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Osteonecrosis of the Jaws and its Relation to Bisphosphonates

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Abstract: ***Aim: The aim of the article is to evaluate the usage of bisphosphonate and it's prevalence to osteonecrosis of the jaw. Objective: To determine the correlation between history of bisphosphonate use and osteonecrosis of the jaw after surgery. Background: Bisphosphonates are drugs prescribed for the treatment of osteoporosis. However, long time use of bisphosphonate has shown evidence of osteonecrosis of the bone mainly affecting the jaw. Hence this article emphasizes on the effects of bisphosphonate on osteonecrosis. Reason: The importance of this article is to assess the relationship and the effects of bisphosphonate to osteonecrosis.***

Keywords: Osteonecrosis, Bisphosphonates

1. Introduction

Osteoradionecrosis is an inflammatory condition of bone. It occurs after the bone has been exposed to therapeutic doses of radiation. Doses above 50 Gy usually are required to cause this irreversible damage. Osteoradionecrosis is a due to of radiation damage to bone with consequent hypoxia, hypocellularity and hypovascularity. An area of exposed devitalised irradiated bone that fails to heal over a period of 3 to 6 months in the absence of local neoplastic disease. Osteoradionecrosis can spontaneously occur due to periodontal and periapical disease and also due to trauma induced by extraction or surgery. Extraction before or after irradiation is the most common initiating factor in the development of osteoradionecrosis in irradiated jaws. It presents with a loss of epithelial covering and exposure of bone. This may occur spontaneously after dental extraction or denture ulceration. Pathologic fracture may also occur as a result of loss of vascularity and periosteum and subsequently sequestrates often leading to more bone exposure. Pain may or may not be present. Intense pain often occurs with intermittent swelling and drainage extraorally. Secondary infection is common and further contributes to an increase of the inflammatory reaction. Osteoradionecrosis carries a high morbidity rate as the management of this condition is difficult and often leads to poor outcome and deformity.

Bisphosphonates are stable analogs of pyrophosphates which are naturally occurring modulators of bone metabolism. They are used in the treatment of bone diseases such as hypercalcemia caused by malignancy, bone lesions from multiple myeloma, Pagets disease, breast cancer, prostate cancer and osteoporosis. Bisphosphonates can be administered either orally or intravenously. The chemical structure of bisphosphonates include a P-C-P backbone which has a strong affinity for hydroxyapatite crystals on bony surfaces and it inhibits bone turnover both in vivo and in vitro. They are potent inhibitors of osteoclastic action and have cytotoxic effects on mature osteoclasts and inhibit the formation of osteoclast from precursors.(1) Bisphosphonates also have antiangiogenic effects, being able to decrease endothelial cell proliferation. On a cellular basis, bisphosphonates inhibit osteoclast function by inhibition of osteoclast recruitment, decreasing the osteoclast life span and inhibiting osteoclastic activity at the bone surface.(2) They bind to the mineralised bone tissue at the sites of osteoclast lacunae and are then internalised by the osteoclast. Bisphosphonates have a selective concentration at the interface of the active osteoclast and the bone resorption surface.

The side effects associated with bisphosphonates are acute phase reactions with transient influenza-like symptoms, hypocalcemia, impaired renal function and complications of the upper aerodigestive tract. The most complicated adverse effect of bisphosphonates is osteonecrosis of the jaw and has primarily been described in patients with prolonged intravenous bisphosphonate therapy.(3)

2. Discussion

The etiology of bisphosphonate related osteonecrosis of the jaw is due to the long term use of the drug and the intravenous route of administration of the drug. Bisphosphonates inhibits osteoclastic activity which in turn leads to inhibition of normal bone turnover leading to necrosis of the bone.(4) The bone becomes susceptible to necrosis when there is a raise in demand for bone repair from trauma or infection. Species of Actinomyces, Moraxella and Eikenella have been found on debrided bone from bisphosphonate related osteonecrosis of jaw sites, which indicates that microbial infection may play a role in its etiology. Moreover, Agrillo et al reviewed that a possible effect of bisphosphonates on endothelial cell may cause bisphosphonate related osteonecrosis of the jaw. This is because drug can initiate vascular endothelial cell damage and accelerate disturbances in the microcirculation of the jaws resulting in thrombosis of nutrient end arteries. (5)

