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A SYSTEMATIC REVIEW ON ADVERSE EFFECTS FOLLOWING ADMINISTRATION OF PENTOXIFYLLINE,TOCOPHEROL FOR MEDICAL MANAGEMENT OF OSTEORADIONECROSIS

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ABSTRACT

Exposure of bone to ionizing radiation results in devitalization of facial skeleton and necrosis of overlying soft tissues. The incidence of osteoradionecrosis ranges from 2% to 22% 1. It usually presents with symptoms ranging from pain, difficulty in chewing, trismus, non-healing ulcers, fistulas to extensive osteolysis resulting in a deterioration of quality of life1. Anatomically, head and neck is particularly more susceptible to Osteoradionecrosis. The mandible appears to be most commonly affected structure owing to factors such as relatively poor vascularity within this region, thin soft tissue coverage, mechanical stress and remodelling within this region due to masticatory forces3. Pentoxifylline has traditionally been used in the treatment of peripheral vascular and cerebrovascular diseases owing to its vasodilatory properties as well as anti-tumour necrosis effects.2In vivo studies have shown pentoxifylline to inhibit inflammatory reactions, increase erythrocyte flexibility thereby decreases viscosity of blood resulting in reduced potential for clotting1. Pentoxifylline has also shown to inhibit neutrophil adhesion and the production of some cytokines, such as TNF-α and IL-1 Vitamin E (Tochopherol) has proven antioxidant effects that is effective in preventing lipid peroxidation which Is driven by free radical formation.4 This has potential effects in reducing the risk of coronary artery disease ,atherosclerosis and some cancers. This systematic review has been designed to address the medical management options and its outcomes with respect to the adverse effects in treating mild and moderate stages of osteoradionecrosis

KEYWORDS

INTRODUCTION:

Osteoradionecrosis of jaws, which was first reported in 1920s,is one among the commonly encountered complication following radiotherapy to head and neck region which can be debilitating as well as disfiguring to facial skeleton even in this era. Osteoradionecrosis (ORN) of the mandible is a disease of devitalized bone that occurs as a consequence of radiation therapy for oral and oropharyngeal cancers.Exposure of bone to ionizing radiation results in devitalization of facial skeleton and necrosis of overlying soft tissues. The incidence of osteoradionecrosis ranges from 2% to 22% [1]. The symptoms ranges from pain, difficulty in chewing, trismus, non-healing ulcers, fistulas to extensive osteolysis resulting in a deterioration of quality of life[2].

The mandible appears to be most commonly affected structure owing to factors such as relatively poor vascularity within this region, thin soft tissue coverage, mechanical stress and remodelling within this region due to masticatory forces[3].Multiple risk factors predispose to its development that includes treatment-dependent factors like radiotherapy (dose, volume,brachytherapy);surgery (number, volume, hematoma,infection) and concomitant chemotherapy; and patient dependent factors including age,hypersensitivity, high blood pressure, diabetes and collagen vascular disease.[(4)]

Pentoxifylline is the most common drug of choice in the medical management of osteoradionecrosis.Pentoxifylline is a methylxanthine derivative that exerts an Anti-TNF alpha effect,increases flexibility of erythrocytes,dilates blood vessels and inhibits inflammatory reaction in vivo.It is administered with tochopherol (Vitamin E),which scavenges the reactive free radicles. These drugs work synergestically to reduce fibrosis[(6)]. In a randomized placebo-controlled trial, the use of combination of these two drugs showed significant improvement in radiation induced fibrosis.

Owing to its high success rate in treatment of osteoradionecrosis,it has been solely relied upon for treatment of osteoradionecrosis.As there are very few reports of adverse effects following administration of pentoxifylline, This systematic review has been designed to address the adverse effects following medical management of osteo radionecrosis using pentoxifylline and tochopherol.

