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ORIGINAL RESEARCH

Effectiveness of Pentoxifylline and Tocopherol in patients with Osteoradionecrosis

[1]Dr. Sumera Gul, [2]Dr. Sheikh Tafazul, [3]Dr. Najma Banoo, [4]Dr. Mahapara Safder

[1]Senior Resident, [2,3]PG Student, [4]Junior Resident, Department of Oral and Maxillofacial Surgery, Government Dental College and Hospital, Srinagar, Jammu and Kashmir, India.

Corresponding author:Dr. Sumera Gul,
sumeragul667@gmail.com

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Abstract:

INTRODUCTION: Osteoradionecrosis of jaw is a serious complication in patients who have received radiotherapy in the head and neck region for malignant diseases. The use of pentoxyfylline and tocopherol as an adjunctive in the conservative management of ORN patients has been found to be effective due to their desirable properties. MATERIAL AND METHOD: Fifteen patients with ORN (Type I –Type III) were given pentoxyfylline and tocopherol for a period of 8-10 months and the efficacy was evaluated in terms of clinical relief in signs and symptoms and radiographic evaluation. RESULTS: 11 out of 15 patients showed clinical relief in symptoms with no significant radiographic progress in the necrotic process whereas 4 patients showed no significant improvement. CONCLUSION: Pentoxifylline and tocopherol can be used as a safe and effective adjunct in the management of ORN patients without significant side-effects.
Keywords: ORN – Osteoradionecrosis.

Introduction:

Majority of head and neck malignancies are treated either by surgery alone or by combination of surgery, radiotherapy and chemotherapy. Incidence of ORN is approximately 7.4% of all patients receiving radiotherapy mostly in patients treated with over 60 Gray of radiation or advanced age, smokers, alcoholics and those with poor nutritional status.[1] Osteoradionecrosis has been defined by Harris in 1992 as "exposed and necrotic bone associated with ulcerated or necrotic surrounding soft tissue which persists for more than 3 months in an area that has been previously irradiated and is not caused by tumour recurrence". [2] The most common presentation in patients with ORN is pain, bad breath and food lodgement in the affected area. On examination, non- healing extraction sockets after tooth extraction or exposed necrotic bone with radiographic evidence of sequestrum formation is seen with ulcerated and necrosed associated soft tissues. The etiology of ORN is multifactorial, with trauma being the initiating factor in majority cases.[3-5] Watson and Scarborough in 1938 first identified three crucial factors in the development of ORN which include radiation, trauma and infection which was modified by Marx in 1983 by giving 3 H's (Hypocellularity, Hypovascularity and Hypoxia) involved in the pathogenesis of the disease process.

The use of pentoxyfylline and Vitamin E in the management of ORN has not been studied much, hence this study was conducted to determine the efficacy of both drugs in ORN.[2.3,6]

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Aims and Objectives:
To evaluate the effectiveness of pentoxyfylline and tocopherol (Vitamin E) in the management of Osteoradionecrosis of jaws(ORN) in fifteen patients in terms of clinical relief of symptoms and radiographic presentation.

Material and Method:
The present study was done in the Department of Oral & Maxillofacial Surgery, Govt. Dental College & Hospital, Srinagar after explaining the procedure to all the patients in their vernacular language & taking their written informed consent. Total of fifteen patients fulfilling the inclusion criteria were taken and prescribed pentoxyfylline 400mg BD and Tocopherol (Vit E) 1000 IU OD for a mean period of 8-10 months and were evaluated for clinical relief in symptoms and improvement in radiographic presentation.

Inclusion criteria
1. Grade 1 and 2 ORN patients as given by Glanzmann and Gratz 1995.[7]
2. Disease free patient at the time of study.

Exclusion criteria
1. Medically compromised patients.
2. Patients with known allergy to the prescribed drugs or xanthenes.