There are various risk factors leading to the occurrence of bisphosphonate related osteonecrosis of the jaws. Both oral and systemic factors are thought to predispose this condition. For example, previous history of cancer like multiple myeloma and metastatic bone diseases, osteoporosis, Pagets disease, and chronic renal failure. Oral factors includes dental an periodontal disease, dental surgery, trauma and poor dental hygiene.(6) Systemic factors includes dose, duration and type of bisphosphonate therapy, chemotherapy, corticosteroids, alcohol intake,

habits like smoking, advanced age and underlying diseases like diabetes mellitus and peripheral vascular diseases. The intravenous route of administration causes a greater drug exposure compared to the oral route. Patients under higher doses of intravenous bisphosphonates are at higher risk in developing osteonecrosis of the jaws compared to patients taking lower doses of intravenous bisphosphonates. The risk of developing bisphosphonate related osteonecrosis of the jaw increases when the duration of therapy exceeds 3 years. Certain genetic factors also acts as a predisposing factor like a single-nucleotide polymorphism in cytochrome P450-2C gene in multiple myeloma patients that were treated with intravenous bisphosphonates.

The clinical features varies in every case. Bisphosphonate related osteonecrosis of the jaws is found to be more common in women than men and the occurrence in the mandible is more frequently seen than the maxilla. The initial clinically detectable features are tooth mobility, pain, mucosal swelling, erythema and ulceration. Pain is correlated directly with infection which is indicated by an inflammatory response. The typical presenting lesions were either a non-healing extraction sockets or spontaneous exposed jawbone.(7) Ruggiero developed a clinical staging system which was updated in 2009 AAOMS guidelines. This guideline has served to more accurately categorize patients with bisphosphonate related osteonecrosis of the jaw. Patients with no evidence of exposed or necrotic bone but have under the treatment of oral or intravenous bisphosphonate is considered to be 'at risk' category. Patient with Stage 1 disease have exposed bone but are typically asymptomatic. There are no evidence of significant regional soft tissue inflammatory swelling or infection. Stage 2 disease is characterized by exposed bone associated with pain, adjacent and regional soft tissue inflammatory swelling or secondary infection. In Stage 3, patient have exposed bone associated with pain, adjacent or regional soft tissue inflammatory swelling or secondary infection in addition to a pathologic fracture, or an extraoral fistula or radiographic feature of osteolysis extending into the inferior border.(4)

Various case series and retrospective studies have established a relationship between osteonecrosis of the jaw bone and the chronic use of bisphosphonate therapy. In June 2004, Ruggiero et al reported a case of 63 patients with osteonecrosis of the jaw by which 56 of them were under intravenous bisphosphonate treatment and 7 under oral treatment. 9 consecutive cases of osteonecrosis of maxilla and mandible were reported, where patients were receiving intravenous bisphosphonate therapy. All patients showed lesion both in the maxilla and the mandible. Typical signs and symptoms were present like pain, soft tissue swelling, tooth mobility, infection and draining fistula. It may be explained that once metabolically damaged by the treatment of bisphosphonate, the entire skeleton becomes susceptible to even minor trauma.(8)

Bamias et al proposed a study of 17 cancer patients with osteonecrosis of jaw with a history of being under bisphosphonate therapy, showing that the cumulative hazard of developing osteonecrosis of jaw increased over time of exposure to bisphosphonates and the risk was higher in the zolendronic acid group. Boonyapakorn et al also published results that correlates with the previous study. This result explained that the development of osteonecrosis of jaw seen in 2 patients developed after 10 to 12 months after receiving zolendronic acid, compared to the patient who developed the lesion after 35 months after taking pamidronate later followed by ibandronate.(9)

Three cases of patients with bisphosphonate related osteonecrosis of the jaw was reported having a history of sunitinib therapy intake. In both patients, the time between the first administration of sunitinib and the appearance of oral mucositis was 6 months. The third patient showed relapse of completely healed bisphosphonate related osteonecrosis of jaw (BRONJ) lesions shortly after resumption of sunitinib therapy.(10)

The potency of ibandronate was demonstrated in three case reports of patients with bisphosphonate related osteonecrosis of the jaw. In one of the case, the drug being taken only for one month prior to the extraction of the tooth and subsequent development of bisphosphonate related osteonecrosis of the jaw, The other two case, reports that the bisphosphonate regimes was administered for a period of over a year and other co morbidity factors were noted like long term corticosteroid use and heavy smoking habit. Dental extraction appeared to have played a role in initiating the lesion in all of the three cases.(11)

