

Prophylactic Use of Pentoxifylline and Tocopherol in Patients Undergoing Dental Extractions Following Radiotherapy for Head and Neck Cancer

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ABSTRACT

Background: In head and neck cancer patients undergoing radiotherapy, osteoradionecrosis (ORN) of the jaw is one of the major but uncommon complications. Satisfactorily results have been observed while treating ORN patients with upcoming treatment modalities such as combination therapy of pentoxifylline and Vitamin E (PVe). It is believed that in patients undergoing dental extractions, these treatment modalities can be used prophylactically for lowering the risk of development of ORN. Hence, keeping all these things in mind, we planned the present study to assess the prophylactic role of pentoxifylline and tocopherol in patients who require dental extractions after radiotherapy for cancer of head and neck. **Materials and Methods:** A total of 110 patients were included in this retrospective study, which had radiotherapy for cancer of the head and neck. After radiotherapy, a total of 450 dental extractions were done in these 110 patients. **Results:** External beam therapy was given in 92.72% of the patients. 7.27% and 40% of the patients received intensity modulated radiotherapy combination of chemotherapy and intensity modulated radiotherapy, respectively. ORN developed only in 2 patients. Patients had taken PVe for a mean of 12 (24) weeks preoperatively and 14 (18) weeks postoperatively. The incidence was lower than that normally associated with dental extractions in irradiated patients. **Conclusion:** In patients undergoing dental extractions, after receiving radiotherapy of head and neck region, combination therapy of pentoxifylline and tocopherol are sufficiently effective.

KEYWORDS: Osteoradionecrosis, pentoxifylline, radiotherapy, tocopherol

INTRODUCTION

The treatment of head and neck cancers remains a major challenge to medical practitioners because of the varied nature of clinic-histological patterns sites of origin, natural history, and varied treatment modalities involving extensive, delicate, and sometimes repeated surgeries, radiotherapy and chemotherapy. Most of the patients require adjuvant therapy in addition to surgery, concurrent chemotherapy or as palliative treatment for head and neck malignancies. Certainly, radiotherapy has been proved to increase cure rates; the irradiated patient is susceptible to secondary effects and a series of potential orofacial complications. One of the nastiest complications is osteoradionecrosis (ORN).^[1]

ORN is a condition of nonvital bone in a site of radiation injury. ORN can be spontaneous, but it most commonly results from tissue injury. The absence of reserve reparative capacity is a result of the prior radiation injury.^[2]

Symptoms can include pain, trismus, bad breath, difficulty with mastication, deglutition, and/or speech, dysgeusia, dysesthesia or anesthesia, pathologic fracture,

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and local, spreading, or systemic infection. It is common in the posterior mandible. Incidence rate has been reported as 11%.^[3]

The etiology of ORN is multifactorial. There is radiation-induced tissue damage. It is most common in mandible. Mandible is supplied by inferior alveolar artery and minor supply from bony attachment. With aging and due to atherosclerotic changes, there is increased dependence on blood supply from these attachments. In an irradiated area such as in case of radiotherapy of head and neck, the source of infection such as periodontal disease or pulpal exposure leads to delay wound healing resulting in ORN.^[4]

Thus, ORN is very common in patients undergoing extraction after radiation therapy. Hence to prevent it, proper care should be taken.

New treatment in the form of pentoxifylline and Vitamin E (PVe) has been introduced pentoxifylline acts as a tumor necrotic factor. Tocopherol scavenges free radicals generated during oxidative stress and protects cell membranes against lipid peroxidation. The combination of these two drugs proved to be synergistic antifibrotic agents.^[5] This article aims to demonstrate the role of pentoxifylline and tocopherol in patients who require dental extractions after radiotherapy for cancer of head and neck.

MATERIALS AND METHODS

This study was conducted in the Oral and Maxillofacial Surgery Department from 2010 to 2015. Ethical permission from Institutional Ethical Committee was taken before the commencement of the study. Consent had been taken from all the patients involved in the study.

