Original Article

Can topical phenytoin combined with tetracycline enhance the healing process in medication-related osteonecrosis of jaw? A comparative study

ABSTRACT

Introduction: Treatment of Medication-related osteonecrosis of the jaw (MRONJ) is challenging. The aim of this study was to assess the effect of topical phenytoin on the healing process of MRONJ after debridement.

Materials and Methods: In this study, patients with stage II of MRONJ were randomly allocated to two groups: Group 1 received debridement of the necrotic bone, with additional 5% topical phenytoin + tetracycline. Patients in group 2 underwent debridement and the involved area was primarily closed. Patients were evaluated after 1 (T1), 6 (T2), and 12 (T3) months. The presence of wound dehiscence (stage 0: No dehiscence, stage 1: Less than 10 mm dehiscence, stage 2: More than 10 mm dehiscence) and infection (presence or absence of pus and sinus tract) was evaluated. At the 12-month follow-up (T3), the number of patients who were asymptomatic for 3 months was documented in each group.

Results: Twenty patients completed the study protocol (10 patients in each group). At T1 and T3, a significant difference was noted in the stage of healing between the two groups ($P < 0.05$). At T3, nine patients in group 1 and four patients in group 2 were symptom-free for 3 months. ($P = 0.03$).

Conclusion: These results demonstrated that debridement combined with topical administration of phenytoin and tetracycline improved the healing process and relapse rate after treatment in stage II of MRONJ patients.

Keywords: Bisphosphonate-associated osteonecrosis of the jaw, jaw diseases, osteonecrosis, phenytoin

INTRODUCTION

Medication-related osteonecrosis of the jaw (MRONJ) is characterized by an exposed area of bone in the maxillofacial region that is present for more than 8 weeks in a patient who is or has been under treatment with bisphosphonates or other medications disrupting bone's normal metabolisms with no history of radiation therapy. The pathophysiology of MRONJ has yet to be completely understood.[1]

Tooth extraction is considered to be the main initiating factor for MRONJ; but, odontogenic infection, dental implant surgery, local trauma, or spontaneous occurrence are among other causes of this condition.[2] The most controversial topic about MRONJ is its treatment. Various treatment options are available for this condition including drug therapy (antibacterial mouthwashes and systematic antibiotics) and surgical debridement in more severe cases.[3-5] Since the outcome of these treatments is not always satisfactory, new

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methods such as recombinant human parathyroid hormone therapy,[6] laser phototherapy, and platelet concentrates have been suggested for this purpose.[7]

As suggested by many clinical, animal, and *in vitro* studies, phenytoin can enhance the wound healing process.[8,9] Topical phenytoin was used in osteopetrosis patients to enhance bone and soft tissue healing in the mandible.[10] Induction of fibroblast proliferation, enhancing the formation of granulation tissue, decreasing collagenase activity, promoting the deposition of collagen and other connective tissue components, preventing bacterial contamination, and decreasing wound exudate are some of the phenytoin's mechanisms of action for enhancing the healing process.[11,12] Applying topical antibacterial agents through their high local therapeutic levels in bony lesions can enhance the healing process of MRONJ lesions.[13,14] The use of topical tetracycline with its broad-spectrum antibiotic activity could be beneficial in this type of lesion.

The purpose of this study was to answer the following clinical question: Can topical phenytoin enhance the healing process in patients with stage II of MRONJ? We hypothesized that phenytoin could improve the healing process in MRONJ after debridement. The aim of this study was to assess the effect of topical phenytoin on the healing process in Medication-related osteonecrosis of the mandible after debridement.

MATERIALS AND METHODS

The authors designed a comparative study. The sample was derived from the population of patients who presented in the Oral and Maxillofacial Surgery Department (October 31, 2014 to September 1, 2016). The research was approved by the Committee of Medical Ethics (NCT03269214). Patients eligible for inclusion had MRONJ with (a) consumption of bisphosphonates or history of previous treatment with bisphosphonates, (b) exposed necrotic bone in the mandible lasting for more than 8 weeks, (c) no head and neck radiation therapy, (d) Radiographic appearance such as bone destruction, cortical bone erosion, bone sclerosis, sequestration, lamina dura thickening, and persisting alveolar sockets,[15,16] and (E) histopathologically proven osteonecrosis. All patients were in stage II MRONJ (patients had exposed necrotic bone with pain and infection) (according to Medication-Related Osteonecrosis of the Jaw—2014 update, American Association of Oral and Maxillofacial Surgeons) [Figure 1]. Patients were excluded from the study if they had a malignancy in the area, a history of chemotherapy, diabetes mellitus, and HIV or odontogenic infection. Those undergoing dialysis and patients who required internal fixation after local debridement of the lesion were excluded from the study.