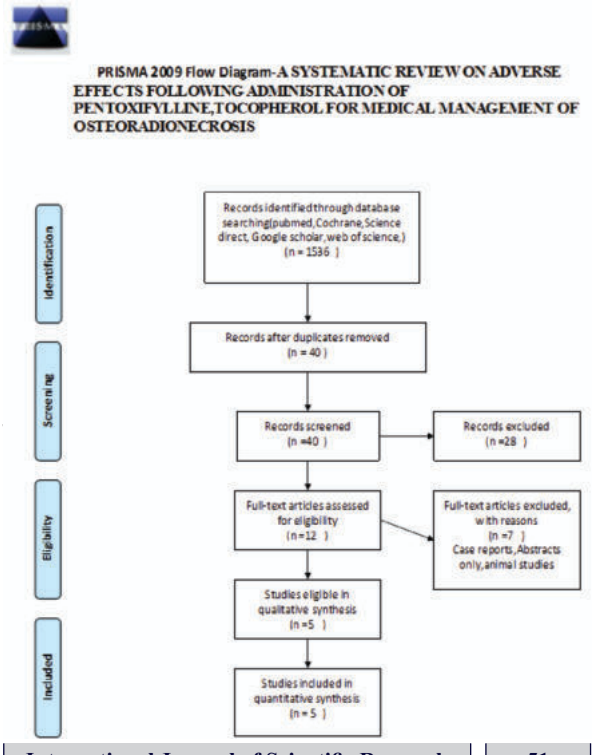
Research Design And Methods:

Inclusion Criteria:

The study sample included all articles on use of pentoxifylline and tochopherol (with or without clodronate) for management of osteoradionecrosis which was published between 2000-2021.

The inclusion criteria were full length articles and case series studies, Cohort studies, RCTs,retrospective studies on the treatment of ORN of jaws in humans.

Exclusion criteria were case reports, animal studies,in vivo studies, studies that combine surgical management of Osteordionecrosis along with conservative management.



Literature Search And Selection Criteria:
A computer database search of PubMed, Web of Science, Cochrane library,Google scholar was performed to select studies based on inclusion criteria for the study. A search stratergy was developed for PubMed using MeSH words (drug therapy, therapy) and BOOLEAN search was revised appropriately for each database.

Methods Of Review:
Three reviewers R1, R2, R3 independently screened titles and abstracts to identify articles that closely met the inclusion criteria. From these selected articles, full text versions were fetched and screened by the reviewers to determine whether they met inclusion criteria. Disagreements about whether the inclusion criteria were met were resolved through discussion among reviewers.

RESULTS:
In a study conducted by Vinod patel,Yusuf Gadiwalla,Isabel Sassoon et al on prophylactic use of pentoxifylline and tochopherol in patients who require dental extraction after radiotherapy for cancer of head and neck,a total of 82 patients (58 men, 24 women) who had 390 extractions were included. All patients had radiotherapy to the head and neck. Patients were started on the standard regimen of pentoxifylline 400 mg OD and tocopherol 1000 IU daily one month before extraction, and postoperatively, until the socket had healed.6 patients were unable to tolerate the combination of pentoxifylline and tocopherol so 2 patients had pentoxifylline alone, and 4 patients tocopherol alone. The adverse effects reported were gastric irritation, nausea, disturbed vision, difficulty in swallowing[1].

A study was conducted by Raissa Soares, Giovana Noberega et al on Pentoxifylline, tocopherol and sequestrectomy are effective for management of advanced osteoradionerosis of jaws;25 patients were included in the study.3 patients were identified with adverse effects. Palpitations, Upper gastrointestinal discomfort were reported.[5]

Alexis Dissard, et al., demonstrated the Efficacy of Pentoxifylline–Tocopherol–Clodronate in Mandibular Osteoradionecrosis. Twenty-seven patients with mandibular ORN following upper-airway cancer treatment were included in this study.4 patients reported with adverse effects such as maculopapular exanthema immune allergic taxidermy, diarrhea,epigastralgia, asthenia,nausea and insomnia.[7]

Sylvie Delanian et.al, in a PHASE II TRIAL demonstrated a complete restoration of refractory mandibular osteoradionecrosis by prolonged treatment with a pentoxifylline-tocopherol-clodronate combination (PENTOCLO). The study included 80 patients with head and neck cancer and 27 patients with miscellaneous ORN.12 patients reported with severe adverse effects such as nausea,epigastralgia, asthenia, headache, vertigo,insomnia.[2]

Matthew S. Epstein et al performed a case series in the Management of bisphosphonate-associated osteonecrosis pentoxifylline and tocopherol in addition to antimicrobial therapy. 6 cases were included among that five patients were female and 1 was male and no averse effects were reported.[7]

