European Journal of Molecular & Clinical Medicine
ISSN 2515-8260 Volume 7, Issue 4, 2020

Type of article: Review article
Title of the article: OSTEORADIONECROSIS AND ITS MANAGEMENT: A REVIEW

Contributors :
[1]Dr.L.Malathi, [2]Dr. R.Hariharan, [3]Dr.N.AravindhaBabu, [4]Dr.N.Anitha

Reader, Department of Oral pathology and Microbiology, Sree Balaji Dental College and Hospital, Bharath Institute of Higher Education and Research
Post graduate student, Department of Oral pathology and Microbiology, Sree Balaji Dental College and Hospital, Bharath Institute of Higher Education and Research
Professor, Department of Oral pathology and Microbiology, Sree Balaji Dental College and Hospital, Bharath Institute of Higher Education and Research
Reader, Department of Oral pathology and Microbiology, Sree Balaji Dental College and Hospital, Bharath Institute of Higher Education and Research
Corresponding Author:

OSTEORADIONECROSIS AND ITS MANAGEMENT:A REVIEW

ABSTRACT:
One of the major side effects of radiotherapy o the head and neck region is the osteoradionecrosis (ORN)of the jaws. It requires a multidisciplinary approach for treatment. Various treatments have been proposed for the treatment of osteoradionecrosis. This review article discusses the etiology, pathophysiology and management of osteoradionecrosis.

KEYWORDS: radiation therapy, osteoradionecrosis, osteolysis, radiation osteitis

1. INTRODUCTION:

Currently around 50-60% of patients with head and neck malignant growth get radiation treatment as part of their treatment.[1] Radiotherapy focuses on all cells with a high turnover rate, regardless of whether harmful or typical host tissue. A harmony between tumor destruction and healthy tissue conservation is basic to be accomplished without any more harm to the patient.[2]

The current oncologic administration of head and neck malignancies depends intensely on the utilization of radiation treatment for advanced stage sickness just as for organ protection. According to the American Medical Association, radiation treatment can be separated into 2 subgroups: external and internal.

External radiation involves beams of high-energy radiation directed to the affected area, whereas internal radiation (also called brachytherapy) involves radioactive material placed near the affected tissue, thus minimizing radiation of healthy tissue and maximizing radioactive concentration at target sites.[3]

As early as 1926, Ewing recorded the bone changes related with radiation treatment and portrayed them utilizing the expression "radiation osteitis."[4] Osteoradionecrosis (ORN), is an area of exposed devitalized irradiated bone that fails to heal over a period of 3 to 6 months in the absence of local neoplastic disease.[5-9] Histologically, in ORN, there is clear obliteration of osteocytes, nonappearance of osteoblasts from bone edges, and absence of new osteoid. Atrophic bone changes take after those related with atrophic changes of skin or mucous membranes.[10]

The diagnosis of ORN of the jaws depends basically on the clinical assessment of incessantly uncovered bone. Radiographic assessment can show diminished bone thickness, different degrees of osteolysis, sequestra, and even pathologic breaks. Computed tomography (CT) uncovers rigid irregularities in more detail, including central lytic territories, cortical interferences, and loss of medullary trabeculation in the suggestive region, usually joined by delicate tissue thickening. Magnetic resonance imaging (MRI) exhibits irregular marrow signal, cortical pulverization, and irregular enhancement after gadolinium administration. Dental professionals play a significant part in the diagnosis and management of this disease progress. Dental assessment and proper treatment of oral ailment before administration of radiotherapy for head and neck malignant growth has been accounted for in the literature to lessen the danger of complications, including ORN.

Basic manifestations of ORN include pain, paresthesia and additionally dysesthesia, and trismus. Clinical signs include ulceration, foulness in oral cavity, pathologic breaks, depleting fistulas, and ulceration of overlying skin.[11,12] Even after meticulous dental considerations, teeth can crumble and require extraction months or years after organization of radiation to the head and neck region. Dental extractions are accounted for to be among the most well-known initiating elements in the advancement of ORN in lighted jaws. The occurrence of ORN after tooth extraction in radiated patients is assessed to be somewhere in the range of 2% and 18%. The specific occurence, the viability of the techniques to lessen the frequency of ORN in patients with post irradiation extraction is to a great extent unknown. There is an especially higher danger of ORN and radiation-related complications in the mandible in contrast with the maxilla, with a proportion of 24:1. Radiation induced vascular damage rather than cell damage has been proposed as an explanation for the solid inclination of the mandible to ORN.