The present study included assessment of a total of 110 patients, who had previously undergone radiotherapy for head and neck cancer. After careful clinical and radiographic examination, 450 unrestored teeth, root stumps, periodontally weak teeth of these 110 patients were extracted. Following injection of 2% lidocaine/1:800,000 adrenaline, treatment of all patients was started. Patients were put on a standard regimen of pentoxifylline 400 mg twice daily and tocopherol (Vitamin E) 1000 IU daily, ideally 1 month before extraction, and postoperatively, until the socket healed properly. To analyze the results, patients were categorized as having a high, moderate, or low risk of development of ORN after dental extraction. Extractions on the same side as the primary tumor and in a direct line of the radiation beam, for example, the lower right first molar in a patient with a squamous cell carcinoma (SCC) of the right tonsil, were

considered at high risk. Those on the contralateral side to the primary tumor in an area in line with the radiation beam, for example, the lower left first molar in a patient with SCC of the right tonsil, were considered to have a moderate risk. Those in an area distant from the site of the primary tumor but still within the radiation field, for example, a posterior mandibular extraction in a patient with SCC of the larynx, were considered to have a low risk. In patients who required multiple extractions, we used the classification of the tooth with the highest risk. All the results were recorded and analyzed.

RESULTS

Results showed that out of total 110 patients, who underwent extractions after radiotherapy of head and neck region, 70 were male and 40 were female. Out of total 110 patients, 290 mandibular teeth and 160 maxillary teeth were extracted for various reasons cited in Table 1. It has been found that radiation caries is the main reason behind the extraction of teeth followed by apical periodontitis and periodontal diseases.

Most of the primary tumors were in the oropharynx region 36 (32.73%) and oral cavity 26 (23.64%), whereas few of them occurred at hypopharynx 17 (15.45%), nasopharynx 14 (12.73%), and other sites 17 (15.45%).

All the 110 patients received radiotherapy. One hundred and two (92.72%) patients underwent external beam therapy and 8 (7.27%) had intensity modulated radiotherapy whereas 44 (40%) patients also received a combination of chemotherapy and intensity modulated radiotherapy.

Patients who have undergone radiotherapy were at high risk to develop ORN. These patients were categorized into high, moderate, and low depending on the level of risk associated. When patients had multiple extractions, all teeth were classified according to those at highest risk [Table 2].

Time interval from radiation to extraction was evaluated in patients who had extraction within 1 year, more than 2 years, and more than 5 years after radiotherapy. Results showed that 6% developed ORN in 1st year and 12% in more than 2 years and 16% in more than 5 years after radiotherapy.

Antibiotics were given preoperatively in 40 patients and postoperatively in 70 patients. Fifty patients were put on a single antibiotic such as penicillin while the remaining 60 patients had dual antibiotics such as penicillin and metronidazole. The mean (standard deviation) duration of PVe was 12 (24) weeks preoperatively and 14 (18) weeks postoperatively.

Table 1: Reasons for dental extractions

Diagnosis	Number of patients (n=110), n (%)
Apical periodontitis	28 (25.45)
Unrestorable caries	12 (10.90)
Periodontal disease	20 (18.18)
Irreversible pulpitis	8 (7.27)
Radiation caries	42 (38.18)

Table 2: Patients on the basis of risk of osteoradionecrosis

Risk of ORN	Number of patients (n=110)	Number of who had chemotherapy (n=44)	Total extractions (n=450)
High	38	16	248
Moderate	32	7	104
Low	40	21	98
Total	110	44	450

ORN: Osteoradionecrosis

DISCUSSION

ORN is one of the serious complications of radiation therapy. The hallmark of the disease includes the presence of exposed bone in an irradiated area which fails to heal with a time period of 3 months.^[6] Various risk factors which increase the chances of development of ORN includes:

- Dose of external beam radiation above 50 gray units
- Delivery of large dose in a comparatively short period
- Irradiation in less vascularized parts such as posterior part of the mandible
- Any surgical procedure performed after radiotherapy.^[7]

In ORN, there is hypocellularity, hypoxia and hypovascularity. There is damage to microvesiculation, resulted in initial hyperemia followed by endarteritis, thrombosis, and obliteration.^[8]

Several protocols have been proposed to reduce the risk of ORN after dental extractions, of which the two most commonly quoted are antibiotic prophylaxis, and hyperbaric oxygen therapy (HBOT). Thirty HBOT dives to 2.4 atmosphere for 90 min has been proposed.^[9]

Hence, we planned the present study to assess the prophylactic role of pentoxifylline and tocopherol in patients who require dental extractions after radiotherapy for cancer of head and neck.

