International Journal of Applied Dental Sciences 2018; 4(1): 147-150

ISSN Print: 2394-7489
ISSN Online: 2394-7497
IJADS 2018; 4(1): 147-150

www.oraljournal.com
Received: 25-11-2017
Accepted: 26-12-2017

Altaf H Chalkoo
Department of Oral Medicine and Radiology, Govt. Dental College, Srinagar, Jammu and Kashmir India

Rizwan Hamid
Department of Oral Medicine and Radiology, Govt. Dental College, Srinagar, Jammu and Kashmir India

Dr. Zahoor Bhat
Department of Oral Medicine and Radiology, Govt. Dental College, Srinagar, Jammu and Kashmir India

Correspondence
Altaf H. Chalkoo
Department of Oral Medicine and Radiology, Govt. Dental College, Srinagar, Jammu and Kashmir India

Single application of topical doxycycline hyclate in the management of recurrent aphthous stomatitis

Altaf H Chalkoo, Rizwan Hamid and Dr. Zahoor Bhat

Abstract
Objective: Topical application of tetracyclines have been used in recurrent aphthous stomatitis (RAS) patients but there are few studies describing the use of doxycycline. We evaluated the therapeutic efficacy of topical doxycycline hyclate in RAS.
Study design: A single-blinded placebo-controlled trial was performed, dividing 50 RAS subjects into group A and group B with 25 subjects in each group. Patients in group A received topical application of crushed doxycycline hyclate tablet with denture adhesive (Fixon) and few drops of saline solution just once at the first visit. Group B received placebo similarly. Treatment response was assessed by measuring pain reduction, ulcer duration, and adhesive retention time. Data were analyzed using the Student's t-test.
Results: Participants who received doxycycline hyclate had significantly less pain by day 1 (P<.001) and the lesion healed faster (P< 001) compared with placebo.
Conclusion: Doxycycline hyclate as a single application decreased pain and speeded recovery.

Keywords: Aphthous ulcer, denture adhesive, doxycycline hyclate

Introduction
Recurrent aphthous ulcers (RAUs), one of the most common oral disorders are known to affect 20% of the population at sometimes in their lives.1 Recurrent aphthous stomatitis (RAS) is an inflammatory condition of unknown aetiology characterized by painful, recurrent, single, or multiple ulcers of the oral mucosa.2 RAS is found in men and women of all races and geographic regions.3 The exact aetio-pathogenesis of the disease is unknown. Heredity, hematinic deficiencies, immune dysregulation, some foods, drugs, stress, local trauma, mechanical injury, hormonal disturbances, infections, smoking habits, and poor oral hygiene are proposed factors.4,5 It has been suggested that interstitial collagenases [matrix metalloproteinase-1 (MMP-1) and MMP-8] play a major role in tissue destructive events in RAU.6 The common clinical presentation is recurrent, round to ovoid , clearly defined small painful ulcers with shallow necrotic centres , raised margins, and erythematous halos.2 The duration of the ulcers is usually 7-10 days.7 A multitude of treatment modalities exist for the symptomatic management of aphthous ulcers from topical applications (including analgesics, anaesthetics, antiseptics, anti-inflammatory agents, steroids, sucralfate, tetracycline suspension, and silver nitrate) to dietary modifications. In recalcitrant cases or aphthae with systemic involvement, systemic treatment can be selected from a wide spectrum of immunomodulators that include dexamethasone, tacrolimus, azathioprine, cyclophosphamide, colchicine, prednisolone, cyclosporine A, interferon-a, tumour necrosis factor-a antagonists, antimetabolites, and alkylating agents.8-10 Despite many therapeutic options , no treatment is specific and definitive for RAS.11 Topical and systemic tetracycline regimens have been used since several decades in the treatment of RAS.8-10 The properties of doxycycline such as inhibition of prostaglandin production, leukocyte suppression, and inhibition of collagenase and gelatinase have promoted its use as an effective modality in the management of this disease.6 RAS is a self-limiting disease, but the pain and ulceration affects the quality of life. Many treatments have emerged to treat RAS and most treatment regimens use medication throughout the course of the ulcer. However, the aim of the present study is to evaluate the efficacy of Single application of topical doxycycline hyclate in the management of minor RAS.

