Journal of Advanced Medical and Dental Sciences Research

@Society of Scientific Research and Studies ***NLM ID:*** *101716117*

Journal home page: www.jamdsr.com doi: 10.21276/jamdsr Indian Citation Index (ICI) Index Copernicus value = 100

(e) ISSN Online: 2321-9599; (p) ISSN Print: 2348-6805

Original Research

Efficacy of pentoxifylline and tocopherol in the management of medication related osteonecrosis of jaw

[1]Sumera Gul, [2]Sarish Latief, [3]Farukh Masoodi, [4]Adil Ahmad Shah

[1,2]Senior Resident, [3]Junior Resident, OMFS, GDC Srinagar, Jammu and Kashmir, India;
[4]Intern, GDC Srinagar, Jammu and Kashmir, India

ABSTRACT:
Introduction: Medication-related Osteonecrosis of jaw (MRONJ) is a significant complication seen in patients receiving anti-resorptive medication resulting in jaw necrosis. The prophylactic and therapeutic use of pentoxyfylline and tocopherol in the management of MRONJ has grown interest because of their efficacy in its management. **Aims and objectives:** Eight initial to established(Stage O – Stage II) cases of MRONJ were provided PENT-E for a mean period of 12-16 months and the efficacy was evaluated in terms of clinical relief in symptoms and radiographic evaluation. **Result:** Seven out of eight cases presented with clinical relief in symptoms and improvement in radiographic presentation whereas one case showed no significant improvement. **Conclusion:** PENT-E could be a safe and effective prophylactic and therapeutic adjunct in the management of MRONJ.

Received: 22 August, 2022 Accepted: 28 September, 2022

Corresponding author: Sumera Gul, Senior Resident, OMFS, GDC Srinagar, Jammu and Kashmir, India

This article may be cited as: Gul S, Latief S, Masoodi F, Shah AA. Efficacy of pentoxifylline and tocopherol in the management of medication related osteonecrosis of jaw. J Adv Med Dent Scie Res 2022;10(10):109-112.

INTRODUCTION

Marx (2003) first reported MRONJ as a complication in patients who were on i.v/ oral bisphosphonates.The term BRONJ was replaced with MRONJ in 2009 by the American Association of Oral & Maxillofacial Surgeons(AAOMS)to include other anti-resorptive (Denosumab) and anti-angiogenic(Sunitinib) medications in the group producing similar effects and it was defined as "exposure of portion of jaw bone in patients who have been exposed to bisphosphonates other related medication that has persisted for more than 8 weeks with no history of radiation therapy to the jaws".[1]Based on definite clinical signs and symptoms,MRONJ has been classified into 4 stages. The widespread use of anti-resorptive medications has led to increased number of MRONJ cases worldwide.The most common presentation in such patients is non- healing extraction sockets after tooth extraction or exposed necrotic bone with radiographic evidence of sequestrum formation with/without localised swelling and infection.[2]Although the pathophysiology of MRONJ remain doubtful, it is mostly believed to be multifactorial and several mechanisms for the same have been proposed which include alteration in bone remodelling, inhibition of angiogenesis, infection and suppression of immunity. Their is stage- specific management of MRONJ,although again largely controversial.[3-6]However the use of pentoxyfylline and tocopherol in prophylactic and therapeutic manner for the management of MRONJ has been studied less and hence this study aims to evaluate the efficacy of these drugs in the management of osteonecrosis caused by drugs.

AIMS & OBJECTIVES

To evaluate the efficacy of pentoxyfylline and tocopherol(Vitamin E) in the management of Medication-related Osteonecrosis of jaws(MRONJ) in eight 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 eight patients fulfilling the inclusion criteria were taken and prescribed pentoxyfylline 400mg BD and Tocopherol

(Vit E) 1000 IU OD for a mean period of 12-16 months and were evaluated for clinical relief in symptoms and improvement in radiographic presentation.

INCLUSION CRITERIA

1. Stage 0, I, II or III MRONJ patients as defined by AAOMS Position Paper -2014 Update.
2. Disease free jaws at the time of study.
3. Patients in an age group of 20-70 years.

