Effects of tetracycline and *Myrtus communis* extract on the treatment of recurrent aphthous ulcers: A comparative study

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Abstract

Introduction: It is widely accepted that recurrent aphthous stomatitis (RAS) is the most common recurrent oral ulcer. Since none of the various symptomatic therapies recommended for painful periods can affect the etiology of the disease, the goal is only to reduce the severity of the pain, irritation, and duration of the ulcers. The purpose of this study was to compare the effects of tetracycline and *Myrtus communis* extract (*Myrtex*) on the treatment of RAS.

Materials and Methods: The patients (n=54) enrolled in the study consisted of two groups of 26 and 28 people who received tetracycline and *Myrtex*, respectively. The case group received *Myrtex* solution and the control group received 250-mg tetracycline capsules. The patients in both groups kept the drug on the ulcer for 30 seconds four times a day. They answered the visual analogue scale (VAS) on days 0, 2, and 6 and were clinically examined to check any chenges in ulcer size and healing.

Results: According to VAS analysis, the pain and irritation levels in the *Myrtex* group were 34.8% less than in the tetracycline group ($P<0.02$). The ulcer size was 40% higher on the second day in the *Myrtex* group than in the tetracycline group, which was statistically significant ($P<0.02$), but the ulcer size changes on the sixth day of follow-up were not statistically significant ($P<0.15$).

Conclusion: According to the study, the administration of *Myrtex* is more effective in reducing the severity of pain and irritation and improving the quality of life. Therefore, it is recommended to prescribe *Myrtex* (*Myrtex* 5%) on the basis of the mentioned method for the treatment of minor aphthous.

Keywords: Recurrent aphthous stomatitis, Tetracycline, *Myrtus communis* extract, Visual analogue scale, Ulcer duration

Introduction

Recurrent aphthous stomatitis (RAS) is one of the most common oral mucosal ulcers that despite its high prevalence, due to lack of accurate etiology and pathogenesis, has not yet been conclusively treated,. Therefore,

various symptomatic therapies have been proposed for this disease, which are associated with several side effects in some cases (1).

Since none of the treatments can affect the etiology of the disease, efforts are being made to alleviate the appearance and symptoms of these ulcers, as the goal of treatments is to reduce the severity of pain and irritation and shortening the ulcer duration (1, 2).

Due to the recurrent nature of the disease, long-term use of chemical drugs can lead to several side effects. Therefore, the need to achieve other compounds with fewer side effects has always been considered. Medicine, on the other hand, is now turning to herbal and traditional medicines.

There are numerous statements and reports in traditional Iranian medicine about the use of the herbal medicine *Myrtus communis extract(Myrtex)* in washing and disinfecting ulcers and relieving oral mucosal irritation (3- 5). In addition, the strong antimicrobial effects of this plant extract against various microorganisms and fungi have been reported in various studies (7, 6). Various therapeutic uses of *Myrtex* have been reported in other countries, with minimum side effects in topical use. Moreover, several studies have shown that *Myrtex* has potent antibacterial, anti-inflammatory and antioxidant effects that can be effective in relieving RAS symptoms (3, 5).

The prevalence of RAS in the population, causing discomfort in the oral cavity, impaired daily functioning, and symptomatic treatment of existing therapies have led researchers to seek solutions in traditional and herbal medicine in the treatment of oral mucosal lesions. Therefore, we decided to compare *Myrtex* extract whose beneficial effects have been confirmed on aphthous ulcers with tetracycline that has been confirmed as a synthetic drug commonly used in the treatment of such lesions.

Materials and Methods

The present randomized interventional study was conducted on 54 patients referred to Shahed Dental School. The patients who had minor aphthous after examining and confirming the RAS diagnosis based on the clinical appearance of the ulcer and related diagnostic criteria, and had willingness to participate in the project were enrolled in the study. Sampling began after obtaining written consent from the patients to participate in the study. Inclusion criteria were: presence of minor aphthous in the area of the oral cavity where it is possible to access the topical application of the drug, age in the range of 15-50 years, voluntary willingness to cooperate in this research and follow the recommendations on how to use the drug.

The study exclusion criteria were history of systemic disease or syndrome associated with aphthous or psuedo-aphthous ulcers (including ulcerative colitis and Reiter's disease), smoking, pregnancy or breastfeeding, taking other drugs for treatment and more than 48 hours from the onset of aphthous ulcers. Furthermore because there is no clear distinction between minor or major aphthous ulcers, the patients experiencing severe discomfort due to successive courses with more than 10 ulcers (though each of these ulcers is less than one centimeter in diameter, which is called "severe minor" ulcers) were excluded from the study.