All patients underwent surgical necrotic bone debridement in combination with antibiotic therapy (clindamycin 300 mg q8h) for 4 weeks.

The necrotic bone, bone sequestra, and granulation tissue were removed to reach the perfused (bleeding) bone.

Patients who had MRONJ in the mandible were randomly divided into two groups. An independent researcher made random allocation cards using computer-generated random numbers. Then, the cards were placed in sealed envelopes. Group 1 underwent debridement of the necrotic bone consisting of sequestrectomy, soft tissue debridement, and bone curettage, and received 5% topical phenytoin (250 mg/5 ml, phenytoin sodium injection USP, STERI MAX, Ontario, Canada) + tetracycline (tetracycline Najo 1%, Iran). In group 2, patients received surgical debridement and the involved area was primarily closed. Patients were evaluated after one (T1), 6 (T2), and 12 (T3) months [Figures 2 and 3].

The size of the bone lesion was measured using cone-beam computed tomography.

The presence of wound dehiscence (stage 0: No dehiscence, stage 1: Less than 10 mm dehiscence, stage 2: More than 10 mm dehiscence) and infection including pus formation and sinus tract (Yes/NO) were determined.

The number of patients who were symptom-free for 3 months prior to the 12 month follow-up time was documented in each group.

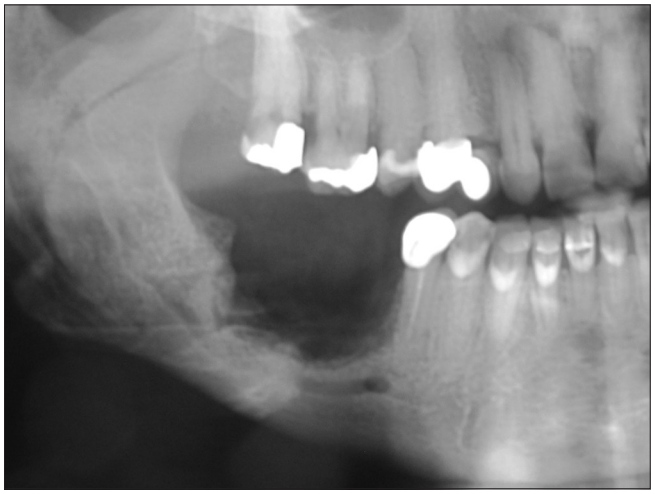

Figure 1: Radiographic view of stage II of MRONJ before treatment

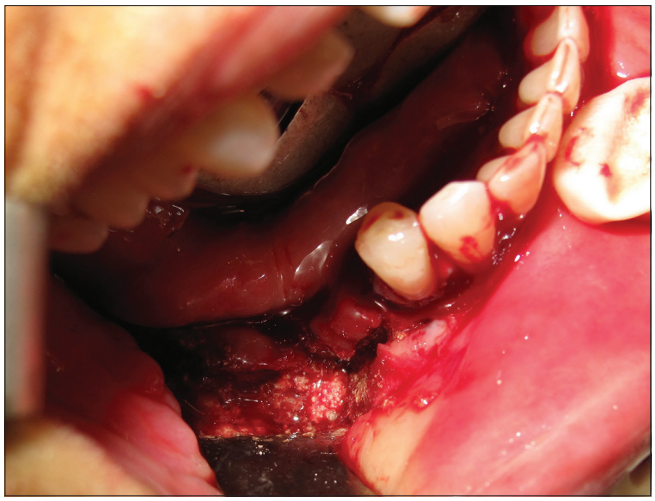

Figure 2: Phenytoin in combination with tetracycline was used after debridement

Patients were evaluated clinically and radiographically in each recall session. Any dehiscence, pus, evidence of bone destruction in the panoramic view, and self-reported pain was documented.

The aim and design of the study and the surgical procedure were thoroughly explained to the patients, and written informed consent was obtained from all participants. Moreover, this study was performed according to the principles outlined by the World Medical Association's Declaration of Helsinki on experiments involving human subjects, as revised in 2000.

The soft tissue healing on the necrotic sites (with dehiscence and without dehiscence) was the primary outcome of the study, while the status of patients (with symptoms and without symptoms) was the secondary outcome of the study. Age, gender, and the primary lesion's size were variables of the study.