A case report of 3 patients with bisphosphonate related osteonecrosis of the jaw was presented in Bulgaria. Two of the patients had necrotic bone in the mandible and one patient had the lesion in the maxilla. Two of the patients have been treated with zolendronate for metastatic endometrioid cancer. All three patients underwent surgical treatment and conservative management. No evidence of disease progression was observed during the follow up period of 3 to 12 months.(12)

A 67 year old female patient was presented with worsening pain in the lower jaw. The patient was previously under intravenous bisphosphonate therapy, zolendronic acid. Signs and symptoms includes myofacial pain bilaterally, marked thinning and erythema of alveolar mucosa with definite necrosis of the bone. Bone exposure appeared intermittent.(13)

Another case was reported of a 54 year old woman in July 2007 with a chief complaint of ulceration of the gums, severe pain and bone exposure around implants in the upper left molar area. She had been diagnosed with left breast cancer at another hospital and had undergone left mastectomy in April 2001. She also received postoperative external radiation therapy and chemotherapy with paclitaxel. She then received an anticancer drug and intravenous bisphosphonate after developing multiple metastases of breast cancer in the liver and bone in March 2005. Based on the results obtained, the patient was diagnosed with osteonecrosis of jaw caused by bisphosphonate administration.(14)

Investigations like screening test used for the purpose of determining a patients risk of developing bisphosphonate

related osteonecrosis of the jaw such as C-terminal cross-linking telopeptide of Type 1 collagen (CTX). In situations of increased bone turnover, Type 1 collagen is degraded by osteoclasts, which releases CTX molecules. It has been demonstrated that a decrease in serum level of CTX can be quantified within weeks of initiation of bisphosphonate therapy. Studies have shown that within 6 weeks of initiation of bisphosphonate administration at conventional dosages, CTX levels may decrease by 60%.(7). Another investigation method is the antimicrobial susceptibility testing. Here, the potentially causative microorganisms from purulent exudates of intraoral and extraoral fistulas were isolated and rapidly identified using the API 20 Strep and Vitek anaerobe identification card system (Sysmex BioMerieux, Tokyo, Japan). Antimicrobial sensitivity testing of the isolated bacteria was done with sitafloxacin and the other antimicrobial agents was performed according to Clinical and Laboratory Standards Institute (CLSI) guidelines.(15)

Management strategies need to be both preventive measures and treatment for bisphosphonate related osteonecrosis of the jaw. Ripamonti et al showed that preventive measures helps in reducing occurrence of this lesion from 7.8% to 1.7%. A reduction in dose is also effective in controlling the progression of the condition. Invasive dental procedures should be avoided as in can trigger necrosis of bone. Antibiotic prophylaxis before dental procedures may prevent the occurrence of osteonecrosis of jaws after dental procedures.(6). The standard care for the management of this lesion includes symptom palliation, treatment of dental and periodontal infection and conservative surgical intervention. Many authors strictly have proposed conservative treatment modalities for the management of bisphosphonate related osteonecrosis of the jaw such as antiseptic mouthwash, antibiotic therapy by general route added on with antibiotic irrigants and local application of hydrogel. Follow up after conservative treatment have showed no signs of recurrence and the disease has subsequently improved.(16) Recently, teriparatide was reported as an adjunctive treatment modality. Teriparatide has anabolic effects and promotes osteoblasts differentiation and activity resulting n an increase in bone formation.(6) Studies have also shown success of treatment after management of bisphosphonate related osteonecrosis of jaws with a platelet rich fibrin membrane.(17) The use of the drug Sitafloxacin have shown evident reduction of infection from the lesion and epithelialization and improvement of that site was noticed.(15) The physical property of ErCrYSGG-laser was found to be suitable for bone surgery. The inorganic calcium salts and the organic matrix of bone have very high absorption for the laser beam. This laser provides bactericidal and biostimulatory effect that reduces secondary infection by Actinomyces, Candida and anaerobes. Marked revascularization and healing of bone was noticed which makes the ErCrYSGG laser a good treatment option for bisphosphonate related osteonecrosis of the jaw.(18)

3. Conclusion

Osteonecrosis of the jaws due to bisphosphonates produce significant morbidity and the treatment for this condition is limited. An early diagnosis of the lesion may reduce the progression of the disease. The most important approach for prevention of this condition is patient education on the consequences of bisphosphonate treatment and for the maintenance of proper oral care.

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