ORIGINAL RESEARCH

Comparison of colchicine versus prednisolone in recurrent aphthous stomatitis: A double-blind randomized clinical trial

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Abstract

Purpose: Recurrent aphthous stomatitis (RAS) is one of the most common ulcers of the oral cavity with a reported prevalence of 5- 50%. There is still no definitive treatment for RAS; however, immunosuppressive and immunomodulant agents have been proposed. In this study, we compared the therapeutic effects of 5 mg/d prednisolone with 0.5 mg/d colchicine in the treatment of RAS.

Methods: In a double-blind randomized clinical trial, 34 patients with RAS were randomly divided into two groups for treatment with prednisolone or colchicine. All patients took the medication for three months and were assessed at two weeks intervals. The groups were compared for size and number of lesions, severity of pain and burning sensation, duration of pain-free episodes and any side effects of the prescribed medicines. Both colchicine and prednisolone treatments significantly reduced RAS ($p<0.001$). No significant differences in size and number of lesions, recurrence and severity of pain and duration of pain-free period

were seen between the two treatment groups. Colchicine (52.9%) had significantly more side effects than prednisolone (11.8%).

Conclusion: Low dose prednisolone and colchicine were both effective in treating RAS. Given that the two therapies had similar efficacy, yet colchicine was associated with more side effects, 5mg/d of prednisolone seems to be a better alternative in reducing the signs and symptoms of the disease.

Recurrent aphthous stomatitis (RAS) is one of the most common ulcers of the oral cavity with a reported prevalence of 5-50%.¹⁻³ Several etiologies have been proposed for RAS but the exact cause still remains unknown. According to severity and location of the lesions, different types of topical or systemic treatments have been used, but none of them have shown

great benefits.³⁻⁵ It has been demonstrated that irregularity in cellular immunity plays the main role in the pathogenesis of RAS; therefore, immunosuppressive and immunomodulator agents have been used in the management of patients with major or recurring aphthous ulcers.^{1-4,6,7} Positive effects of corticosteroids in reducing the pain and burning sensation and the number of ulcers, as well as ability of colchicine to minimize the duration and number of aphthous ulcers have been shown in several studies.⁸⁻¹¹ Proposed mechanisms of action of prednisolone include suppression of granulocyte migration to the site of tissue injury, phagocytosis, prostaglandin and leukotriene synthesis and the cellular immunity.^{4,12,13} The anti-inflammatory action of colchicine is caused by the binding to microtubular protein and suppressing the migration and phagocytosis of leukocytes, and the generation of leukotriene B4 and lactic acid products.¹⁴⁻¹⁶

At present, the main aim of RAS treatment is to enhance the patient's quality of life by decreasing the pain and burning of recurring ulcers. Accordingly, the best treatment is that which can manage the ulcers for the longest period and with the lowest dose and the fewest and least severe side effects.^{3,4} In this study, we compared the treatment efficacy of prednisolone (5 mg/d) and colchicine (0.5 mg/d). The daily dose of colchicine with prophylactic effects on RAS is considered to be 0.5-1.8 mg¹⁶ and the lowest recommended dose was used in this study.

Methods

Patients

A total of 34 patients with frequent RAS from the patients who were regularly attending the oral medicine clinics of two universities including Tehran and Mashhad dental schools were enrolled in this double-blind randomized clinical trial. Patients with history of RAS (at least three episodes each month), who were unresponsive to conventional topical treatments and

did not take any medicine for treatment of RAS in the two weeks prior to the beginning of the study, were included. All of the participants were 18 years of age or older, and had normal results of biochemical screening (cell blood count, fasting plasma glucose, hepatic transaminases, serum antibodies to gliadin and endomysium, serums levels of ferritin, iron, zinc, vitamins B12, B6, and folate). Patients with previous medical history of any systemic disease (including diabetes mellitus, blood dyscrasia, liver disease, inflammatory bowel disease, renal insufficiency and rheumatologic diseases such as Behcet's disease), patients who had taken any medicine that might have an effect on the immune system (such as glucocorticoids), and those who had involvement of other mucous membranes were not included in this study. None of patients had prior history of exposure to prednisolone or colchicine.