Sample size calculation

Sample size was calculated through $[(Z^{\alpha/2} + Z^{\beta})^2 \times \{(p1\ (1\text{-}p1) + (p2\ (1\text{-}p2))\}/(p1 - p2)^2$. $Z^{\alpha/2}$ was considered as 1.96 in 5% of the level of significance (Type I error) and Z^{β} 0.84 in the power of 80%. According to a previous study, p1 was considered 0.7 and p2 0.3. The minimum sample size was calculated as nine subjects in the treatment and control groups.[17]

Statistical analysis

The statistical analyses were performed using the statistical package SPSS for PCs, version 19 (SPSS Inc., IL, USA). An independent t-test was used to compare the age of the two groups. Fisher's exact test was applied to assess infection, dehiscence, and healing stage.

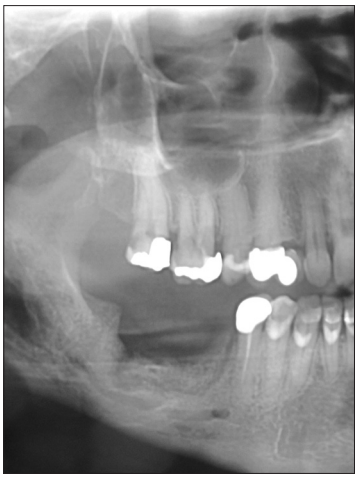

Figure 3: Bone formation 12 months after treatment

RESULTS

Finally, 20 patients completed the study protocol (10 patients in group 1 and 10 patients in group 2). All patients had a consumption of bisphosphonates or a history of previous treatment with intravenous Bisphosphonates (i.e. Alendronate, Ibandronate, or Risedronate) due to their previous cancer therapy protocol with 1 ± 0.1 years Length of therapy. All lesions were located in the mandibular posterior region and the mean duration of the current lesions was 1 ± 0.4 years based on the patient's reports. A comparison of variables (age, gender, and size of lesions) did not demonstrate any significant difference between the two groups ($P > 0.05$, Table 1).

At T1, six patients (60%) in group 1 and two patients (20%) in group 2 showed complete healing (stage 0: No clinical evidence of necrotic bone, but non-specific clinical findings, radiographic changes, and symptoms). Analysis of the data showed a significant difference in the healing stage at T1 ($P = 0.042$, Table 2).

At T2, eight patients (80%) in group 1 and four patients (40%) in group 2 had proper healing. The results did not demonstrate a significant difference in the stage of healing between the two groups ($P = 0.085$, Table 2).

At T3, nine patients (90%) in group 1 and four patients (40%) in group 2 had complete healing. Analysis of the data revealed a significant difference between the two groups in this respect ($P = 0.03$, Table 2).

At T3, nine patients in group 1 and four patients in group 2 were symptom-free for 3 months. The number of patients who were and were not symptom-free for 3 months was

significantly different between the two groups ($P = 0.03$, Table 3).

DISCUSSION

MRONJ is a serious disease, which affects the hard and soft tissue and has a low prevalence rate. The risk of MRONJ in cancer patients receiving intravenous bisphosphonates ranges from 0% to 6.7%.[18] No clear explanation has been offered for the pathophysiology of this disease.[19] Two theories have been suggested, namely, the inside-out theory, which is concerned with bone changes, and the outside-in theory, which is concerned with the effects of the surrounding tissues on the bone. Ischemia, reduced bone turnover, anti-angiogenic effect, bisphosphonate toxicity for the bone, bisphosphonate toxicity for the soft tissue, microcracks, inflammation, compromised immune response, and infection are the possible mechanisms proposed for the pathogenesis of MRONJ.[2,3,10] Bisphosphonates have an inhibitory effect on osteoclasts and consequently on bone resorption, bone metabolism, and bone remodeling.[11,12]

One of the main features of MRONJ is the reduced vascularization of bone tissue, which results in lower levels of oxygen supply and cellular nutrition. The continued presence of gaps arising from atrophy of the bone-tissue microvasculature describes the alternative name of this pathological entity i.e., avascular osteonecrosis. Drug accumulation in the soft tissue lining the jaw supports the hypertrophic effect of bisphosphonates.[20] Treatment of MRONJ directly depends on the stage of the disease. Although surgery combined with antibiotic therapy forms the basis of most treatment protocols for MRONJ, this approach is not always effective.[20]