Materials and Methods

A randomized, single-blinded, placebo-controlled study was conducted in the Department of Oral Medicine and Radiology. The sample size comprised of 50 subjects of either sex above the age of 19 years. Diagnosis of RAS was made on the basis of history and clinical features. Patients who are physically healthy with history of duration of ulcers for more than 24 h but not exceeding 72 h with symptoms like pain and burning sensation secondary to oral aphthous ulcers and with the characteristic clinical features of recurrent minor oral aphthous ulcers were included in the study. Pregnant and lactating women, patients with any other coexisting oral mucosal diseases, hematologic abnormalities, history of hypersensitivity to tetracyclines, end stage renal disease, or those taking any other medications for RAS were excluded from study. The subjects were explained about the design of the study, benefits of therapy, possible adverse effects, and possibility of being allocated to the placebo group at the beginning of the study. Informed consent was taken from all subjects. Drugs used for the study included doxycycline hyclate 100 mg tablets and placebo 100 mg tablets (starch, lactose, sodium starch glycolate, talc, and magnesium stearate).

The initial appointment consisted of collecting the demographic data, general history, a history of past experiences with the lesions and a clinical examination. Treatment was administered on the day of the initial visit. Under adequate illumination, a pair of sterile gloves and mouth mirror was used to examine the lesion. A diagnosis of aphthous ulcer was made if it occurred on the non-keratinized mucosa as a small (≤1cm) , round to ovoid ulcers, with circumscribed margins, having yellow or gray floors and are surrounded by erythematous halo(figure 1). During clinical examination, pain intensity using a visual analog scale (VAS) of 0-10 (with 1 mm division, where‘0’ is no pain and ‘10’ is worst possible pain), number of ulcers, size of each ulcer (a graduated periodontal probe was used to measure the ulcer size at the maximum diameter of the ulcer), and the duration of each ulcer (the day of onset of the first prodromal symptom of each ulcer) were recorded.

The 50 subjects included in the study were divided into 2 groups, group A and group B. Every alternate patient was allocated to each group. In group A, 25 patients received crushed tablet of doxycycline hyclate (100mg) topically whereas in group B, 25 patients received powdered placebo tablet topically. After complete clinical examination of the ulcer, pre-treatment photographs were taken before the start of treatment. The ulcer and its surrounding mucosa was dried thoroughly. Cotton rolls and high evacuation suction tips were used for isolation. Glass mortar and pestle was used to grind the doxycycline hyclate and placebo tablets. The ground tablet was mixed with denture adhesive (fixon) in the ratio of 4:1(by size/volume) in a dappen dish using a stainless steel cement spatula. Fifty percent of the medicament or placebo was used for ulcers <5 mm and 100% of the medicament was used for ulcers >5 mm. A few drops of saline solution were added to this mixture. Then, the final mixture was placed over the ulcer using a plastic instrument. After topically applying the medicament or the placebo over the ulcer, the patient was asked to refrain from eating or drinking for a period of 120 minutes. A single topical application of the medicament or placebo was applied during the initial visit and every patient was recalled after 10 days following the treatment procedure (figure 2). A pain scale sheet to record the daily status of the patient was given at the initial visit. The patients were instructed to self-evaluate the pain on the next following day after treatment for about 10 days. After 10 days, the patients were asked to return the pain scale record. Patients were questioned about any adverse effects. The patients were also asked to record the adhesive retention time and mark the day when the ulcer healed by looking in the mirror.

Post-treatment follow-up involved the evaluation of subjects on the 10th day. The pain scale sheet was collected from the subjects and post-treatment photographs (figure 2) were taken for comparing with the pre-treatment photographs (figure 1). Response was assessed on the basis of pre- vs posttreatment scores. The rate of ulcer healing and adhesive retention time in both the groups was compared. Intragroup comparisons of posttreatment pain reduction were performed using paired t test. Intergroup comparisons of posttreatment pain reduction, the rate of ulcer healing, and the adhesive retention time were performed using unpaired t test.

