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The efficacy of 3% diclofenac in 2.5% hyaluronan gel base for treatment of recurrent aphthous stomatitis (RAS): A double blind study.

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Abstract

Purpose: To evaluate the effects of 3% Diclofenac in 2.5% hyaluronan base versus 2.5% gel base alone on the pain duration and healing time of the minor aphthous ulcers.

Materials and Methods: 44 patients with minor RAS were selected randomly and treated with 3% Diclofenac in 2.5% hyaluronan or the 2.5% hyaluronan base alone. Pain duration and healing duration of the lesions were evaluated.

The collected data were analyzed statistically by SPSS 10 program and Student's t-test.

Results: The mean of time for lesions to become pain free was 5.5 ± 1.5 days and 4.09 ± 1.3 days, for controls and cases patients respectively and this difference was significant (P value = 0.002) The mean of healing time for lesions in the controls and cases group were 8.18 ± 0.9 days and 8 ± 1.19 , respectively, and this difference was not significant statistically (P-value=0.57).

Conclusion: diclofenac gel is effective in reducing pain duration of the minor RAS although it is not effective in healing of them.

Introduction

Recurrent Aphthous stomatitis (RAS) is a chronic condition, usually with a childhood or adolescent onset and with a tendency to diminish in frequency and severity with age. Most patients are otherwise healthy. RAS affects 5-25% of the general population [1]. It is most commonly found in women [2], but there are studies that report a prevalence of more than 50% in men [3], with a significantly greater involvement among high socioeconomic groups [4].

Typical RAS lesions involve self-limited, painful, clearly defined shallow round or oval 1-3 mm ulcers, each with a shallow necrotic center. These ulcers are covered with a yellow-grayish pseudomembrane and are surrounded by minimal raised margins and an erythematous halo representing superficial vasculitis and foci of extravasated erythrocytes located in the superficial layers of the lamina propria [1]. Minor aphthae, also known as Mikulicz's aphthae, named for Johann von Mikulicz-Radecki, who was probably the first to describe it in late 19th century (1898), or mild aphthous ulcer, accounts for 75-85% of all aphthous lesions [5]. These ulcers are not larger than 8-10 mm and tend to heal within 10-14 days (average 12 days) without scarring. Minor aphthae can involve every nonkeratinized mucosa of the oral cavity and is usually observed in the labial mucosa, buccal mucosa, floor of the mouth, and on the ventral or border of the tongue. The labial mucosa is the most prevalent area [6].

The precise cause of RAS remains unclear [7] but it has been associated with a deficit of folic acid, iron, zinc, vitamin B1, B2, B6 or B12; Behcet's syndrome, gastrointestinal disorders (Crohn's disease, celiac disease, ulcerative colitis); Immunodeficiencies (HIV and others); stress, trauma, cessation of smoking, luteal phase of the menstrual cycle and oral healthcare products containing sodium lauryl sulfate [8-12].

Several treatment options have been suggested for treatment of the RAS. One study has suggested the use of 3% Diclofenac in 2.5% hyaluronan as the treatment modality for RAS [13]. In this study, we evaluated the effects of this treatment on the pain duration and healing time of the minor aphthous ulcers.

Patients and methods

This study was a double-blind clinical trial and was performed in skin diseases and leishmaniasis research center. 44 patients with minor recurrent aphthous stomatitis were selected randomly.

The patients had no Predisposing diseases and all of the patients had signed the informed consent form. All of the patients had at least 1 attack of aphthous ulceration in the recent 6 months and their diseases had enough severity to interfere with their normal activities such as nutrition, sleep and etc.

Exclusion criteria included pregnancy or breast feeding, allergy to diclofenac, age less than 7 years old, predisposing systemic disease (such as renal failure, sweet syndrome, Behcet's syndrome, anemia, immune deficiency, inflammatory bowel diseases and etc), and careless patients.

After history taking and complete physical examinations, relevant laboratory examinations were done to rule out predisposing disease.

After confirmation of the presence of the minor RAS without predisposing diseases,

enough information and instruction was given to patients and informed consent was taken from them and patients asked to fill out the relevant questionnaires.