The selected patient completed the visual analogue scale (VAS) to check the severity of the symptoms and was clinically examined by the researcher to assess the condition and measure the ulcer size using a checkered stencil. Patients responded to the questionnaire on days 0, 2, and 6 and were clinically examined. On day zero, the day of admission and before receiving treatment (baseline), six patients were excluded from the study, each of whom was unable to

cooperate for some reason or did not visit on the appointed days, including 4 in the tetracycline group and 2 in the myrtex group. The patients (n=54) enrolled in the study consisted of two groups of 26 and 28 people who received tetracycline and myrtex, respectively.The case group received myrtex solution and the control group received 250-mg tetracycline capsule.Patients in the case group used 15 drops each time according to the manufacturer's instructions. The control group was advised to mix one tetracycline capsule with 10 cc of water each time and to refrain from preparing the high-volume suspension or maintaining for later use during the day. The members of this group each received a dropper so that the concentration of the suspension prepared by them would be the same at different times and in different people. In each group, it was recommended that each small piece of cotton swab be smeared with 0.35 cm of the drug and kept on the wound for 30 seconds. They repeated the procedure four times a day, and refrained from eating and drinking or rinsing the mouth for at least 30 minutes after taking the drug to improve the effect of the medication. It was also used once after the night toothbrush.When the drug was placed on the ulcer, there was a slight feeling of normal irritation, which had already been warned to patients.

Because tetracycline mouthwash can lead to changes in the oral microflora and subsequently develop fungal infection of oral candidiasis, which also requires treatment with antifungal drug of nystatin, the study recommended that topical tetracycline be used only on the ulcer (by placing drug-soaked cotton), which did not cause severe irritation or chemical burns due to the limited positioning on the ulcer. Patients continued these instructions from the beginning of treatment until the ulcer was healed. If the ulcers had not yet healed on day 6, the appointment would be made on days 7 and 8 and, if necessary, on days 9 or 10.

The patients were instructed to be very careful about the severity of pain and irritation caused by aphthous ulcers and duration of healing, and to complete the questionnaire patiently, as well as to avoid any other treatment during the research collaboration.

Results

The study was carried out on 54 patients with RAS in two groups of tetracycline (n=26) and myrtex (n=28), including 35 women and 18 men. the minimum and maximum age was 18 and 42 years, respectively.

The characteristics of individuals, the duration of treatment and the duration of illness separately for the case and control group are presented in Table 1. The results showed that individuals in both groups were homogeneous in terms of age, sex, duration of treatment, duration of illness and pain at the baseline, and the difference was not statistically significant ($P<0.1$).

The severity of pain and irritation according to the follow-up days separately for the case and control group is presented in Table 2. The results showed that the severity of pain and irritation on the second day was 3.2 ± 3.1 in the tetracycline group and 5.1 ± 0.9 in the myrtex group, which was 8.0 or 8.3% lower in the myrtex group than in the tetracycline group ($P<0.02$).

It was also about 33% in the tetracycline group ($P<0.06$) on the sixth day. On the seventh day, the myrtex group had no pain and the tetracycline group had mild pain, but there was no significant difference ($P<0.3$).

The ulcer size according to the follow-up days and separately for the case and control groups is presented in Table 3. The results showed that the ulcer size on the second day of follow-up in the myrtex group was 2 mm^2 or 40% higher than the tetracycline group, and this difference was significant ($P<0.02$).

On the sixth day of follow-up, the ulcer size was bigger in the myrtex group than in the tetracycline group, but was not statistically significant (P<0.15).

On the seventh and eighth day, the ulcer size was still bigger in the myrtex group than in the tetracycline group, and this difference was statistically significant (P<0.008).

Table 1. Characteristics of the individual, duration of the disease and time of referral in the Tetracycline and *Myrtex* treatment groups.

Charactristic	Tetracycline (n=26)	*Myrtex* (n=28)	P value
Age (year)			0.08
≥28	18 (64.3)	13 (46.4)	
<28	8 (28.7)	15 (53.6)	
Sex			0.7
male	8 (30.8)	10 (35.7)	
female	18 (33.3)	17 (64.3)	
Duration (day)			0.2
≥7	19 (73.1)	16 (54.1)	
<7	7 (26.9)	12 (42.9)	
Day			0.9
0	20 (76.9)	22 (78.6)	
1	6 (23.1)	6 (21.4)	
Size in day 0 (mm)	7 ± 3.01	7 ± 2.91	0.4
Pain and irritation in day 0	3 ± 0.81	2.9 ± 0.93	0.6

Data are shown as number (perecent) or mean ± SD.