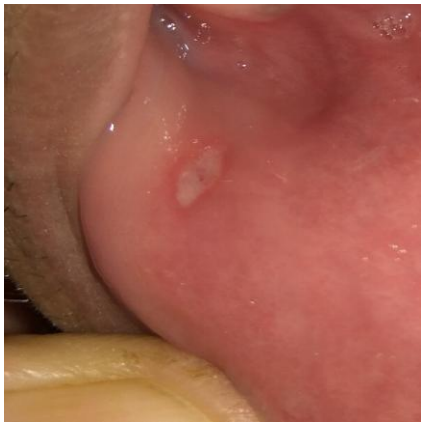

Fig 1: RAS on Labial Mucosa

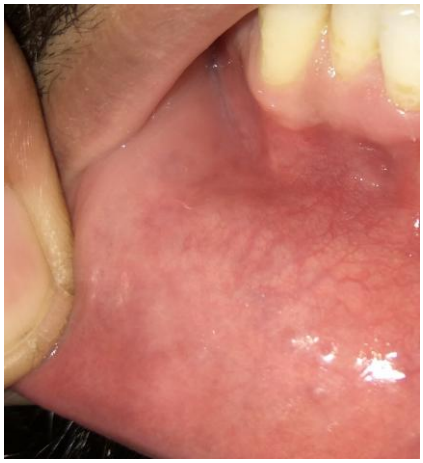

Fig 2: Healed Lesion

Results

A total of 50 patients with age ranging from 17 to 55 years were enrolled for study, among these 20 were females and 30 were males. The mean pain score at baseline for the patients of group A was 6.4 ± 2.3. The mean pain scores on day 1, 2, 3, 4, 5, and 6 were 3.7 ± 2.2, 2.3 ±1.8, 0.9 ± 1.2, 0.4 ± 0.9, 0.1 ± 0.4, and 0.1 ± 0.4, respectively. The mean pain score at baseline for the patients in group B was 5.9 ± 2.3. After treatment, mean pain scores on day 1, 2, 3, 4, 5, and 6 were 5.3 ± 2.1, 4.5 ± 2.0, 3.1 ± 1.8, 1.9 ± 1.7, 0.9 ± 1.2, and 0.2 ± 0.7, respectively. These data indicate a significant reduction in pain in group A (i.e., faster reduction in pain) compared with group B (P<.001 using unpaired t test). Intergroup comparison of days taken for ulcer healing and adhesive

retention time shows that the mean time required for ulcer healing was significantly less in group A (3.7 ± 1.3 days, range 2-7 days) than that of group B (5.3 ± 1.2 days, range 3-7 days, *P*<.001). The mean adhesive retention time for drug agent in group A was similar to that of group B (2.1 ± 1.2 h, range 0.5-6 h vs 1.8 ± 0.8 h, range 1.0-4 h, respectively, P = 0.30). None of the patients in our study reported any serious adverse effects. In the doxycycline hyclate group, 8 patients experienced a transient bitter sensation shortly following the application of drug.

Discussion

RAS is a common oral disorder affecting 5%-66% of examined adult patient groups.14 The difficulty in establishing the exact nature of aphthous stomatitis is in part because of the nonspecific histopathologic features of the ulcers and the lack of any reproducibly identifiable cause, endogenous or exogenous.15 Although the trigger of an episode of RAU is unknown, extensive investigations in large patient series have identified a range of local, hematologic, gastrointestinal, immunologic, genetic, nutritional, allergic, psychological, and medication reactions as probable triggers in some RAU patients.16 Various pathogenic factors have been implicated in the causation of RAS. Interstitial collagenases (MMP-1 and MMP-8) are enzymes that are able to degrade the main oral mucosal collagen types I and III. It has been suggested that interstitial collagenases MMP-8 and MMP-1 play a role in tissue destruction events in RAU. Tetracyclines have been shown to inhibit prostaglandin production, suppress leukocyte activities, and inhibit collagenase and gelatinase activities as well as the oxidative activation of their latent forms.6 As there is no specific management for RAS,17 this study was undertaken to examine pain reduction in RAS following single topical application of doxycycline hyclate, an inhibitor of MMPs. Tetracyclines have been used in varying regimens in the treatment of RAS. Gorsky *et al*. conducted a crossover trial to assess the efficacy of 0.2% minocycline and 0.25% tetracycline oral rinses in patients with frequent episodes of RAS, and concluded that Minocycline mouth rinses resulted in significantly improved pain control, by reducing the severity and duration of pain.18 Denman and Schiff in a study on 20 patients with recurrent oral ulceration to determine the efficacy of tetracycline hydrochloride as a mouthwash given 5 mL 3 times a day for 16 weeks, concluded thart tetracycline was efficacious in significantly reducing the pain and frequency of RAS.19 Their findings show that Mysteclin syrup (tetracycline hydrochloride and amphotericin) is efficacious irrespective of the phase of the disorder and suggest that the improvement is maintained for at least four weeks after treatment is stopped.

