appliance is adopted to make sutural expansion where in synthesized bone fill appeared as physiological activity of the tissues. The suture involves remodeling covering deposition, resorption, and change in the orientation of the fibers. The interaction of mechanical expansion with suture remodeling was deliberately viewed by Miyawaki and Forbes, Ten Cate *et al.*, and Vardimon *et al.*[28-30] They concluded that mode of action of BPs might reduce skeletal relapse following therapeutic maxillary expansion treatment.

Bisphosphonates uses in mandibular osteogenesis distraction

Many studies and literature have envisaged that a couple of study alone was appeared addressing on the impacts of zoledronic acid mandibular distraction. Appropriate mode of administration of BPs minimize the therapeutic duration and thereby induces bone synthesis where the gap exists. It also resulted that 23% elevation in bone density was quantified in the anterior pin region, 20% at the regeneration space, whereas 31% in the region posterior to the pin, with remarkable synthesis of mineral. The bone content was increased by 22, 24, and 32%, respectively, in the same regions. The authors concluded that prolonged retention has been observed evidently while BPs added with mechanical retention after mechanical expansion methods. Finally, it was concluded that additional clinical trials are required for using BPs in orthodontics.

BPs impact on bone necrosis associated

Jachewicz and Jakiel[31] demonstrated a multi-month perception of the understanding and portrays the sequestrectomy method performed, which was supplemented by covering the bone tissue with a collagen sponge. The treatment connected was marginally distinctive from the acknowledged algorithms of procedures. The distinction was associated with the utilizing of a collagen wipe containing gentamicin (utilized to cover the bone's surface) after the sequestrectomy. The collagen texture, in separate to the revealed dead bone, can be a surface which may be powerless to epithelization. This gives a possibility to the auxiliary closing of the wound as a result of granulation and epithelialization without the bone's re-exposure. In addition, it characterize the signs for the utilization of bisphosphonates, their chemical structure, and a component of the activity. It appears the definition of BRONJ (bisphosphonate-related osteonecrosis of the jaw) and hazard components for its event, as well as anticipation and treatment methods.

Rare adverse effects

Several observations highlight the rare adverse effects in specific osteonecrosis of the jaw and atypical femoral breaks, and have driven to extra safeguards. In patients with dental infection or other hazard variables (e.g., glucocorticoids, tobacco utilize), dental examination with preventive dentistry is suggested earlier to treatment with oral or IV BPs, whereas on treatment, patients ought to dodge obtrusive dental methods in the event that was conceivable. For patients requiring dental strategies, there was no information accessible to show whether the suspension of treatment diminishes the hazard of osteonecrosis of the jaw. Clinical judgment of the treating doctor ought to direct the administration arrange of each quiet based on person benefit/risk evaluation. Amid treatment, all patients ought to be encouraged to preserve great oral cleanliness, get schedule dental check-ups, and report any oral side effects such as dental portability, pain, or swelling. It is also reported in few studies that osteonecrosis of the external auditory canal in ear found and occur as rare cases covering infection on the ear. It includes risk factors such as trauma and infection were observed while undergoing therapy. The patient should have been well informed to provide information on pain at thighs and can be evaluated for chances of occurrence of atypical femur fracture.

Side effects of bisphosphonates

Administration of BPs can trigger disorder such as nausea, epigastric torment, esophagitis, and gastric ulcer. Myalgia, arthralgia, low-grade fever, migraine, and bone torment caused by a transitory acute-phase reaction with an interval of 24–72 h after IV administration of BPs. A study criticized relation between atrial fibrillation and BPs therapeutic effect. There is no authenticated evident of esophageal cancer or gastric cancer in both genders taking BPs.[32]

Adverse effects of bisphosphonates usage on prolonging treatment against Osteonecrosis

Several study reports revealed that osteonecrosis of the jaw happens as it were exceptionally once in a while in patients getting

BP treatment for osteoporosis. The evaluated rate in those getting BPs is 1-90/100,000, a long time of quiet introduction. Hazard components for osteonecrosis of the jaw incorporate destitute oral cleanliness, dental infection, dental intercessions, cancer, chemotherapy, or glucocorticoid treatment.[33] Several studies revealed that the process and occurrence of osteonecrosis of the jaw are found prevalent treated with a high dose of BPs. Atypical femur fracture had occasionally observed basically due to sub-top and diaphyseal locules of the femoral shaft, in patients used with BPs. According to ASBMR Assignment and Constraints, elucidated that on long terms BPs required a systematic review of a variety of relative hazards of atypical femoral fracture related with BPs usage. It has been statistically enumerated that outright chance was reliable with extending 32–50 cases out of 100,000 persons per annum.[34] Suspension of BP treatment ought to be considered in patients who create an atypical fracture, weight-bearing movement ought to be confined, and elective treatment alternatives considered where fitting. Surgical treatment with intramedullary nailing is frequently recommended.