None of the studies reported serious adverse events and all the

STUDY	TYPE OF STUDY	NO OF PATIENTS IN THE STUDY	NO OF PATIENTS WHO REPORTED WITH ADVERSE EFFECTS	MEAN AGE GROUP	ADVERSE EFFECTS	ANY DOSAGE IF MENTIONED	RESOLUTION OF EFFECTS IF NOTED
1.Prophylactic use of pentoxifylline and tocopherol in patients who require dental extraction after radiotherapy for cancer of head& neck;Vinod patel,Yusuf Gadiwalla,Isabel Sassoon et al.	Prospective observational study	82	6 (7%)	55 (range 17-83 yrs)	Gastric irritation(3.6%),nausea,disturbed vision,difficulty in swallowing	Pentoxifylline-400mg Tocopherol-1000mg	
2.Pentoxifylline,tocopherol and sequestrectomy are effective for management of advanced osteoradionerosis of jaws- A case series; Raissa Soares Dos Anjos, Giovana Noberega de padua Walfrido,Luiz Alcino Gueiros et al.	Retrospective study	25	3 (12%)	58.6 (Range 30-83yrs)	Palpitations(8%), Upper gastrointestinal discomfort(4%)	Pentoxifylline-400mg Tocopherol-400mg	
`3.Efficacy of Pentoxifylline,Tocopherol-Clodronate in mandibular Osteoradionecrosis;Alexis Dissard MD;Nathalie P Dang;Isabelle Barthelemy;Candice Delbt et al.	Prospective study	27	4 (14.8%)	63.6 (Range 45-93 yrs)	Maculopapular exanthema immune allergic taxidermy(14.8%), diarrhea (22.2%),epigastralgia(11.1%), asthenia(11.1%), nausea (7.4%) and insomnia(3.7%)	Pentoxifylline-400mg Twice daily; Tocopherol-500mg Twice daily; Clodronate-800mg Twice daily	
4.Complete restoration of refractory mandibular osteoradionecrosis by prolonged treatment with Pentoxifylline-Tocopherol-Clodronate Combination- A Phase II trial; Sylvie Delanian,Cecile Chatel, Raphael Porcher,Joel Depondt et al	RCT	54	12 (22%)	59 Range(30-81yrs)	Nausea(7.4%),Epigastralgia(7.4%),Asthenia(3.7%),headache(1.8%),Vertigo((1.8%),Insomnia(1.8%)	Pentoxifylline-400mg Twice daily Tochopherol-500IU Twice daily Clodronate-1600mg	Complete resolution in all patients
5.Management of Bisphosphonate associated osteoradionecrosis:Pentoxifylline and tocopherol in addition to antimicrobial therapy: An initial case series; Matthew S. Epstein, Fredrick W. Wicknick et al	Case series	6	Nil	75 Range (55-90yrs)	No adverse effects identified	Pentoxifylline-400mg Tochopherol-400mg	

recorded adverse effects were mild/ moderate. Nausea, Insomnia and GI discomfort were reported commonly in most of the studies.

DISCUSSION:

Osteoradionecrosis is a complication noted in patients who have undergone radiotherapy to the head and neck.The current advances in head and neck oncology, has concomitantly increased the use of chemoradiation; and results of treatment of Osteoradionecrosis with pentoxifylline and tocopherol have been a hopeful prospect. Thus, some authors argue that this should be used prophylactically to lower the risk of ORN after dental extractions in this group. Pentoxifylline and tocopherol has been reported to be associated with some adverse effects.[1]

The exact pathophysiological sequence suggested by Marx is: irradiation; formation of hypoxic-hypocellular hypovascular tissue; and breakdown of tissue (cellular death and breakdown of collagen that exceeds cellular replication and synthesis) driven by persistent hypoxia that can cause a chronic non-healing wound (a wound in which metabolic demands exceed supply) Marx's initial proposal of hypoxia, hypo vascularity and hypo cellularity theory, leading to a non-healing wound has recently been challenged and Is not supported by subsequent studies [8]. In 2004,Delania et al, introduced the radiation induced fibroatrophic process. Based on this theory, a new theory for the pathogenesis of ORN has proposed that damage to bone is caused by radiation-induced fibrosis. Cells in bone are damaged as a result of acute inflammation, free radicals,chronic activation of fibroblasts by a series of growth factors,microvascular thrombosis, remodelling and finally bone tissue necrosis. The group then developed an etiological treatment based on RIF theory and concluded in phase 2 trial that the condition regresses with antioxidant treatment, specifically with combination of pentoxifylline and tocopherol[9].

