

CASE REPORT

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Pentoxifylline and Tocopherol in the Management of Stage III Medication- Related Osteonecrosis of the Jaw: A Case Report

Evre III MRONJ Tedavisinde Pentoksifilin ve Tokoferol Protokolü: Bir Olgu Sunumu

ABSTRACT

The regimen of pentoxifylline and tocopherol (PENTO) has been widely recommended in the prevention and treatment of osteoradionecrosis, however, limited data have been found regarding the efficacy of this protocol in the management of MRONJ. This report aims to present the outcomes of the PENTO protocol in a stage III MRONJ case with a pathologic mandible fracture that was not convenient for surgery.

A 68-year-old male patient with prostate cancer and a 3 year history of intravenous zoledronic acid was referred to our clinic for impaired healing of the extraction site in the mandible in 2018. He was non-cooperated for follow-up and control appointments and 2 years later from the first visit, it was observed that a pathologic fracture occurred in the region. Due to the ongoing chemotherapy of the patient, the PENTO protocol was initiated. At the end of a 7 month period, spontaneous sequestration, healing of the fracture and healing of the mucosa was observed.

Findings of the presented case and current literature suggest that the PENTO protocol may be a promising treatment modality in MRONJ management. However, further clinical and experimental research involving a larger sample size is necessary to clarify the role of this regimen in the treatment of MRONJ.

Key Words:

MRONJ, Pathologic Fracture, PENTO, Pentoxifylline, Tocopherol

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ÖZ

Pentoksifilin ve tokoferol rejiminin osteoradyonekrozun önlenmesi ve tedavisinde olumlu sonuçları bildirilmekle beraber, MRONJ tedavisindeki rolü ile ilgili çalışmaların sayısı limitlidir. Bu vaka raporunda, patolojik mandibula fraktürü gelişmiş ve cerrahi tedavi uygulanamayan bir evre III MRONJ olgusunda PENTO protokolü ile elde edilen sonuçlar sunulacaktır.

68 yaşında prostat kanseri ve 3 yıllık intravenöz zoledronik asit kullanım öyküsü bulunan erkek hasta, 2018 yılında kliniğimize iyileşmeyen çekim bölgesi şikâyeti ile başvurmuştur. Takip ve kontrol bakımından kooperasyon kurulamayan hastada, 2 yıl sonra patolojik mandibula fraktürü gözlenmiştir. Hastanın devam eden kemoterapisi göz önünde bulundurularak, PENTO protokolüne başlanmış, 7 aylık sürenin sonunda hastada spontan sekestrasyon, kırık hattında iyileşme ve yumuşak dokuda kapanma izlenmiştir. Bu vakadan elde edilen bulgular ve mevcut literatür değerlendirildiğinde, PENTO protokolü MRONJ yönetiminde umut vaat eden bir tedavi yaklaşımı olarak düşünülebilir. Bununla birlikte, bu rejimin MRONJ tedavisindeki yerinin daha net bir biçimde aydınlatılması için, daha geniş hasta gruplarını içeren ileri klinik ve deneysel araştırmalara ihtiyaç vardır.

Anahtar Sözcükler:

MRONJ, Patolojik Fraktür, PENTO, Pentoksifilin, Tokoferol

INTRODUCTION

In 2014, the American Association of Oral and Maxillofacial Surgeons (AAOMS) defined MRONJ (Medication-related osteonecrosis of the jaw) as *"the presence of open necrotic bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region for more than eight weeks, which is seen in patients treated with radiation therapy or antiresorptive or antiangiogenic agents without a history of significant metastatic disease in the jaws"* (1-2). The AAOMS recommends symptomatic conservative treatment with chlorhexidine mouthwash and antibiotics and limited local debridement in the treatment of stages 0-II. In the literature, the treatment of stage III MRONJ with inferior border involvement with or without pathological fracture is still controversial (3-5). The use of pentoxifylline (PEN) was first described by Delanian in 2004 in the management of ORN (osteoradionecrosis) (6). Significant symptom improvement was observed in patients with ORN treated with the pentoxifylline and tocopherol (TO) (PENTO) protocol (5,6). Pentoxifylline is a methylxanthine derivative approved by the Food and Drug Administration (FDA) for the treatment of vascular diseases such as intermittent claudication and ischaemic heart disease. It works by improving peripheral blood flow by increasing erythrocyte elasticity and vasodilatation. It also has an antitumour necrosis factor effect and inhibits inflammatory reactions and reduces fibrosis. It probably has an effect on radiation-induced soft tissue necrosis, reducing pain and

accelerating healing. Tocopherol is a powerful antioxidant. It shows its antioxidant properties by inhibition of platelet aggregation. It also disrupts tissue fibrosis (7-9). This report aims to present the outcomes of the PENTO protocol in a stage III MRONJ case with pathologic mandible fracture that was not convenient for surgery.