The research was carried out according to the principles of the Declaration of Helsinki. The local ethics review committee of Tehran University of Medical Sciences and institutional review board approved the study protocol. All participants gave written informed consent before participation.

Study design and intervention

This study was designed as a randomized double blind clinical trial. Patients were randomly divided into two groups of treatment with daily dose of 5 mg prednisolone or 0.5 mg/d colchicine. Both groups took the medicines for three months. After determining the eligibility and obtaining the consent, to guarantee the blinding, a random number was generated for each participant using SPSS software (version 16.0; SPSS Inc., Chicago, USA), and patients were referred to the pharmacist to pick up their assigned medication according to their number. All tablets were enclosed in identical sealed dark boxes. The patients were asked to report immediately if there was any side effect at any time of study until six months after treatment.

TABLE 1. Baseline characteristics of patients in groups of treatment with prednisolone or colchicine

	Colchicine (n=17)	Prednisolone (n=17)	P value
Gender (Females, %)	9 (52.9.1%)	13 (76.5%)	0.282
Age (year)*	33.11 ± 11.83	29.82 ± 12.09	0.428
Pain and burning sensation score*	8.53 ± 1.59	9.18 ± 1.19	0.187
Number of aphthous ulcers per case*	3.06 ± 1.39	4.18 ± 2.16	0.082
Aggregate number of aphthous ulcers (size: <1 , >1 cm)	26, 18	30, 22	0.890

*Mean ± SD

Patients were also assessed for any possible side effects by researchers at each appointment.

Measurements

Clinical findings of both study groups were evaluated every two weeks: researchers assessed size (cm) and number of lesions, recurrences, intensity of pain and burning sensation, and any side effects. The size of the lesions was measured by a transparent calibrated grid. Severity of pain and burning sensation was ranked on a scale of 0-10 using a visual analogue scale (VAS).¹⁷ Two evaluators were involved in the patients' assessment and the investigators were previously calibrated on 15 patients with kappa=0.8.

Outcomes

Objective measures to assess outcome include reductions in ulcer size (cm), number of aphthous ulcers per case, and total number of aphthous lesions. Subjective outcome measures were pain score measured by VAS (mm), and pain free period (weeks).

Statistical analysis

Data were analyzed using SPSS software (version 16.0; SPSS Inc., Chicago, USA). The required sample size for this study using $\alpha = 0.05$ and power = 0.80 was calculated to be 17 patients in each group. The null hypothesis was that the change in the number of oral aphthous ulcers (per case) that occurred after treatment is similar between the colchicine and prednisolone groups. Quantitative variables are expressed as mean ± SD. To evaluate the efficacy of

each individual treatment (colchicine or prednisolone) on the oral aphthous ulcers, before-and-after analysis was performed using paired sample t-test for comparison of variables with normal distribution or non-parametric Wilcoxon rank test for variables that deviated from normal distribution. The baseline characteristics and the changes that occurred in the characteristics of the two groups after treatment were compared using chi-square analysis for categorical variables, Students' sample T test for normally distributed continuous variables, and Mann-Whitney U test for continuous variables which were deviated from normal distribution. $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics of study participants are presented in Table 1. None of the participants showed reluctance to finish the study due to side effects and all of the participants completed the study. There were no significant differences between the two groups with respect to age, gender, pain and burning sensation score, number and size of aphthous lesions. The mean age of patients was 31.5 ± 11.9 years. Maximum prevalence of RAS was seen in the 35-40 years age group.

