

Efficacy of Single Application of Doxycycline Hyclate in Treatment of Recurrent Aphthous Stomatitis

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Abstract: ***Aim:** The aim of the present study is to evaluate the efficacy of topical application of single dose of doxycycline hyclate 100mg tablet as a new therapeutic regimen in the treatment of minor RAU for pain reduction. **Methods:** The patients diagnosed with minor recurrent aphthous ulcers fulfilling the inclusion and exclusion criteria were enrolled. The study was conducted in the Department of ENT, H&NS, SKIMS-MC, Srinagar (J&K) India from January 2017 to January 2018 after approval by institutional ethical committee. This study included a total of 50 patients which were divided into two groups each of 25 patients. Group I: 25 patients receiving doxycycline hyclate 100 mg tablets (Doxt 100). Group II: 25 patients receiving placebo tablet. **Results:** The data indicated a significant reduction in pain in group A (i.e., faster reduction in pain) compared with group B. On the third day, pain score was 3.80 in the study group and 5.65 in the control group [Table 1] with P value of 0.079 and it was found highly significant on the fifth day with a P value of <0.001 using unpaired t-test. **Conclusion:** Healing of the ulcer was significantly faster for the doxycycline group compared to placebo group. The doxycycline was found to be effective in treating oral aphthous ulceration. It appears advantageous because of its cost-effectiveness, single application, and faster symptomatic relief than other drugs.*

Keywords: Doxycycline hyclate, recurrent aphthous ulcer (RAU), VAS (Visual Analogue Scale)

1. Introduction

Recurrent Aphthous Ulcers (RAU) is one of the most common oral ulcerative diseases of the oral mucosa with high recurrence rate^[1, 2]. Although many precipitating factors have been identified, the cause as yet remains unknown.

Etiological factors such as local trauma, immunodeficiency, hereditary influences, allergic agents, nutritional deficiency, hormonal imbalances in women, physical or psychic stress, chemical irritants and infective agents have been proposed^[2-4].

Recurrent aphthous ulceration has three different variants minor aphthous ulcers, major aphthous ulcers and herpetiform ulcers^[3, 4]. Diagnosis of RAU is based on history, clinical manifestations, and histopathology. Natahet al., in 2004^[5] proposed the diagnostic criteria for minor RAU.

Management of minor aphthous may be usefully divided into three phases, these include (1) Symptomatic and supportive treatment (2) Specific treatment; and (3) Preventive treatment [6]. Standard topical treatment options that provide symptomatic relief include analgesics, anaesthetics, antiseptics, anti-inflammatory agents, steroids, sucralfate, tetracycline and silver nitrate^[7].

Various treatment modalities such as anti-inflammatory agents, steroids, sucralfate, tetracycline suspension, analgesics, anesthetics, antiseptics, and silver nitrate which are the standard topical treatment options that provide symptomatic relief. Beneficial results are obtained with topical or systemic steroids for some subjects. Many therapeutic options are available either to cure or reduce the

duration of recurrences but in all current therapy does not provide a satisfactory means for curing aphthous stomatitis, moreover, their clinical value remains unproven.^[8-13] Since 1960, local regimens of tetracycline have been used in the treatment of RAU based on its antimicrobial property. However, newer properties of doxycycline such as leukocyte suppression, inhibition of prostaglandin production, and inhibition of collagenase and gelatinase have further promoted its use in the management of RAU as an effective modality.^[14,15,16,17]

Recently, tissue adhesives have been preferred in the treatment of RAU, as it is having property to keep the medication attached in close contact with the ulcer as long as possible.^[6] Therefore, the aim of the present study is to evaluate the efficacy of topical application of single dose of doxycycline hyclate 100mg tablet as a therapeutic regimen in the treatment of minor RAU for pain reduction.

2. Materials and Methods

The patients diagnosed with minor recurrent aphthous ulcers fulfilling the inclusion and exclusion criteria were enrolled. The study was conducted in the Department of ENT, H&NS, SKIMS-MC, Srinagar (J&K) India from January 2017 to January 2018 after approval by institutional ethical committee. This study included a total of 50 patients which were divided into two groups each of 25 patients. Group I: 25 patients receiving doxycycline hyclate 100 mg tablets (Doxt 100).

Group II: 25 patients receiving placebo tablet.

The sample was selected randomly those who came in Department of ENT, H&NS, Males and female adult outpatients with age ranging from 15 to 40 years, 16 females

and 14 were males; age group was not matched among both groups.

Inclusion criteria:-Patients were enrolled in the study after clinical examination and documentation of clinical history. Healthy controls were included with a history of the duration of ulcers for more than 24 h and not exceeding 72 h with symptoms and ulcers with the characteristic clinical features of recurrent minor oral aphthous were included in the study.

Exclusion criteria:- (i) pregnant and lactating women, (ii) existing other oral mucosal diseases, (iii) hematologic abnormalities, (iv) history of hypersensitivity to tetracycline, (v) end-stage renal disease, or (vi) those taking any other medications for an oral aphthous ulcer.