Table 2. The severity of pain and irritation according to the days of followup in the Tetracycline and *Myrtex* treatment groups.

Followup day	Tetracycline (n=26)	*Myrtex* (n=28)	P value
2	2.3 ± 1.3	1.5 ± 0.09	0.02
6	0.95 ± 0.64	0.51 ± 0.23	0.06
7	0.4 ± 0.09	0	-
8	0.3 ± 0.08	0	-
9	0	0	-

Data are shown as mean ± SD.

Table 3. The ulcer size according to the followup days in the Tetracycline and *Myrtex* treatment groups.

Ulcer size after folowup days	Tetracycline (n=26)	*Myrtex* (n=28)	P value
2	5 ± 2.3	7.00 ± 0.09	0.02
6	2.30 ± 1.80	3.4 ± 3.03	0.15
7	1.00 ± 0.65	2.01 ± 0.23	0.005
8	0.5 ± 0.19	1.2 ± 0.9	0.008
9	0	0	-

Data are shown as mean ± SD.

Discussion

Due to the high prevalence of aphthous ulcers and recurrent discomfort for patients, as well as the lack of accurate knowledge of the etiological causes of the disease, a symptomatic treatment with low side effects has been consistently considered.

Considering the antimicrobial and sedative effects of tetracycline and myrtex, as well as the unavailability of studies comparing the two, each of which has been identified in separate studies as an effective drug for treatment of recurrent aphthous ulcers, the present study is an attempt to achieve this.

In this study, the prevalence of the disease was slightly greater in women than in men, although this difference was not statistically significant and two groups were considered

to be homogeneous; this finding is consistent with other studies, including statistical results reported by Azimi and Badiee in 1997 (8-11). Clinically changed ulcer size on the second day were found to be less in the tetracycline group, and this difference was statistically significant. This may be related to the cauterization of myrtex, which has led to an increase in ulcer size at the beginning of the course of the drug administration compared to tetracycline. This finding confirms previous research by Babaei and Mansourian in 2009, as well as Azimi and Badiee in 1997, in which they stated that myrtex had antimicrobial and, to some extent, ulcer-cauterizing effects (11,12). This result was consistent with the findings of Graykowski and Kingman et al., as well as Hayder et al. in 2004 (13,14), who achieved statistically significant reduction in the aphthous ulcer size following tetracycline treatment. Altenburg in 2008 examined tetracycline mouthwash and reported findings similar to the results of the present study (15).

In the last days of the treatment period, i.e. days 7 and 8, this difference in the ulcer size was significant between the two groups .

The mean duration of complete clinical healing of ulcers in the tetracycline and myrtex groups was lower compared to other studies that reported an overall improvement of 10.5 days (9), which was obtained less than 7 days in each group, so that myrtex and tetracycline groups accounted for 57.1% and 73.1%, respectively. Comparing tetracycline and myrtex in this study, the statistical results showed no significant difference. Although tetracycline caused a further decrease in ulcer size, both drugs showed almost the same effects in reducing the duration of illness.

Graykowski et al. reported significant reductions in the duration of treatment followed by topical tetracycline, but no results were available to compare with myrtex (14,16).

Relying on the fact that both of these drugs had antimicrobial effects, each could shorten the duration of ulcer healing.

According to studies, the mean severity of pain and irritation caused by ulcer on days 2 and 6 in each group. It seems that the effect of myrtex on reducing the severity of pain and irritation compared with tetracycline is reasonably evident on the second day and on the sixth day. In fact, the myrtex reduces pain over a shorter period of time.

Rezvaninejad et al. in 2017 achieved similar results in confirming the palliative effect of myrtex on recurrent aphthous ulcers, which is consistent with the findings of the present study (17).The available review articles also confirm this finding (18-20).

To support the findings of Graykowski, Hayrinen et al. in 1994 (21) also showed the acceleration of ulcer healing process of this disease following topical administration of tetracycline (14).

Conclusion

According to the findings of the present study, it can be concluded that although myrtex showed no superiority over tetracycline in reducing ulcer size and that both drugs caused ulcer healing in almost the same time, the myrtex can be more effective in improving the quality of life in patients with RAS due to reduceding pain severity in a shorter time, and indeed, accelaration in relieving pain. Therefore, the present study recommends the administration of myrtex (Myrtus communis extract 5%) in accordance with the protocol mentioned for the treatment of patients with minor aphthous ulcers.

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