After three months of follow up (Table 2), no significant differences were found between the two groups considering changes occurred in degree of pain and burning sensation ($p=0.209$), number of RAS per each patient ($p=0.673$), and size of aphthous lesions ($p=0.947$). Both treatment groups showed a significant reduction in pain and burning sensation score ($7.92 \pm$

TABLE 2. Characteristics of patient after treatment with prednisolone or colchicine

	Colchicine (n=17)	Prednisolone (n=17)	P value
Pain and burning sensation score (mean $\pm$ SD)			
Week 0	8.53 $\pm$ 1.59	9.18 $\pm$ 1.19	
Week 2	2.53 $\pm$ 2.98	4.59 $\pm$ 3.02	
Week 4	2.41 $\pm$ 2.48	2.00 $\pm$ 2.42	
Week 6	1.41 $\pm$ 2.15	1.88 $\pm$ 2.69	
Week 8	1.59 $\pm$ 1.84	2.35 $\pm$ 1.73	
Week 10	0.56 $\pm$ 1.03	0.75 $\pm$ 1.77	
Week 12	0.77 $\pm$ 1.48	0.93 $\pm$ 1.54	0.209 [†]
Number of aphthous ulcers per case (mean $\pm$ SD)			
Week 0	3.06 $\pm$ 1.39	4.18 $\pm$ 2.16	
Week 2	1.06 $\pm$ 1.52	2.35 $\pm$ 2.26	
Week 4	0.94 $\pm$ 0.97	1.24 $\pm$ 1.52	
Week 6	0.82 $\pm$ 0.95	1.12 $\pm$ 1.50	
Week 8	0.82 $\pm$ 1.13	1.29 $\pm$ 1.40	
Week 10	0.25 $\pm$ 0.45	0.56 $\pm$ 0.89	
Week 12	0.23 $\pm$ 0.44	0.36 $\pm$ 0.63	0.673 [†]
Aggregate number of aphthous ulcers (size: <1 , >1 cm)			
Week 0	26, 18	30, 22	
Week 2	14, 1	21, 3	
Week 4	10, 1	14, 2	
Week 6	12, 0	13, 1	
Week 8	9, 1	8, 1	
Week 10	4, 0	5, 1	
Week 12	3, 0	4, 1	0.947 [†]
Side effects (n, %)	9 (52.9%)	2 (11.8%)	0.027
Recurrence during treatment (n, %)			
0	0	4 (23.5)	0.171
1	7 (41.2)	5 (29.4)	
2	10 (58.8)	8 (47.1)	
Pain free period (Weeks)	4.29 $\pm$ 2.81	3.66 $\pm$ 2.07	0.571

[†] P values are calculated for comparison of the changes occurred, after 12 weeks of follow up, in pain and burning sensation score, number or size of aphthous ulcers, between the two groups.

Variables are expressed as mean $\pm$ SD, unless otherwise is indicated.

2.39, $p < 0.001$ for colchicine and 8.21 ± 2.01 , $p < 0.001$ for prednisolone group) and number of RAS lesions (2.77 ± 1.49 , $p < 0.001$ for colchicine and 3.79 ± 2.49 , $p < 0.001$ for prednisolone group) (Figure 1). In the follow up period, 9.1% of the patients did not show any recurrences, while in 36.4% of the patients, one time recurrence and in 45.5% of the patients two times recurrences were seen. Number of recurrences ($p = 0.171$) and the duration of pain-free period ($p = 0.571$)

were not significantly different between the two groups. After treatment with colchicine and prednisolone, respectively, 2 (12%) and 3 (18%) patients, still had aphthous ulcers.

In this study, 67.6% of patients did not show any side effects. Side effects were significantly higher in colchicine (52.9%) group compared with the prednisolone (11.8%) group ($p = 0.027$). The side effects of colchicine were gastric disorders ($n = 8$, 47.1%), head-

FIGURE 1. Treatment with both prednisolone (5 mg/d) and colchicine (0.5 mg/d) resulted in a significant ($p < 0.001$) decline in pain and burning sensation score (A) and number of RAS (B), after 12 weeks of therapy. Handles represent standard error of mean.

ache ($n=1$, 5.9%), and vertigo ($n=3$, 17.6%). The side effects of prednisolone were hypertension ($n=1$, 5.9%), and headache ($n=1$, 5.9%).

Discussion

The main approach prior to treatment of RAS is to determine the probable etiologic factors. As the exact pathogenesis of RAS still remains unknown, none of the proposed treatments have shown satisfying results.¹ Nowadays, systemic administration of colchicine, prednisolone and cyclosporine is considered for the aphthous ulcers which are refractory to common conservative treatments.¹² In fact, there is no consensus on an effective treatment for RAS that can efficiently reduce the signs and symptoms of the disease at a low daily dose and with minimal effects.