A diagnosis of aphthous ulcer was made when it occurred in the nonkeratinized mucosa as a shallow crateriform ulcer covered by a whitish yellow pseudomembrane and presented with a round, regular border with a surrounding erythematous halo. On clinical examination, pain intensity using a visual analogue scale (VAS) (fig.1) 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. After complete clinical examination of the ulcer, pretreatment photographs were taken before the start of treatment. The ulcer and the mucosa surrounding the ulcer were dried thoroughly. Cotton rolls were placed for isolation.



Figure 1: Visual analogue scale

In Group I, doxycycline hyclate was ground to fine powder using a glass mortar and pestle. An appropriate amount of the medicament was mixed with a pinch of denture adhesive and few drops of saline in a glass slab using a stainless steel cement spatula. Then, the final mixture was placed over the ulcer using a plastic instrument. Similarly, in Group II, placebo tablet was mixed in denture adhesive and applied onto the lesion in a similar manner. After topically applying the medicament over the ulcer in each group it was allowed to dry within few minutes with the chip syringe, the patient was asked to refrain from eating or drinking for 2 h.

A pain scale sheet to record the daily status of the pain was given at the initial visit. The patients were instructed to self-evaluate the pain scale sheet on the day after treatment and daily after that for 7 days and also to note any adverse effects with the medication. After 7 days, the patients were asked to return the pain scale record. The results were analysed with unpaired t-test.

3. Results

The comparison of ulcer size and maximum pain was made between first day values (baseline value) and third-day values. The mean pain score of the study group was 8.05 and in control group 7.70 at the baseline level. On the third day, pain score was 3.80 in the study group and 5.65 in the control group [Table 1] with P value of 0.079 and it was found highly significant on the fifth day with a P value of <0.001 using unpaired t-test. These data indicate a

significant reduction in pain in Group A (i.e., faster reduction in pain) compared with Group B (P < 0.014 using unpaired t-test) [Figure 2].

Figure 3 shows that the mean time required for ulcer healing was significantly less in Group A (1.85 ± 0.5, range 2–7 days) than that of Group B (3.32 ± 1.1, range 3–7 days; P < 0.001).

Table 1: Comparison of pain in terms of visual analogue scale (Mean [SD]) among cases and controls at different time intervals using unpaired t-test

	Group	n	Mean	Std. Deviation	t	P
Pretreatment	Cases	25	8.05	0.7	1.418	0.164
	controls	25	7.7	0.8		
Day 1	Cases	25	7.85	0.8	1.309	0.198
	controls	25	7.45	1		
Day 2	Cases	25	6.65	0.6	0.202	0.841
	controls	25	6.6	0.8		
Day 3	Cases	25	3.8	0.7	1.807	0.079
	controls	25	5.65	0.9		
Day 4	Cases	25	3.02	0.8	2.57	0.014
	controls	25	4.5	0.8		
Day 5	Cases	25	1.85	1.2	3.658	<0.001
	controls	25	3.2	1.1		
Day 6	Cases	25	0.75	1	4.196	<0.001
	controls	25	2.15	1		
Day 7	Cases	25	0.15	0.3	3.753	<0.001
	controls	25	1.1	1		