EXCLUSION CRITERIA

1. Stage X(Patients taking anti-resorptive drugs and are at risk of developing MRONJ).
2. Patients with history of external radiation therapy to the jaws.
3. Patients with history of surgical intervention to the jaws in the past 6 months.
4. Medically compromised patients.
5. Patients with known allergy to the prescribed drugs or xanthenes.

RESULTS

Of eight patients- Two patients belonged to Stage 0 MRONJ category, two belonged to Stage I category, three Stage II category and one Stage III category. The two Stage O category were provided PENT –E prophylactically whereas others received therapeutic drug delivery. All eight patients were followed for atleast 12 -16 months and at the latest follow-up visit seven out of eight patients 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. One patients demonstrated complete resolution of exposed bone with soft tissue healing, one with partial resolution of bone exposure whereas one 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

Malignancy such as multiple myeloma and metastases to the bone, a common occurrence in advance-stage disease, may necessitate the use of bone-modifying agents such as anti-resorptive medications, including pamidronate and zolendronate (intravenous bisphosphonates), denosumab (humanized monoclonal antibody) and anti-angiogenics such as sunitinib (tyrosine kinase inhibitor) and bevacizumab (humanized monoclonal antibody).[7-8] BPs and other anti-resorptive therapies may cause serious adverse effects including MRONJ, a subtype of ONJ defined as exposed maxillofacial bone or fistula for at least 8 weeks in a patient receiving anti-resorptive or anti-angiogenic treatment who has no history of radiation therapy or metastatic disease to the jaw.[9]MRONJ lesions can occur in both the mandible and the maxilla, with the mandible being most frequently affected. This most likely occurs due to the restricted localized blood supply to the mandible and the higher bone density in the mandi-ble. Also, in contrast to the mandible, the maxilla has a high number of anastomoses and is usually restricted from the irradiation field.[10–12]While the pathogenesis of MRONJ is still unclear, various risk factors have been identified. These include the duration of medication exposure, type of medication, dental operative treatment, poor dental hygiene, and genetic factors.[13]Clinical management of MRONJ remains controversial, with no established guidelines. Different therapeutic approaches such as chlorhexidine 0.12% -2%rinse, antibiotic therapy,HBO therapy, low level laser therapy, conservative surgery or PRP & pentoxyfylline and tocopherol (PENT-E) have been utilised in the management of MRONJ, with variable success rates.[7,8,14-18]

Pentoxifylline and tocopherol was first used in the management of early ORN as the two agents directly counteracted the proposed fibroatrophic pathogenesis of ORN[19]. Initial studies have shown good results and no significant adverse effects from the medications[14],Pentoxifylline was originally approved by the FDA for the management of peripheral artery disease such as ischemic heart disease and intermittent claudication. It improves peripheral blood flow by enhancing vasodilation, reducing blood viscosity and increases erythrocyte flexibility[20]. It also induces anti-tumor necrosis factor alpha (anti-TNFα) effects, inhibiting inflammation and decreasing fibrosis[21-23]. Tocopherol is a potent oxygen radical scavenger that reduces free radical damage generated during oxidative stress and protects cell membranes [24]. It also reduces inflammation and tissue fibrosis.[25,26]

In the present study,we evaluated the efficacy of pentoxyfylline and tocopherol in the management of medication-related Osteonecrosis of jaws in terms of clinical relief of symptoms and radiographic presentation.All the eight patients included in this study demonstrated clinical relief of symptoms and improvement in radiographic presentation which is in accordance with the initial studies conducted by Adepitan A. Owosho et al, Cavalcante et al and Heifetz-Li JJ. The medication was well-tolerated by almost all the patients with minimal side effects,thereby serving as an inexpensive conservative treatment modality in such patients.

CONCLUSION

The present study reveals that pentoxifylline and tocopherol can serve as a safe, effective and inexpensive treatment modality in the managemen of MRONJ.