Different doses of colchicine and prednisolone has been used for treatment of oral aphthous ulcers in previous studies. Genvo *et al.* compared the treatment effects of daily dose of 3 mg colchicine with 300 mg talidomide in 25 patients with RAS.¹⁸ They reported a greater reduction in pain and burning sensation and a

faster healing with colchicine. Viguier *et al.* compared the effects of 1 mg/kg daily dose of prednisolone with 2 mg/d colchicine in five patients with RAS.¹¹ It was found that prednisolone resulted in faster healing of ulcers while colchicine managed pain and burning sensation much more effectively.¹¹ This study was similar to ours considering type of medications used; however, we found no significant difference between the two medications regarding the healing of ulcers. Apart from the small sample size of the previous study ($n=5$), which necessitates caution when interpreting the results, the high dose of prednisolone (1 mg/kg) could explain the greater efficacy of the medication. Frontes *et al.* evaluated the effects of 1.5 mg/d dose of colchicine for three months in 54 patients with RAS.⁸ The study reported a 50% reduction in pain intensity and burning sensation. Although Frontes' study used a higher dose of colchicine, 37% of patients still reported ulcers after three months of treatment. In our study, only two patients (12%) had aphthous ulcers after treatment with the lower dose of colchicine. Besides the difference in the prescribed dosage, different

estimates on the efficacy of colchicine for RAS treatment might be explained by genetic differences in different populations. This fact can be best revealed by conducting double blind clinical trials.^{9,14} Our results showed that in Middle Eastern populations such as Iran, colchicine seems to have a higher efficacy and can thus be used in low doses. In 1994 in an open trial, Katz and colleagues studied the effects of colchicine on prevention of RAS in 20 patients in a four months follow-up study.⁹ The patients did not take any medication in the first two months of the study, but were given a daily dose of 1.5 mg colchicine over the next two months. There was a 71% and 77% reduction in the number of ulcers and intensity of pain, respectively, in comparison with the first two months ($p < 0.001$). This shows less efficacy for colchicine than our study.

Femiano *et al.* compared treatment effects of 25 mg/d prednisolone with Sulodexide (a low molecular weight heparin derivative that has immunosuppressive effects) on 30 patients with RAS. After three months of treatment, they found better treatment effects with greater reduction in pain and burning sensation (using VAS) and a greater reduction in the number of aphthous lesions in patients taking prednisolone in comparison with Sulodexide, although more side effects were seen in the prednisolone group.¹⁰ Tasher *et al.* evaluated the prophylactic effects of daily dose of 0.5-1 mg colchicine in prevention of RAS in nine children with PFAPA syndrome (periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis). Prior to treatment, these patients had recurrences of RAS at least twice a month. The study found that the treatment significantly increased the RAS disease-free interval.¹⁹ In another study evaluating the therapeutic effects of colchicine (0.6-1.8 mg/d gradually increasing by patient's tolerance) and dapsone (75-100 mg/d gradually increasing by patient's tolerance) on complex aphthous stomatitis, it was shown that both medicines, used in combination or separately, exhibited positive treatment effects.²⁰ The main limitation of this study was its retrospective design.

Although we tried to control all factors, there is an issue with aphthous ulcers that they usually come and go within 1-2 weeks. This can randomly result in the probable evaluation of patients on the days in between outbreaks. Unfortunately, there was no way to control for this unless future studies with daily visit of the patients should be designed. Studies with a longer duration to evaluate the frequency of recurrences would also be beneficial. Moreover, information on the efficacy of different doses of medications in different population groups would be useful.

In conclusion, daily dose of 0.5 mg colchicine or 5 mg prednisolone for treatment of RAS were both equally effective in reducing pain and burning sensation, recurrences, size and number of aphthous lesions. The incidence of side effects in the colchicine group (47.1%) was considerably higher than in the prednisolone group (11.8%). Prednisolone (5 mg/d) is an effective treatment for patients with RAS with high levels of recurrences. Our results provide practical hints for better management of RAS, particularly in Middle Eastern populations.