In the present study, only one patient developed ORN. According to a study conducted by Marx *et al.*^[10] of 37 patients in hyperbaric oxygen group and 11 of 37 in antibiotic group develop ORN. Nabil and Samman^[11] estimated a rate of 4% for the development of ORN after

HBOT and 6% after antibiotic treatment. However, in reality, HBOT is not practical, as it requires 30 sessions in a compression chamber, each lasting 90 min, and a further series of 10 sessions is also usually required after the extraction.

Patel *et al.* in 2016 reported the following effects of pentoxifylline:^[12]

1. It raises intracellular cyclic adenosine monophosphate, activates protein kinase A, inhibits tumor necrosis factor (TNF) and leukotriene synthesis, and reduces inflammation and innate immunity improves red blood cell deformability reduces blood viscosity and decreases the potential for platelet aggregation and thrombus formation
2. Pentoxifylline exerts an anti-TNF- α effect
3. It increases erythrocyte flexibility, vasodilates, inhibits inflammatory reactions *in vivo*, inhibits human dermal fibroblast proliferation and extracellular matrix production, and increases collagenase activity *in vitro*^[2]
4. Pentoxifylline and its metabolites improve blood flow by decreasing its viscosity.

Tocopherols are a class of organic chemical compounds consisting of various methylated phenols, many of which have Vitamin E activity. Its vitamin activity was identified in 1936 as a dietary fertility factor in rats. Following are the functions of tocopherols:^[13]

1. It scavenges the reactive oxygen species generated during oxidative stress that escape the activity of *in vivo* antioxidant enzymes, to protect cell membranes against lipid peroxidation
2. It partly inhibits transforming growth factor-beta and procollagen gene expression thus reduces fibrosis.

The combination of pentoxifylline and tocopherol has been proven effective both in prevention and treatment of ORN by Delanian and Lefaix.^[13] They act synergistically and have potent anti-fibrotic action. With the emergence of fibroatrophic theory which explains the pathogenesis of ORN, this drug combination reduces fibroatrophic changes in tissues and enhances wound healing by stimulating defective osteoblasts.^[14]

In this study, patients were put on a standard regimen of pentoxifylline 400 mg twice daily and tocopherol (Vitamin E) 1000 IU daily, 1 month before extraction, and postoperatively, until the socket had healed. Delanian *et al.*^[15] treated 18 patients with ORN using pentoxifylline and tocopherol, with (8 patients) and without (10 patients) the addition of clodronate (new generation bisphosphonate that inhibits bone resorption by reducing the number and activity of osteoclasts). Complete healing of mandibular ORN was seen at

6–8 months for 89% of the total sample. Prophylactic use of PVe may help to prevent ORN when dental extractions are required.

The present study showed that 6% patients developed ORN in 1st year and 12% in more than 2 years and 16% in more than 5 years after radiotherapy. This consistent increase in the risk of ORN over the period of time has also been reported by Nabil and Samman^[11] who demonstrated that the incidence of 8% at 1 year after radiotherapy ascended to 16% after 2 years.

Only 10 (9%) patients subjected to PVe in our study demonstrated adverse effects such as nausea, headache, and gastric irritation. Patel *et al.*^[12] reported that 7% of their patients could not tolerate one or other of these medications. Literature has also revealed few side effects of these drugs, which include dyspepsia, nausea, headache or vertigo, asthenia, hot flushes, epigastralgia, and allergy in some patients.^[12-15] Rice *et al.* reported that for the treatment of advanced cases of ORN, surgical treatment, including microvascular reconstructive techniques, remains the only reliable treatment option available.^[16] The efficacy of HBOT in treating ORN varies considerably as reported by Costa *et al.*^[17] Gevorgyan *et al.* advocated conservative approach for treating early cases of ORN while radical resection approach for more advanced cases.^[18]

CONCLUSION

For the prevention of development of ORN, pentoxifylline and tocopherol can be used safely as a prophylactic measure in patients undergoing extractions of head and neck cancer patients. These are newer drugs that are readily available, well tolerated, pain diminishing, and cost-effective. However, large scale studies are required to substantiate the results.

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Conflicts of interest

There are no conflicts of interest.

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