LIMITATIONS OF THE STUDY

Fewer patients were included in the study and thereby further studies with a larger group of patients needs to be conducted.

REFERENCES

1. American Association of Oral and Maxillofacial Surgeons Position Paper on Medication-Related Osteonecrosis of the Jaw—2014 Update Salvatore L. Ruggiero, DMD, MD,* Thomas B. Dodson, DMD, MPH, y John Fantasia, DDS,z Reginald Goodday, DDS, MSc,x Tara Aghaloo, DDS, MD, PhD, K BhoomiMehrotra, MD, and FeliceO'Ryan, DDS.
2. Khosla S, Burr D, Cauley J, Dempster DW, Ebeling PR, Felsenberg D, Gagel RF, Gil-sanz V, Guise T, Koka S, McCauley LK, McGowan J, McKee MD, Mohla S, Pendrys DG, Raisz LG, Ruggiero SL, Shafer DM, Shum L, Silverman SL, Van Poznak CH, Watts N, Woo SB, Shane E. Bisphospho- nate-associated osteonecrosis of the jaw: report of a task force of the American Soci-ety for Bone and Mineral Research. J Bone Miner Res 2007;22:1479–91. http://dx.doi. org/10.1359/jbmr.0707onj.
3. Reid IR, Bolland MJ, Grey AB. Is bisphos-phonate-associated osteonecrosis of the jaw caused by soft tissue toxicity? Bone 2007;41:318–20. http://dx.doi.org/10.1016/ j.bone.2007.04.196.
4. Stockmann P, Wehrhan F, Schwarz-Furlan S, Stelzle F, Trabert S, Neukam FW, Nkenke E. Increased human defensine levels hint at an inflammatory etiology of bisphosphonate- associated osteonecrosis of the jaw: an immunohistological study. J Transl Med 2011;9:135. http://dx.doi.org/10.1186/1479- 5876-9-135.
5. Wehrhan F, Hyckel P, Amann K, Ries J, Stockmann P, Schlegel K, Neukam F, Nkenke E. Msx-1 is suppressed in bisphos-phonate-exposed jaw bone analysis of bone turnover-related cell signalling after bis-phosphonate treatment. Oral Dis 2011;17:433–42. http://dx.doi.org/10.1111/ j.1601-0825.2010.01778.x.
6. Pabst AM, Kruger M, Blatt S, Ziebart T, Rahimi-Nedjat R, Goetze E, Walter C. An-giogenesis in the development of medica-tion-related osteonecrosis of the jaws: an overview. Dent J 2016:5. http://dx.doi.org/ 10.3390/dj5010002.
7. Marx RE, Sawatari Y, Fortin M, Broumand V. Bisphosphonate-induced exposed bone (osteonecrosis/osteopetrosis) of the jaws: risk factors, recognition, prevention, and treatment. *J Oral Maxillofac Surg.* 2005;63:1567–1575. [PubMed] [Google Scholar].
8. Watters AL, Hansen HJ, Williams T, et al. Intravenous bisphosphonate-related osteonecrosis of the jaw: long-term follow-up of 109 patientsz. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2013;115:192–200. [PubMed] [Google Scholar].
9. Estilo CL, Van Poznak CH, Wiliams T, et al. Osteonecrosis of the maxilla and mandible in patients with advanced cancer treated with bisphosphonatetherapy. *Oncologist.* 2008;13:911–920. [PubMed] [Google Scholar].
10. Reuther T, Schuster T, Mende U, Ku¨bler A. Osteoradionecrosis of the jaws as a side effect of radiotherapy of head and neck tumor patients—a report of a thirty year retrospective review. Int J Oral MaxillofacSurg 2003;32:289–95.
11. Fullmer JM, Scarfe WC, Kushner GM, Alpert B, Farman AG. Cone beam computed tomographic findings in refractory chronic suppurative osteomyelitis of the mandible. Br J Oral MaxillofacSurg 2007;45:364–71.
12. Koorbusch GF, Fotos P, Goll KT. Retrospec-tive assessment of osteomyelitis, etiology, demographics, risk factors, and management in 35 cases. Oral Surg Oral Med Oral Pathol 1992;74:149–54.