Vescovi *et al*.[21] debated that since the entire skeleton is affected by the action of bisphosphonates, identifying lesion-free edges is impossible, in contrast to the treatment of patients with lesions such as osteoradionecrosis. Bleeding from edges after surgical intervention does not guarantee any relapse of the primary lesion.[20] Therefore, a surgical intervention aimed at removing the infected tissue may instead result in wider bone exposure and the exacerbation of the symptoms. The success of surgical intervention has been reported to be 59% to 90%.[22] Nine months after surgery is a critical period for recurrence of the disease.[22]

The effect of topical antibiotics on osteomyelitis was studied and recommended.[23] Melichercik *et al*.[24] stated that topical vancomycin was effective on osteomyelitis. The topical antibiotics were recommended for conservative treatment of MRONJ.[25]

Phenytoin was first introduced as an anti-seizure medication in 1937. Shapiro conducted the first controlled clinical trial to evaluate the effects of oral phenytoin on periodontal wounds and declared that phenytoin accelerated wound healing.[26] Topical phenytoin has been used to enhance the healing process of various wounds. Turan *et al*.[27] described that treatment with topical phenytoin increased fibroblastic proliferation, epithelialization, and vascularization in skin incisions in rats. Simsek *et al*.[28] used topical phenytoin for nasal wound healing. They reported that topical phenytoin decreased soft tissue edema and inflammatory cell infiltration, and tissue EGF levels were significantly higher. Tabrizi *et al*.[10] used topical phenytoin for local care of osteomyelitis due to osteopetrosis after debridement.

In this study, the number of patients who were symptom-free for 3 months in the phenytoin group was more than that in the control group. In the early stages of healing, the number of patients who had dehiscence was lower in the phenytoin group compared to the control group.

Topical phenytoin was used in combination with tetracycline in our study. Tetracycline can alter osteoclast function and consequently decrease bone resorption by decreasing the ruffled border area, changing the intracellular calcium concentration and interacting with the putative calcium receptors, decreasing acid production and the secretion

Table 1: Comparison of variables between the two groups

Variables	Group 1	Group 2	*P*
Age (years)	59.8±7.11	58.8±7.17	*P*=0.89*
Gender	Male (3) Female (7)	Male (2) Female (8)	*P*=0.5**
Lesion size (mm)	43.4±6.23 SD	42.5±6.39 SD	*P*=0.75

*Independent t-test **Fisher's exact test

Table 2: Comparison of the stage of healing between the two groups at 1, 6 and 12 months

Stages of healing	Group 1	Group 2	Fisher's exact test
1 month	S0 (6), S1 (4), S2 (0)	S0 (2), S1 (5), S2 (3)	(*P*=0.042)
6 months	S0 (8), S1 (2), S2 (0)	S0 (4), S1 (6)	(*P*=0.085)
12 months	S0 (9), S1 (1)	S0 (4), S1 (6)	(*P*=0.03)

S0: Stage 0, S1: Stage 1, S2: Stage 2

Table 3: Number of patients who were symptom-free for 3 months in the two groups

Study outcome	Group 1	Group 2	Fisher's exact test
Symptom-free for 3 months	Y (9), N (1)	Y (4), N (6)	*P*=0.03

Y: Yes; N: No

of lysosomal cysteine proteinases (cathepsins), inhibiting osteoclast gelatinase activity, inducing apoptosis or programmed cell death of osteoclasts, selectively inhibiting osteoclast ontogeny or development and inducing cell retraction by affecting podosomes. Tetracycline can inhibit connective tissue breakdown by non-antimicrobial mechanisms.[4,13,29,30]

Debridement is a minimally invasive surgical procedure, which is specifically performed to manage stage II lesions. It is indicated for patients who have pain due to osteonecrosis of bone as the result of inflammation of the surrounding soft tissue. Debridement can also be performed when there are thin sharp bone spicules.[20]

CONCLUSION

According to the results of this study, debridement combined with topical administration of phenytoin and tetracycline slightly improved the healing process and relapse rate after treatment in stage II of MRONJ patients. Moreover, in the last follow up (12 months after the procedure), patients who underwent surgical debridement with topical administration of medications, showed a much better healing process compared to the control group. These results strongly suggested further studies with larger study samples regarding the effectiveness of topical antibiotic + phenytoin in MRONJ patients.

Declaration of patient consent

The aim and design of the study and the surgical procedure was thoroughly explained to patients, and written informed consents were obtained from all participants. The authors confirmed that the appropriate consent form for participation in this study and utilization of clinical information and images has been obtained from all patients.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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