Pentoxifylline has traditionally been used in the treatment of peripheral vascular and cerebrovascular diseases owing to its vasodilatory properties as well as anti-tumour necrosis effects.[2]Many studies have shown pentoxifylline to inhibit inflammatory reactions, increase erythrocyte flexibility thereby decreases viscosity of blood resulting in reduced potential for clotting[1]. Pentoxifylline has also shown to inhibit neutrophil adhesion and the production of some cytokines, such as TNF-α and IL-1. Reduction in TNF-α production has been shown to be an important mechanism by which PTXF protects against ischemic injury; this has been shown to occur both in vitro and in vivo[10].

Vitamin E (Tochopherol) has proven antioxidant effects that is effective in preventing lipid peroxidation which is driven by free radical formation. This has potential effects in reducing the risk of coronary artery disease, atherosclerosis and some cancers.[11,12]

About 1365 articles were screened out of which 12 articles were eligible for full text screening reviewed and 4 articles showed evidence of adverse events. Most common adverse effects were upper gastrointestinal discomfort, nausea, Epigastralgia, diarrhea, headache, asthenia,insomnia.

Vinod patel et.al. Proposed that PVe may act as a prophylactic agent to reduce the risk of necrosis after dental extractions. In his study, A total of 82 patients (58 men, 24 women) who had 390 extractions were included. All patients had radiotherapy to the head and neck. Patients were started on the standard regimen of pentoxifylline 400 mg OD and tocopherol 1000 IU daily one month before extraction, and postoperatively, until the socket had healed. Patients in the study were divided into three risk categories for ORN following dental extraction: high, moderate, and low. Six patients were unable to tolerate the combination of pentoxifylline and tocopherol so 2 patients had pentoxifylline alone, and 4 patients tocopherol alone. 3 patients had extractions in a high-risk area, 5 in a moderate-risk area, and one in a low-risk area. This study concludes that PVe is simpler, cheaper, better tolerated and could result in a lower incidence of ORN after extraction, also if an established regimen can be formulated, patients may need less radical dental treatment before radiotherapy, which would considerably improve their quality of life.[1]

Matthew S. Epstein et al performed a case series in the Management of bisphosphonate-associated osteonecrosis pentoxifylline and tocopherol in addition to antimicrobial therapy. 6 cases were included among that five patients were female and 1 was male. Four patients had a history of cancer and 2 had a history of severe osteoporosis. In one case, symptoms and bone exposure increased following initial improvement with PT and tocopherol when these agents were discontinued for 3 months, and improved upon resuming these agents. All patients were without pain, erythema, or purulence following initiation of treatment with PT. The medications were well tolerated with no adverse effects identified. Potential comorbid risk factors were present in 4 patients and included use of tobacco, prednisone, lenalidomide, and lack of oral hygiene. The findings in the 6 patients who were treated with PT here suggest that this drug combination with antimicrobial agents may have utility in the medical management of BON. The patients in this series improved with the introduction of PT and tocopherol without noticeable adverse effects which satisfies the aim of our study.[7]

SYLVIE DELANIAN et.al, in a PHASE II TRIAL demonstrated a complete restoration of refractory mandibular osteoradionecrosis by prolonged treatment with a pentoxifylline-tocopherol-clodronate combination (PENTOCLO). The study included 80 patients with head and neck cancer and 27 patients with miscellaneous ORN. 43 male patients had a history of tobacco and alcohol consumption, showed no evidence of recurrent disease on entering the trial. All patients had combined symptoms as local pain or minimal infection, but 36/54 patients had one or more combined severe symptoms such as skin fistula in 16, chronic osteitis in 23, facial edema in 6, fracture without shifting in 8, and inferior dental neuropathy in 12. Fifty-four patients had very severe ORN. No patient stopped the treatment because of an adverse event. 12 patients experienced minimal adverse effects nausea-epigastralgia (4), asthenia (2), Headache (1), vertigo (1), insomnia (1). After stoppage of PENTOCLO, no rebound exposed bone osteonecrosis (EB-orn) effect was observed. All patients responded to treatment and symptom severity diminished, which was assessed by the SOMA score. The study findings also show that none of the drugs included in PENTOCLO proved able to reverse ORN. PENTOCLO allowed rapid and definitive mucosa and skin healing in mandibular ORN patients and slow progressive new bone formation. PENTOCLO long-term safety in this study was good and seems to be safe. This study concludes that PENTOCLO effectively reduces progressive septic mandible ORN. The impressive and rapid clinical recovery achieved suggests that theory and practice could be the basis of ORN management in the future. PENTOCLO, an etiology-based treatment, improves prognosis; inexpensive, well tolerated, and safe.[2]