Clinical guidelines issued as per NOGG 2017 in using bisphosphonates

Alendronate has been often recommended for the treatment of postmenopausal osteoporosis as 10 mg for everyday and 10 mg for day-by-day, respectively. 70 mg per week and throughout the month would be effective for preventing postmenopausal osteoporosis in women. 5 mg everyday or anticipating intake of alendronate for the treatment of glucocorticoids induced osteoporosis. It was admitted that 10 mg of alendronate intake daily was found to be effective in minimizing oral and non-oral and hip break occurred.[35] Side effects cover upper gastrointestinal side effects, bowel unsettling influence, migraines, and musculoskeletal torment. Alendronate ought to be taken after an overnight quick and at slightest 30 min sometime recently the primary nourishment or drink (other than water) of the day or any other oral therapeutic items or supplementation (counting calcium). Tablets may be taken up with a glass of water approximately 200 ml were in quite is a sitting or upright position. BPs users were not to lie down for half an hour after swallowing the tablets. Commercially, alendronic acid can be got as in 70 mg soluble or effervescent pills to be dissolved in normal water.

Ibandronate 150 mg once monthly by mouth or 3 mg as an IV infusion, every ache 3 months is endorsed for the treatment of osteoporosis in postmenopausal ladies at the expanded chance of a break. In a measurement of 2.5 mg day-by-day by mouth, a critical decrease in vertebral breaks was illustrated.[36] In a post-hoc investigation of tall break chance ladies (femoral neck BMD T-score underneath -3.0), a noteworthy diminishment in non-vertebral breaks was appeared.[37] No information is accessible for hip fracture. Endorsement for the oral 150 mg once a month-to-month and 3 mg IV every 3 months' definitions were allowed on the premise of BMD bridging studies. Side effects with the oral planning incorporate upper gastrointestinal side effects and bowel unsettling influence. An IV organization may be related with an intense stage response, characterized by an influenza-like ailment; typically, generally short-lived and ordinarily happens as it were after the primary injection. Oral ibandronate administration to be taken up while recently drink (instead of water) of the day or supplementation any other therapeutic items (calcium counting). The method of administration was mentioned above. For the treatment of postmenopausal osteoporosis, risedronate is endorsed by prescribing 5 mg for a day or else 35 mg once week through oral administration to avoid the risk of vertebral fracture. Besides, risedronate 5 mg everyday can also be recommended to the woman patient of glucocorticoid-induced osteoporosis. Adverse side effects caused upper gastrointestinal disturbances, bowel irritation, headache, and pain on musculoskeletal part. 5 mg zoledronic corrosive was endorsed once a year for postmenopausal women and men. It is found that zoledronic acid has drastically reduced the occurrence of vertebral, non-vertebral, and hip break of postmenopausal women affected by osteoporosis.[38] It also minimizes the risk of clinical fracture, administered IV to the patient after foremost hip fracture.[39] Intake sometime lead to side effects such as chronic phase reaction and gastrointestinal disturbances.

Conclusion

There is no scientific proof illustrating that BPs are specifically included with etiopathogenic instruments of osteonecrosis and jaw osteomyelitis[40]. Such reality is based on proficient supposition, case reports, and individual encounter or test trials with coming up short strategies. Extra considers will continuously be fundamental; in any case, in-depth information on bone science is of vital significance to offer a conclusion almost the clinical utility of bisphosphonates in OTM and their advance implications. In orthodontics, the helpful utilization of BPs ought to be taken care of with caution considering the advantage and disadvantages. Furthermore, studies with animal models also revealed that BPs ascertained to have a deleterious effect on orthodontic therapies and the clinical remarkable outcomes on BPs yet to be unclear still now.[41-43]

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Conflict of interest

There is no conflict of interest.

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