Henricsson and Axéll in Clinical trials with a cross-over double-blind technique to test chlortetracycline (Aureomycin) and the enzyme-containing dentifrice Zendium with regard to therapeutic effects on recurrent aphthous ulcers. Aureomycin was found to reduce the number of ulcers and diminish pain when compared with placebo. When groups of patients treated with Zendium and placebo dentifrice, respectively, were compared, no statistically significant difference could be demonstrated. However, when the pH value of Zendium was stepwise changed from 5.9 to 6.8, an increased fraction of patients reported complete relief from pain and ulcer(s) during the trial periods 20

Apart from tetracyclines, antibiotic like penicillin were used for management of RAS. Both Kerr *et al*. and Zhou *et al*. in a study of 100 and 258 subjects respectively found topical application of 50 mg penicillin G potassium troches effective and safe in the treatment of minor RAS. Troches were applied 4 times daily for 4 consecutive days; this short course therapy significantly reduced ulcer size and alleviated ulcer pain.21,22 A doxycycline hyclate has been used in few studies for RAS. In a study conducted by Ylikontiola *et al*., doxycycline was used in a powdered form as in our study but the adhesive used to retain the medicament was isobutyl cyanoacrylate.6 Another study used sub-antimicrobial dose of doxycycline 20 mg to prevent the recurrence of RAS.23 The present study uses powdered doxycycline in a denture adhesive base for the pain palliation in RAS patients. In the present study, 100 mg of doxycycline hyclate tablet was crushed and appropriate amount of the powder was mixed with denture adhesive for topical application over the ulcer by mixing with few drops of saline solution at their first visit. Re-evaluation of the patients was conducted on day 10. This approach produced highly significant reduction in pain scores. The placebo group also rendered a significant pain reduction after administration of the crushed placebo tablet over the ulcers after 7 days and this could be explained by the fact that the adhesive covering that was provided over the ulcers may have rendered mechanical protection to the mucosa and helped hasten healing. Although significant pain reduction was present in both the groups, the rate of pain reduction was faster in doxycycline group emphasizing the therapeutic efficacy of this drug. Our results are similar to the study conducted by Ylikontiola *et al*. suggesting that the diverse biochemical properties of doxycycline help in alleviating RAS pain.6 The time required for ulcer healing was 3.7+/-1.3 days in the doxycycline hyclate group, whereas it was5.3+/-1.2 days in the placebo group (*P*<.001). A comparative study conducted by Gorsky *et al*. for assessing the efficacy of topical minocycline and tetracycline rinses in RAS also showed that the duration of ulcers was significantly reduced in patients using topical minocycline as therapy.18 Denture adhesive was used as a vehicle for retention of the medicament in the present study. This was in accordance with the study conducted by Muzio *et al*. in which topical clobetasol propionate in an adhesive denture paste was administered to the patients with RAS and a good retention of the medicament to the mucosa was achieved.24 The mean adhesive retention time was approximately 2 h in both groups. The management of RAS using doxycycline hyclate appears to be an efficacious cost-effective therapy because a single application rendered about 65% pain reduction by day 2 posttreatment, whereas other studies with other drugs require up to 10 days to demonstrate a clinically significant response.24 Although pain reduction after 7 days of treatment was significant in both the groups, the intergroup comparison revealed a highly significant reduction in pain and days taken for ulcer healing in the doxycycline hyclate group as compared with the placebo group, thus substantiating the efficacy of the study drug. The first day posttreatment percentage of pain reduction in VAS achieved with the doxycycline hyclate group was 42% whereas with the placebo group, it was 12% with a P value <.001.

Limitations

- The study was a single-blinded, placebo-controlled study, and double blinding offers greater validity.
- The application to posterior region of the oral cavity is relatively difficult because of access.
- Patients with multiple and large ulcers may not be treated

efficaciously

- Pain data were derived from subjective assessment, so there could be interindividual variations in the perception of pain.
- As the pain scale sheet was given to the patient for marking the posttreatment percentage of pain each day until the ulcer healed, subjects who were illiterate faced problem and had to seek help from other literate individuals in the family.
- In the present study, the medicament was applied to the ulcers by the dental professional. It is recommended that if commercial preparation of topical doxycycline hyclate in a proper adhesive is made available in the near future, the patient could self-apply the medicament. Moreover, the frequency of application could also be made based on the patients' convenience.

Conclusion

In conclusion, crushed doxycycline tablets in denture adhesive produced favourable results and appears advantageous because of its cost effectiveness, single application, and faster symptomatic relief than other drugs. We believe that single application of the antibiotic doxycycline is a novel attempt to improve the compliance of patients with RAS. Further studies are recommended on a larger sample of patients, over a longer follow-up period, possibly using a double blind design along with the evaluation of immunologic markers, to minimize the effects of confounding factors and to maximize the sensitivity for detecting subtle changes of the mucosa during the course of the treatment.