Another case series by Raíssa Soares dos Anjos et al on stated that "Pentoxifylline, tocopherol, and sequestrectomy are effective for the management of advanced osteoradionecrosis of the jaws". Twenty-five patients diagnosed with osteoradionecrosis of the jaws treated with pentoxifylline 400 mg + tocopherol 400 mg three times daily were evaluated. Squamous cell carcinoma was the most common diagnosis followed by adenoid cystic carcinoma. The tongue was the most common tumor site followed by the floor of the mouth. Fifteen patients received PENTO for more than 6months. PENTO was well-tolerated, although two patients reported palpitations and another one reported upper gastrointestinal discomfort.[5] PENTO led to complete mucosal healing in 76% (19/25) of the sample. Complete mucosal healing was achieved with PENTO in 9/10 patients, and PENTO with sequestrectomy in 10/19 individuals. Interestingly, all patients who presented partial healing were submitted to sequestrectomy due to advanced disease. The results suggest that the use of PENTO induces oral mucosal healing and may lessen the need for invasive surgical sequestrectomy in both mild and advanced ORN. Also, gender predilection is similar to the head and neck cancer situations. The limitations of the study stated that ORN can also arise with IMRT and to date there is no internationally agreed treatment protocol, the results of the study do points out safe and potentially effective means of at least managing ORN in the short term. Until proper randomized and controlled trials of ORN are not published, the combination of pentoxifylline and tocopherol should be used in the management of ORN, particularly when early diagnosis is possible.

Alexis Dissard, et al., demonstrated the Efficacy of Pentoxifylline–Tocopherol–Clodronate in Mandibular Osteoradionecrosis. Twenty-seven patients with mandibular ORN following upper-airway cancer treatment were included in this study. The treatment protocol comprised two distinct phases. The First, lasted 28 days. It associated ciprofloxacin500 mg oral suspension BD; clindamycin 300 mg, TID; fluconazole 50 mg oral suspension, once daily; prednisone 20 mg, once daily; and omeprazole 20 mg, once daily. The second, therapeutic

phase—PENTOCLO phase began at the end of phase 1. Pentoxifylline 400 mg, BD ; tocopherol 500mg BD; clodronate 800 mg, BD. The end of treatment was determined by a complete clinical cure with all treatment. Follow-up was set at a minimum 2 years. At each consultation, weight, body mass index, alcohol abuse and Smoking status, adherence to treatment, and any adverse effects or ablation of bone sequester (sequestrectomy) were assessed. 15 patients followed treatment until cure. 12 patients were withdrawn from the study. In treatment phase 1, there were four cases of maculopapular exanthema immune-allergic toxidermy, without severity or need to interrupt the implicated treatment. In phase 2, no severe adverse events occurred. 24 patients showed complete adherence to treatment and protocol duration. adverse events comprised diarrhea (22.2%), epigastralgia (11.1%), asthenia (11.1%), nausea (7.4%), and insomnia (3.7%). The study also reported that prophylactic pentoxifylline tocopherol treatment for 11 weeks before and 13 weeks after dental extraction reduced the incidence of mandibular ORN to 1.2%, from the usual 7.41%.The study concludes that, The association of pentoxifylline–tocopherol–clodronate is a new, simple, and safe medical option in the treatment of mandibular ORN. In some cases, PENTOCLO is interesting alternative to difficult and mutilating surgery in irradiated areas. Longitudinal studies are also needed to study long-term effects, as the risk of late recurrence has been little studied.[7]

CONCLUSION OF THE SYSTEMATIC REVIEW:

No serious adverse events were observed and all the observed adverse events were mild/ moderate. Nausea, Insomnia and GI discomfort were seen commonly in most of the studies. These entire study conclusions commonly agree the fact that the use of pentoxifylline and tocopherol in osteonecrosis were safe and has fewer incidences of adverse events. Hence, the results of this systematic review demonstrate that there were successful outcomes with the use of Pentoxifylline and tochopherol with minimal adverse effects.It can be said that PENTOCLO is safely tolerated in patients in treatment of osteoradionecrosis.

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