13. Zhong DN, Wu JZ, Li GJ. Association be-tween CYP2C8 (rs1934951) polymorphism and bisphosphonate-related osteonecrosis of the jaws in patients on bisphosphonate ther-apy: a meta-analysis. ActaHaematol 2013;129:90–5. http://dx.doi.org/10.1159/ 000342120.
14. Owosho AA, Blanchard A, Levi L, et al. Osteonecrosis of the jaw in patients treated with denosumab for metastatic tumors to the bone: A series of thirteen patients. *J Craniomaxillofac Surg.* 2016;44:265–270. [PMC free article] [PubMed] [Google Scholar].
15. Lazarovici TS, Yahalom R, Taicher S, et al. Bisphosphonate-related osteonecrosis of the jaws: a single-center study of 101 patients. *J Oral Maxillofac Surg.* 2009;67:850–855. [PubMed] [Google Scholar].
16. Voss PJ, Joshi Oshero J, Kovalova-Muller A, et al. Surgical treatment of bisphosphonate-associated osteonecrosis of the jaw: technical report and follow up of 21 patients. *J Craniomaxillofac Surg.* 2012;40:719–725. [PubMed] [Google Scholar].
17. Stockmann P, Vairaktaris E, Wehrhan F, et al. Osteotomy and primary wound closure in bisphosphonate-associated osteonecrosis of the jaw: a prospective clinical study with 12 months follow-up. *Support Care Cancer.* 2010;18:449–460. [PubMed] [Google Scholar].
18. Pautke C, Bauer F, Otto S, et al. Fluorescence-guided bone resection in bisphosphonate-related osteonecrosis of the jaws: first clinical results of a prospective pilot study. *J Oral Maxillofac Surg.* 2011;69:84–91. [PubMed] [Google Scholar].
19. Delanian S, Lefaix JL. The radiation-in-ducedfibroatrophic process: therapeutic per- spective via the antioxidant pathway. RadiotherOncol 2004;73:119–31.
20. Delanian S, Porcher R, Rudant J, Lefaix JL. Kinetics of response to long-term treatment combining pentoxifylline and tocopherol in patients with superficial radiation-induced fibrosis. *J ClinOncol.* 2005;23:8570–8579. [PubMed] [Google Scholar..
21. Delanian S, Lefaix JL. Current management for late normal tissue injury: radiation-induced fibrosis and necrosis. *SeminRadiatOncol.* 2007;17:99–107. [PubMed] [Google Scholar].
22. Lyons A, Ghazali N. Osteoradionecrosis of the jaws: current understanding of its pathophysiology and treatment. *Br J Oral Maxillofac Surg.* 2008;46:653–660. [PubMed] [Google Scholar].
23. Delanian S, Porcher R, Balla-Mekias S, Lefaix JL. Randomized, placebo-controlled trial of combined pentoxifylline and tocopherol for regression of superficial radiation-induced fibrosis. *J ClinOncol.* 2003;21:2545–2550. [PubMed] [Google Scholar].
24. Delanian S, Porcher R, Balla-Mekias S, Lefaix JL. Randomized, placebo-controlled trial of combined

pentoxifylline and tocopherol for regression of superficial radiation-induced fibrosis. *J ClinOncol*. 2003;21:2545–2550. [PubMed] [Google Scholar].
25. Georges C, Lefaix JL, Delanian S. Case report: resolution of symptomatic epidural fibrosis following treatment with combined pentoxifylline-tocopherol. *Br J Radiol*. 2004;77:885–887. [PubMed] [Google Scholar].
26. Freiberger JJ, Padilla-Burgos R, Chhoeu AH, et al. Hyperbaric oxygen treatment and bisphosphonate-induced osteonecrosis of the jaw: a case series. *J Oral Maxillofac Surg*. 2007;65:1321–1327. [PubMed] [Google Scholar].