Results
Of fifteen patients six were female and nine male and all belonged to fourth – fifth decade of life. Five patients belonged to Grade 1 ORN category and ten belonged to Grade 2 ORN category. The eight Grade 1 category patients were provided PENT –E prophylactically whereas others received it as a part of therapeutic drug delivery. All the patients were followed for atleast 10 - 12 months and at the latest follow-up visit eleven out of fifteen patients's demonstrated clinical relief in symptoms. There was radiographic evidence of new bone formation in previous radiolucent areas (areas where sequestrectomy was performed) in 2 patients. Five patients demonstrated complete resolution of exposed bone with soft tissue healing, three with partial resolution of bone exposure whereas three patient demonstrated no change in bone exposure .One patient developed allergy to pentoxyfylline and discontinued it,however it was not documented because of lack of sufficient evidence and was put on tocopherol alone. Both the drugs were well tolerated by all other patients.

Discussion
Osteoradionecrosis was first noted in 1920's by Regaud as a serious complication of head and neck cancers.[5] It was defined by Marx in 1983 as an area greater than 1cm of exposed bone in a field of radiation that has failed to show any evidence of healing for at least 6 months.[2] The definition was later amended by Harris in 1992 as "exposed and necrotic bone associated with ulcerated or necrotic surrounding soft tissue which persists for more than 3 months in an area that has been previously irradiated and is not caused by tumour recurrence. The pathophysiology of ORN was given by Marx in 1983 as the hypoxic– hypocellular–hypovascular theory until Delanain and Lefaix proposed the fibro-atrophic theory in 2004 which states that irradiation results in activation and dysregulation of fibroblasts, which cause fibro-atrophy of cellular bone marrow. Delanain et al suggested two pathways for this radiation induced fibrosis – the Gradual hypoxia and Stromal theory.[8-9]
ORN occurs most commonly in the mandible, this most likely occurs due to the limited blood supply and higher mandibular bone density. Also, in contrast to the mandible, maxilla has a high number of vascular anastomosis and is usually restricted from the irradiation field. ORN

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has a definite male predominance explained by significantly greater consumption of alcohol and tobacco by the same resulting in associated malignancies and thereby ORN as side effect.[10,11]

The goal of treatment of ORN is aimed at- removal of necrotic bone and enhancement of vascularity of remaining radiation damaged tissues.[3] Steps in the management of ORN include conservative measures such as antibiotic therapy, debridement, and irrigation, whereas for advanced cases surgical resection and reconstruction are done.[6] The use of HBO as an adjunct in the management of ORN had been advocated widely because of its multiple properties including hyper oxygenation of ischemic tissues, down –regulation of inflammatory cytokines, neo-vascularisation and leucocytic effect, however its limited availability, cost factor and no significant additional benefit has led to development to several other measures like use of pentoxyfylline and tocopherol drug regime as both the drugs directly counteract the proposed fibroatrophic pathogenesis of ORN[12] .

Pentoxifylline was originally approved by the FDA for the management of peripheral artery disease such as ischemic heart disease and intermittent claudication.[8] it improves peripheral blood flow by enhancing vasodilation, reducing blood viscosity and increases erythrocyte flexibility[13]. It also induces anti-tumor necrosis factor alpha (anti-TNFα) effects, inhibiting inflammation and decreasing fibrosis[14-16]. Tocopherol is a potent oxygen radical scavenger that reduces free radical damage generated during oxidative stress and protects cell membranes[17]. It also reduces inflammation and tissue fibrosis.[18,-20] Pentoxifylline and tocopherol combined have been shown to have a synergistic effect on the regression of ORN.[21]

In the present study, combined therapeutic effect of pentoxyfylline and tocopherol was found to have significant improvement in clinical relief of symptoms and radiographic presentation of patients with ORN. Eleven out of fifteen patients reported with complete resolution of symptoms associated with exposed necrotic bone and soft tissue healing. There was complete soft tissue closure and healing of necrotic bone in five patients, partial healing of bone and soft tissue in three patients and apparent cessation of disease process in three patients.

Conclusion:

Pentoxifylline and Tocopherol is an easy, viable and cost effective treatment modality in patients with osteoradionecrosis, though preventive measures being the priority.

Limitations of the study:

- Fewer patients were included in the study; hence study with larger group of patients needs to be conducted.
- Bias because of adjunctive treatment modalities affects the results.

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