References

1. Bischoff EW, Uijen A, van der Wel M. Aphthous ulcers. *BMJ* 2009;339:b2382.
2. Scully C, Gorsky M, Lozada-Nur F. The diagnosis and management of recurrent aphthous stomatitis: a consensus approach. *J Am Dent Assoc* 2003;134:200-207.
3. Scully C. Clinical practice. Aphthous ulceration. *N Engl J Med* 2006;355:165-172.
4. Altenburg A, Abdel-Naser MB, Seeber H, Abdallah M, Zouboulis CC. Practical aspects of management of recurrent aphthous stomatitis. *J Eur Acad Dermatol Venereol* 2007;21:1019-1026.
5. Babae N, Mansourian A, Momen-Heravi F, Moghadamnia A, Momen-Beitollahi J. The efficacy of a paste containing *Myrtus communis* (Myrtle) in the management of recurrent aphthous stomatitis: a randomized controlled trial. *Clin Oral Invest* 2009
6. Munoz-Corcuera M, Esparza-Gomez G, Gonzalez-Moles MA, Bascones-Martinez A. Oral ulcers: clinical aspects. A tool for dermatologists. Part II. Chronic ulcers. *Clin Exp Dermatol* 2009;34:456-461.

7. Munoz-Corcuera M, Esparza-Gomez G, Gonzalez-Moles MA, Bascones-Martinez A. Oral ulcers: clinical aspects. A tool for dermatologists. Part I. Acute ulcers. *Clin Exp Dermatol* 2009;34:289-294.
8. Fontes V, Machet L, Huttenberger B, Lorette G, Vailant L. Recurrent aphthous stomatitis: treatment with colchicine. An open trial of 54 cases. *Ann Dermatol Venereol* 2002;129:1365-1369.
9. Katz J, Langevitz P, Shemer J, Barak S, Livneh A. Prevention of recurrent aphthous stomatitis with colchicine: an open trial. *J Am Acad Dermatol* 1994;31:459-461.
10. Femiano F, Gombos F, Scully C. Recurrent aphthous stomatitis unresponsive to topical corticosteroids: a study of the comparative therapeutic effects of systemic prednisone and systemic sulodexide. *Int J Dermatol* 2003;42:394-397.
11. Viguier M, Fouere S, Pascal F, Morel P. Herpetiform ulceration: 5 cases. *Ann Dermatol Venereol* 2000;127:707-710.
12. Altenburg A, Zouboulis CC. Current concepts in the treatment of recurrent aphthous stomatitis. *Skin Therapy Lett* 2008;13:1-4.
13. Pedersen A, Klausen B. Glucocorticosteroids and oral medicine. *J Oral Pathol* 1984;13:1-15.
14. Altinor S, Ozturkcan S, Hah MM. The effects of colchicine on neutrophil function in subjects with recurrent aphthous stomatitis. *J Eur Acad Dermatol Venereol* 2003;17:469-470.
15. Sullivan TP, King LE, Jr., Boyd AS. Colchicine in dermatology. *J Am Acad Dermatol* 1998;39:993-999.
16. Terkeltaub RA. Colchicine update: 2008. *Semin Arthritis Rheum* 2009;38:411-419.
17. Scott J, Huskisson EC. Graphic representation of pain. *Pain* 1976;2:175-184.
18. Genvo MF, Faure M, Thivolet J. Treatment of aphthosis with thalidomide and with colchicine. *Dermatologica* 1984;168:182-188.
19. Tasher D, Stein M, Dalal I, Somekh E. Colchicine prophylaxis for frequent periodic fever, aphthous stomatitis, pharyngitis and adenitis episodes. *Acta Paediatr* 2008;97:1090-1092.
20. Lynde CB, Bruce AJ, Rogers RS, 3rd. Successful treatment of complex aphthosis with colchicine and dapsone. *Arch Dermatol* 2009;145:273-276.

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