Case Report

A 68-year-old male patient was admitted to our clinic in November 2018 with the complaint of persistent pain in the mandibular posterior region after a tooth extraction three weeks ago. His medical history was significant for prostate cancer and he had been receiving monthly 4 mg zoledronic acid infusion for three years. Intraoral examination and panoramic radiography revealed a non-healing extraction site (Fig.1).

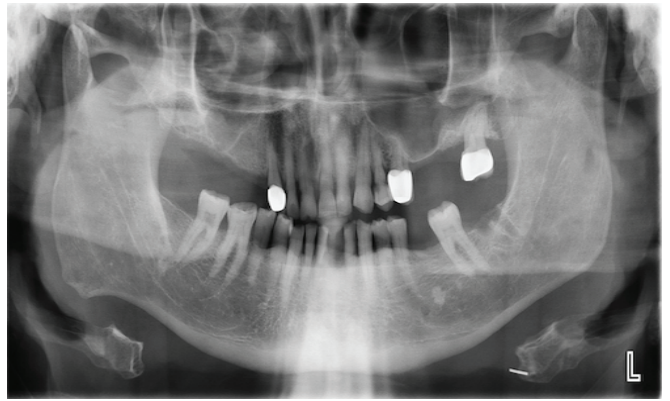


Figure 1. Initial presentation of the patient with unhealed extraction socket.

Upon consultation with his medical doctor, bisphosphonate treatment was suspended. When the patient re-presented to our clinic in October 2019, intraoral examination revealed pain, edema, hyperaemia and an exposed bone area accompanied by pus drainage (Fig.2).



Figure 2. Intraoral bone exposure area.

Panoramic radiography showed a large area of necrosis extending to the ramus on the posterior aspect of the mandible (Fig. 3).

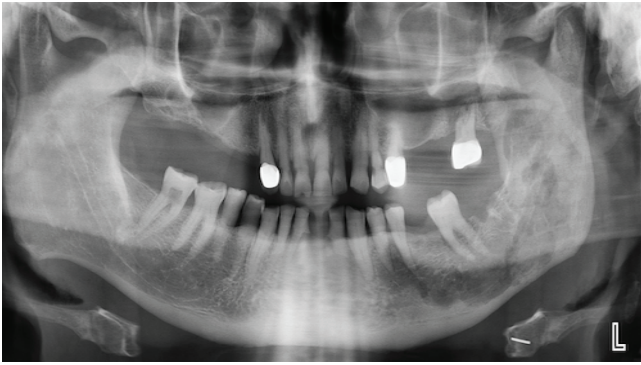


Figure 3. Radiographic image of the osteonecrosis area

Chlorhexidine mouthwash, analgesics and combined antibiotic treatment (amoxicillin + clavulanate and metronidazole) were prescribed for symptomatic treatment. In the following 2 years, the patient did not attend the follow-up visits regularly and a pathological fracture was observed on the radiograph taken in November 2020 (Fig. 4).

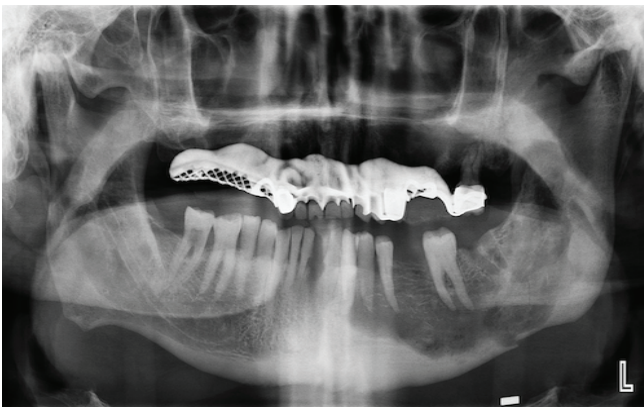


Figure 4. Pathological fracture of the mandibular angulus.

During this period, the patient was not suitable for surgery due to the ongoing chemotherapy regimen. In November 2021, in addition to antibiotic treatment, PEN 400 mg (TRENTILIN 400 mg Retard, Santa Pharma, İstanbul, Türkiye) and TO 400 IU (EVICAP Forte 400 IU, Koçak Pharma, İstanbul, Türkiye) were administered orally twice daily. The patient tolerated the treatment well, pain and paresthesia decreased rapidly, antibiotics and analgesics were gradually discontinued. At the end of an approximately six months of PENTO use, the clinical and radiological assessment revealed spontaneous healing of the fracture and bone formation and healing of oral mucosa in the necrosis area (Fig. 5 and 6).