References

1. Besu I, Jankovic L, Magdu IU, Konic-Ristic A, Raskovic S, Juranic Z. Humoral immunity to cow's milk proteins and gliadin within the etiology of recurrent aphthous ulcers? Oral Dis. 2009; 15:560-564.
2. Natah SS, Konttinen YT, Enattah NS, Ashammakhi N, Sharkey KA, Hayrinen-Immonen R. Recurrent aphthous ulcers today: a review of the growing knowledge. Int J Oral Maxillofac Surg. 2004; 33:221-234.
3. Ship JA. Recurrent aphthous stomatitis. An update. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1996; 81:141-147.
4. Koybasi S, Parlak AH, Serin E, Yilmaz F, Serin D. Recurrent aphthous stomatitis: investigation of possible etiologic factors. Am J Otolaryngol. 2006; 27:229-232.
5. Wray D, Graykowski EA, Notkins AL. Role of mucosal injury in initiating recurrent aphthous stomatitis. Br Med J (Clin Res Ed). 1981; 283:1569-1570.
6. Ylikontiola L, Sorsa T, Immonmen RH, Salo T. Doxymycinecyanoacrylate treatment of recurrent aphthous ulcers. Oral surg Oral Med Oral Pathol Oral Radiol Endod. 1997; 83:329-333.
7. Khandwala A, Van Inwegen RG, Alfano MC. 5% Amlexanox oral paste, a new treatment for recurrent minor aphthous ulcers. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1997; 83: 222-230.
8. Altenburg A, Zouboulis CC. Current concepts in the treatment of recurrent aphthous stomatitis. Skin Therapy Lett. 2008; 13:1-4.
9. Liu C, Zhou Z, Liu G, Wang Q, Chen J, Wang L. Efficacy and safety of dexamethasone ointment on recurrent aphthous ulceration. Am J Med. 2012; 125:292-301.
10. Bruce A, Rogers RS. New and old therapeutics for oral ulcerations. Arch Dermatol. 2007; 143:519-523.
11. De Abreu MA, Hirata CH, Pimentel DR, Weckx LL. Treatment of recurrent aphthous stomatitis with clofazimine. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2009; 108:714-721.
12. Drugs.com. Doxycycline hyclate. http://www.drugs.com/pro/ doxycycline-hyclate.html.
13. Meiller TF, Kutcher MJ, Overholser CD, Niehaus C, DePaola LG, Siegel MA. Effect of an antimicrobial mouthrinse on recurrent aphthous ulcerations. Oral Surg Oral Med Oral Pathol. 1991; 72:425-429.
14. Porter SR, Hegarty A, Kaliakatsou A, Hodgson TA, Scully C. Recurrent aphthous stomatitis. Clin Dermatol. 2000; 18:569-578.
15. Vincent SD, Lilly GE. Clinical, historic, and therapeutic features of aphthous stomatitis. Literature review and open clinical trial employing steroids. Oral Surg Oral Med Oral Pathol. 1992; 74:79-86.
16. Boras VV, Savage NW. Recurrent aphthous ulcerative disease: presentation and management. Aust Dent J. 2007; 52:10-15.
17. Scully C, Porter S. Recurrent aphthous stomatitis: current concepts of etiology, pathogenesis and management. J Oral Pathol Med. 1989; 18:21-27.
18. Gorsky M, Epstein JB, Rabenstein S, Elishoov H, Yarom N. Topical minocycline and tetracycline rinses in treatment of recurrent aphthous stomatitis: a randomized cross-over study. Dermatol Online J. 2007; 13:1.
19. Denman AM, Schiff AA. Recurrent oral ulceration treated with Mysteclin: a controlled study. Br Med J. 1979; 1:1248-1249.
20. Henricsson V, Axéll T. Treatment of recurrent aphthous ulcers with Aureomycin mouth rinse or Zendium dentifrice. Acta Odontol Scand. 1985; 43:47-52.
21. Kerr AR, Drexel CA, Spielman AI. The efficacy and safety of 50 mg penicillin G potassium troches for recurrent aphthous ulcers. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2003; 96:685-694.
22. Zhou Y, Chen Q, Meng W, *et al*. Evaluation of penicillin G potassium troches in the treatment of minor recurrent aphthous ulceration in a Chinese cohort: a randomized, double-blinded, placebo and no-treatment-controlled, multicenter clinical trial. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2010; 109: 561-566.
23. Preshaw PM, Grainger P, Bradshaw MH, Mohammad AR, Powala CV, Nolan A. Subantimicrobial dose doxycycline in the treatment of recurrent oral aphthous ulceration: a pilot study. J Oral Pathol Med. 2007; 36:236-240.
24. Muzio LL, Valle AD, Mignogna MD, *et al*. The treatment of oral aphthous ulceration or erosive lichen planus with topical Clobetasol propionate in three preparations: a clinical and pilot study on 54 patients. J Oral Pathol Med. 2001; 30:611-617.