The most common risk factors for the advancement of ORN:
• Radiation: A radiation portion higher than 60 Gy speaks to the most elevated danger for causing ORN, and it is more normal when brachytherapy is used.[2,4]
• Trauma and medical procedure: Extraction of teeth and insult to bone are viewed as the primary danger factors for the development of ORN. This danger is increased when extractions are performed after radiation treatment and likewise before radiation when the healing isn't complete, particularly in mandibular surgery. The sites of past bone injuries/ surgeries are at a high danger of ORN in patients going through adjuvant radiation therapy.[13]
• Social factors: Abuse of liquor and tobacco is a danger factor.[13,14]
• Poor oral hygiene: Poor oral hygiene brings about increased occurrence of caries, periodontal ailment, and therefore an increased in neighbourhood aggravation and tissue infection.[10]
The management of ORN varies from for example, anti-infection agents and improvement of oral cleanliness, to more obtrusive choices, incorporating segmental resection with free fold reproduction for hard-headed extreme cases.[15]

2. PATHOPHYSIOLOGY:

The most generally accepted pathophysiology:
1. As per Marx,[5] ORN ought to be viewed as a consequence of hypoxic, hypovascular, and hypocellular tissue, followed by tissue breakdown prompting a nonhealing wound. [4,13]
2. Bras et al.[16] recommended that radiation induced obliteration of inferior alveolar nerve leads to necrosis of mandible.
3. Several authors proposed that, compared with vascular alterations, damage to osteoclasts as a result of radiation occurs earlier, and these authors believed this to be the initial event in the development of ORN.[4]
4. Delanian and Lefaix [17] suggested that ORN happens as a result of a radiation-induced fibro atrophic component, endothelial disruption, aggravation, microvascular apoplexy, fibrosis and redesigning, lastly bone and tissue necrosis.
5. Store et al.[6] exhibited that microscopic organisms may play a principal function in the pathogenesis of ORN.

Progression happens in 3 phases [17]:

1. The initial prefibrotic stage, where endothelial cells undergone acute inflammatory reaction.
2. The constitutive phase, in which abnormal fibroblastic movement, and the extracellular grid loses association
3. The late fibro atrophic stage, which rebuilds the tissue.

3. MANAGEMENT:

- With improvement of oral hygiene, water system, anti-microbial treatment, ORN 8% to 33% of patients following 1 year.
- ORN prevention has been focused at reducing the initial factors, especially medical procedure or extractions in a formerly illuminated site.
- Incidences of ORN have declined in recent couple of decades because of preventive measures, which incorporate dodging dental extractions, when conceivable, and suitable planning of extractions in lighted patients.[2,13,15]
- Surgery has been more successful in halting active disease progression, but at the cost of significant morbidity [18]
- Saline water system and anti-toxin prescriptions during the irresistible period are the moderate treatments normally used, particularly in early stage disease.[19]
- Bacterial identification and sensitivity testing can be utilized before organization of anti-microbials.
- Penicillin with metronidazole or clindamycin is recommended until bacterial identification has been completed.
- ORN has a polymicrobial nature with a microflora range that is open to the remedial regimens used for the treatment of odontogenic infections.
- ORN is in some severe cases unavoidable, requiring more extensive measures.
- The careful methodologies for treatment of ORN of the jaws incorporate injury debridement, sequestrectomy, decortication, resection.[20]
- There is no standardized protocol for the prevention ORN following tooth extraction, yet various treatment modalities are used. The utilization of perioperative anti-toxins, hyperbaric oxygen (HBO), severe adherence to careful standards, alveoloplasty, have all been suggested by various authors.[21]