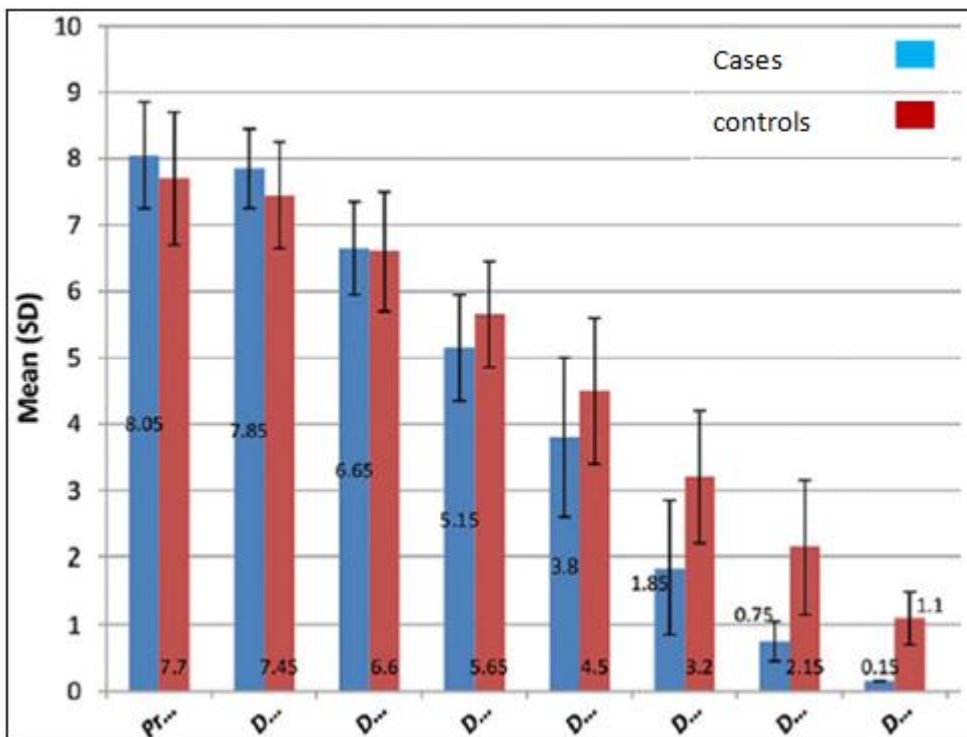


Figure 2: Pain incidence in VAS before and after treatment

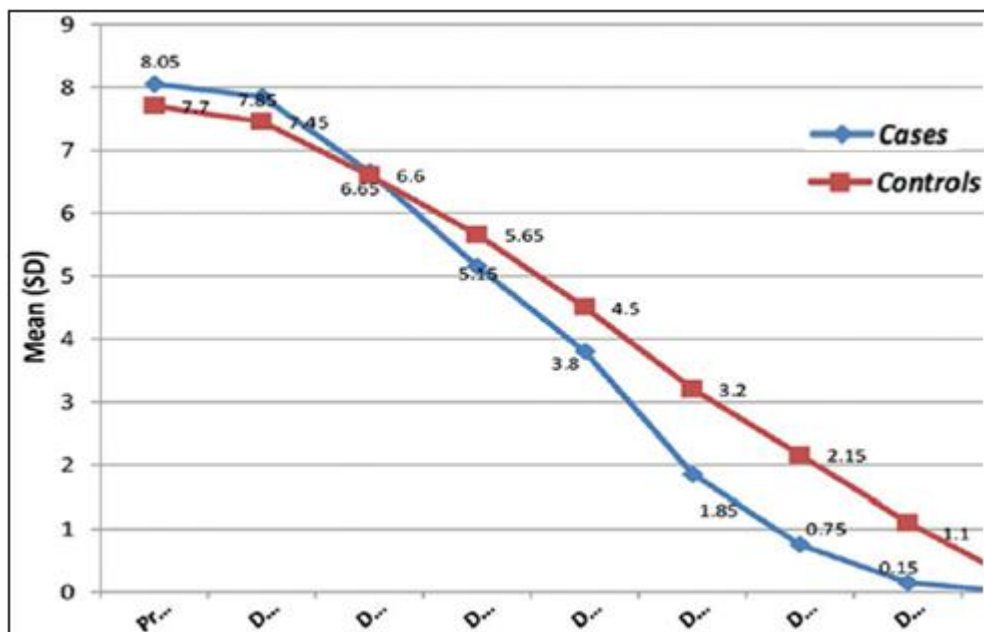


Figure 3: Decrease in intensity of pain in Group A (cases) and Group B (controls)

4. Discussion

Recurrent aphthous stomatitis or aphthous ulcers are more common in younger adults. There are several causes that have been explained for ulcer formation but no single cause is definitive. The cause is still non-specific. There are multiple factors which may be acting together in a complex manner in initiating the formation of ulcer unlike a single etiological factor. This means a combination of host and environmental factors are essential not only for triggering the ulcer but also for an increase in size. The severity of etiological factors to which an individual is exposed would decide the type of ulcer [2,18].

It has been observed that recurrent aphthous ulcers are equally prevalent in both the genders which was also found in our study. The mean age of the subjects in our study was 26.5 years which was in accordance with the patients taken in previous studies and the peak age of occurrence is second decade of the life. It involves whole of the oral mucosa but most commonly it was seen on the lower labial mucosa (fig 4). Recurrent aphthous stomatitis or aphthous ulcers are more common in younger adults. Scully et al.^[19] stated that in about 80% of patients with RAU, the condition develops before 30 years of age and if onset is there in later stages of life it suggests definable predisposing factors leading to more complex form of recurrent aphthous ulceration^[19]. RAU is a significant deterrent to productivity outcome of the individuals especially in younger age groups, which is a loss

to the society as a whole. The painful ulceration may present significant problems to the patient; difficulty eating, speaking and swallowing can severely affect a patient's quality of life.

The lower labial mucosa was the most affected site followed by upper labial mucosa and tongue and least affected was lingual surface. Other studies show no site predilection, though it is most commonly seen in the non-keratinized mucosal surfaces like labial mucosa, buccal mucosa, and floor of the mouth.

Tetracyclines have been shown to inhibit prostaglandin production, suppress leukocyte activities, and inhibit collagenase and gelatinase activities as well as oxidative activation of their latent forms. As there is no specific management for RAS, this study was undertaken to examine pain reduction in RAS following topical application of doxycycline hyclate (single application), an inhibitor of matrix metalloproteinases (MMPs).^[6] Tetracyclines, in addition to their antimicrobial effect, have been shown to reduce collagen breakdown by collagenase activity.^[20]

From the present study, it was evident that the vehicle used in our study denture adhesive showed some beneficial effect with the fact that any topical medication in the oral cavity can be retained for a longer time with the help of tissue adhesive material used.



b) Lower Labial Mucosa
Figure 4

5. Conclusion

Healing of the ulcer was significantly faster for the doxycycline group compared to placebo group. The doxycycline was found to be effective in treating oral aphthous ulceration. It appears advantageous because of its cost-effectiveness, single application, and faster symptomatic relief than other drugs.

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