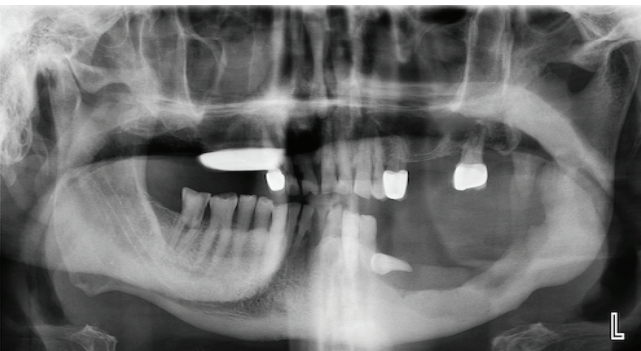


Figure 5. OPG following six months of PENTO use.



Figure 6. Healing of oral mucosa.

DISCUSSION

Currently, MRONJ treatments are largely based on the stage-specific approach described by the AAOMS, the main treatment objectives are to eliminate pain, control infection, and minimize the progression or occurrence of bone necrosis, but there is no consensus on the MRONJ stage III treatment protocol (10).

There are many systematic reviews (10-13) suggesting that surgical treatment is more effective than non-surgical treatment in patients with MRONJ. In these medically compromised stage III patients, a surgical approach may not be desirable or possible. Especially for elderly patients with comorbidities or with (end-stage) metastatic disease, major surgery with resection and reconstruction may not be the treatment of choice.

Pentoxifylline and tocopherol have been previously described for the management of osteoradionecrosis with a significant symptom improvement (14). Plenty of evidence suggests that the PENTO protocol is an inexpensive, safe, and effective treatment for jaw osteoradionecrosis (9).

A systematic review indicated that conservative treatment alone is insufficient to achieve complete mucosal healing in stage III MRONJ; however, conservative treatment may be useful to prevent disease progression in patients in whom surgery is contraindicated (15). In an article by Breik et al. (16), cases of the successful bone union after the use of pentoxifylline and tocopherol to manage grade III osteoradionecrosis of the mandible in 2 patients with pathological fractures and orocutaneous fistulas who were not suitable for surgery were presented. According to a systemic review, non-surgical treatment consisting of systemic antibiotics, pentoxifylline 400 mg, tocopherol in varying doses (400 mg, 500 mg, 400 IU) and 0.12% chlorhexidine rinses 4 times daily significantly improved pain, symptoms and bone exposure in stage 3 MRONJ patients (17-18).

PENTO therapy was reported by Epstein et al. in association with antimicrobial therapy in six patients (4 with cancer and two with osteoporosis) receiving iv bisphosphonate therapy. All lesions resolved in 6 patients who presented

with MRONJ. In these cases, 74% reduction in bone exposure area and release in symptoms were achieved. In a case series of 7 patients with MRONJ in whom PENTO was used, it was suggested that this protocol may be a safe and effective adjunctive treatment modality (19).

Although there are studies showing the benefits of the Pento protocol, various side effects have also been reported. In a meta-analysis, Kolokyttas et al (20). Evaluated 211 patients who underwent the PENTO protocol, it was reported that all patients tolerated the treatment well, and the most frequently reported side effect was gastrointestinal disorders that improved with anti-nausea drugs. In an another study, it was reported gastrointestinal complaints occurred in one of 3 patients using the PENTO protocol (21). Similarly, a case with epigastric pain and nausea was reported following use of PENTO regimen and alternative use of cilostazol was recommended (22).

Possible side effects of the Pento protocol have been associated with PEN and include nausea, epigastralgia, diarrhea, asthenia, insomnia, headache, dizziness, fatigue, chest pain, vision changes, elevation of kidney and liver enzymes (21-22). Pentoxifylline is contraindicated in patients who are pregnant or breastfeeding, acute myocardial infarction, severe cardiac arrhythmias, patients with a history of cerebral haemorrhage, extensive retinal haemorrhage, impaired kidney and liver function, or metastatic disease (23). In this case, in a patient who had a fracture with the enlargement of the necrosis area, PENTO treatment for a short period of time resulted in improvement of symptoms, bone formation in the radiolucent defect area and healing of the pathological fracture, similar to the results in the literature. No side effects were observed during the treatment period. However, since this case is based on the results of a single patient, randomized clinical trials using the same protocol and including more patients are needed.

CONCLUSION

Findings of the presented case and current literature suggest that the PENTO protocol may be a promising treatment modality in MRONJ management. In patients who are medically at risk and not suitable for surgery, the proposed PENTO protocol should be considered as an alternative to interventional treatment.

Author Contribution Statement:

Case preliminary diagnosis and follow-up, article writing: S.E.M., M.D., O.O., A.S., M.A.A.

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Conflict of Interest:

None of the authors mentioned in this case report are or there is no conflict of interest with the organization.

Ethics Committee Approval:

Consent was obtained from the patient. Ethics Committee Approval Certificate was not required.

This case report was presented orally at the 29th International Scientific Congress of the Turkish Oral and Maxillo-facial Surgery Association. Only the abstract was included in the abstract book of the same congress.

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