4. PHARMACOLOGICAL MANAGEMENT :

The idea is a primarily pharmacologic modality based on the etiologic factors
associated with the RIF theory, which describes a fibro atrophic mechanism, including free radical formation, endothelial dysfunction, inflammation, microvascular thrombosis, fibrosis and remodeling, and finally bone and tissue necrosis.[16,21]

Pentoxifylline

Pentoxifylline is a methylxanthine derivative that has different impacts and might be advantageous for ORN. Pentoxifylline instigates vascular increase and increased erythrocyte adaptability bringing about upgraded blood stream. It additionally has an anti-tumor factor α action to diminish the cytokine cascade. Although improvement in symptoms is seen after treatment of peripheral vascular disease with the use of pentoxifylline, it is not intended for long-term therapy replacing surgical bypass or arterial obstruction removal procedures.The specific mode of activity of pentoxifylline are not clearly understood.[21]

Tocopherol

Tocopherols occur in alpha, beta, gamma, and delta forms determined by the number and position of methyl groups on the chromanol ring [22]Alpha-tocopherol, commonly known as nutrient E, has cancer prevention agent properties with inhibition of platelet aggregation, creation of nitric oxide in cells of the endothelium, and creation of superoxide in neutrophils and macrophages.[23] Because α-tocopherol is a

weak antioxidant, it has been proposed to scavenge receptive oxygen species that are associated with ORN pathogenesis by actuating cell layer peroxidation.[24]

Clodronate

Clodronate is another age non-nitrogenous bisphosphonate utilized for treating hyperparathyroidism, osteoporosis, numerous myeloma, and hypercalcemia of danger. Clodronate has been accounted for to hinder bone resorption by diminishing the number and action of osteoclasts.[24] Unlike different bisphosphonates, clodronate acts straightforwardly on osteoblasts increasing the development of bone and diminishing the multiplication of fibroblasts.[25]

Combined pharmacologic therapy:

Pentoxifylline and tocopherol used in combination have been effective in reducing the chronic progressive septic changes associated with ORN of the mandible. Delanian et al.[26] in his study proposed a combination of therapy with pentoxifylline, α-tocopherol, and clodronate. None had a documented improvement in ORN, but in many cases, acute inflammation was alleviated. The pharmacologic protocol of this study involved antibiotic and corticosteroid treatment for up to 1 month to control active infection and allow better penetrance of the drugs. Patients were then treated with daily pentoxifylline (PTX) 800 mg and 1000 IU of vitamin E for at least 6 months. Clodronate 1600 mg daily for 5 days per week as well as alternating 2 days of 1 g ciprofloxacin and 16 mg methyl prednisone were added for patients with severe disease. The study results were promising but ORN couldn't be completely reversed. Hence further studies are required in this front. Prednisone and ciprofloxacin helped curb intermittent acute inflammatory and septic episodes, respectively. Other studies have concluded that PTX or vitamin E alone are inadequate to reverse the development of RIF but that their combined profiles result in excellent antifibrotic ability.[26] As more studies are conducted to learn more about the pathogenesis of ORN and how best to target therapy, it is important that we also consider the prevention of disease.

5. DISCUSSION:

The review discusses the main treatment options for ORN from te published reviews which are antibiotics, surgery, and HBO therapy. From the recent advances done in this field have led to better understanding of the pathogenesis of ORN and this has led to the use of new therapeutic strategies designed to improve tissue healing with a combination of pentoxifylline, tocopherol, and clodronate, collectively referred to as Pentoclo. Studies have demonstrated the effectiveness of the pentoxifylline–tocopherol combination versus placebo and therapy with single agents in radiation-induced trauma at other body sites.[18,25] however due to the risk of bias more histopathologic and biologic research on the molecular level for ORN is required.

6. CONCLUSION:

Currently, there is relative lack of scientific evidence to explain the pathogenesis of ORN and, consequently, lack of efficacious conservative management strategies. Preliminary studies using Pentoclo have been promising, but additional research is needed to elucidate any potential role of pharmacologic therapy in the management of this disease process.

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