These 44 patients were randomly allocated in 2 placebo and control groups. The control patients were treated with 2% hyaluronan gel (as placebo) and case patients were treated with 3% diclofenac in 2% hyaluronan gel. They were blind to the type of treatment. The patients applied the drug on their lesions twice daily and did not drink or eat for at least 10 minutes after gel application.

The patients were visited and assessed in a blind fashion at days 3, 5, 7, 9 and 11 after base time for pain severity and lesion healing. Any side effects were recorded.

Improvement criteria were defined as: 1-duration of pain be less than 4 days; 2- time of complete healing (returnee of oral mucosa to normal condition without any red or white spot) be less than 8 days. We considered the patients improved if one of the aforementioned criteria was reached.

The collected data were analyzed statistically by SPSS 10 program and Student's t-test.

Results

The mean of age in the control group was 30.2 and in the cases group was 32.4. There was no significant difference in age between these 2 groups of patients ($P > 0.05$).

In the control group 12(54%) out of 22 patients were male and 10 patients were female. In the cases group 11(50%) out of 22 patients were male and 11 patients were female. All of the patients completed the study and none of them reported any side effects.

In controls group, 4 patients out of 22(18.2%) had improvement in the pain period of their lesions and in the cases group 12 patients out of 22 (54.5%) had improvement. The mean of time to become pain free was 5.5 ± 1.5 days and 4.09 ± 1.3 days, for controls and cases patients respectively and this difference was significant (P value = 0.002) (table -1).

7 and 9 patients in the controls and case group had improvement in their healing time, respectively. The mean of healing time in the controls and cases group were 8.18 ± 0.9 days and 8 ± 1.19 , respectively, and this difference was not significant statistically (P -value=0.57) (table 2).

Table 1: Comparison of the mean duration of pain in the cases and controls groups		
(P value=0.002)		
Group	Mean duration of pain (days)	Standard deviation
Controls groups	5.54	1.53
Cases group	4.09	1.34

Table 2: Comparison of the mean of healing time in the cases and controls groups (P value=0.57)

Group	Mean of healing time (days)	Standard deviation
Controls groups	8.1	0/9
Cases group	8	1.19

Discussion

Recurrent Aphthous Ulceration (RAS) is a chronic and recurrent disorder and repetitive treatment courses are often necessary. Accordingly several types of treatment have been developed.

Treatment strategies for RAS most take into account the possible immunopathogenesis and the benefit derived from and the potential adverse effects caused by treatment.

The treatment that are used currently for treatment of RAS are largely symptomatic and include treatments such as topical corticosteroids, chlorhexidine gluconate mouth rinse, benzydamine hydrochloride spray or moth rinse, prednisolone, levamisole, pentoxifylline, disodium cromoglycate, colchicine and thalidomide[14-18].

In this study, we evaluated the efficacy of topical diclofenac in hyaluronan gel base for treatment of RAS. Our results showed that this treatment was effective in reducing pain duration of the lesions.

On the other hand, the healing period was less in the diclofenac treated group than placebo group although this difference was not significant.

We can conclude from our results that diclofenac gel is not effective in healing of the aphthous lesions although it is effective in reducing pain duration of the lesions. These effects may be related to anti inflammatory and pain relieving effects of the diclofenac in hyaluronan base.

In the literature review, only one study suggested the use of diclofenac in 2.5% hyaluronan gel for treatment of the RAS [13]. In this study, 60 healthy adults were allocated in 3 groups and were treated with 3% diclofenac in 2.5% hyaluronan, 2.5% hyaluronan and 3% viscous lidocaine. Their results showed a 35% to 52% pain reduction ($P < 0.01$) in 6 hours after the application of diclofenac in hyaluronan, where as hyaluronan gel alone and viscous lidocaine failed to produce pain reductions. They concluded that 3% diclofenac in 2.5% hyaluronan was an effective treatment for this common, painful disorder although they didn't evaluate the effect of this drug on the whole pain duration or healing time of the lesions.

With respect to results of our study and Saxes MA et al studies, we can conclude that 3% diclofenac in hyaluronan gel group is an effective therapy for treatment of the RAS.

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