The effect of *Matricaria chamomilla* (chamomile) extract in Orabase on minor aphthous stomatitis, a randomized clinical trial

Azadeh Andishe Tadbir\(^a\), Sara Pourshahidi\(^b,\)\(^*\), Hooman Ebrahimi\(^c\), Zohre Hajipour\(^d\), Mohammad Reza Memarzade\(^e\), Shiva Shirazian\(^b\)

\(^a\) Department of Oral Pathology, School of Dentistry, Shiraz University of Medical Sciences, Shiraz, Iran
\(^b\) Department of Oral Medicine, School of Dentistry, Tehran University of Medical Sciences, Tehran, Iran
\(^c\) Oral Medicine Department, Dental School, Azad University, Tehran, Iran
\(^d\) Student Research Committee, School of Dentistry, Shiraz University of Medical Sciences, Shiraz, Iran
\(^e\) Research center of herbal medicine of Barij, Department of formulation, Kashan, Iran

**Abstract**

Recurrent aphthous stomatitis (RAS) is a common and painful oral mucosal disease, however, its etiology and pathogenesis is not entirely clear. Many therapeutic protocols have been tried, but effectiveness remains an issue. The aim of this study was to compare *Matricaria chamomilla* (chamomile) extract and triamcinolone in Orabase on oral mucosal minor aphthous stomatitis. The study was a randomized, double-blind clinical trial. 45 patients participated in the study; randomly divided into three groups. The first group received placebo, the second group triamcinolone in Orabase and the third group chamomile in Orabase. Four variables were assessed in the study, including, size of the ulcer, intensity of pain, time required to complete resolution of the ulcer and satisfaction of patients. Triamcinolone and chamomile in Orabase reduced ulcer size by day 3 and pain by days 3 and 6 similarly with a significant difference from the placebo group. But triamcinolone in Orabase was superior to both chamomile in Orabase and placebo at reducing size of the ulcers by day 6 and the time taken to complete resolution of the ulcers. In addition, chamomile in Orabase produced patient satisfaction. According to this study, chamomile decreased the pain of the ulcers and provided satisfaction for the patients.

© 2015 Elsevier GmbH. All rights reserved.

1. Introduction

Recurrent aphthous stomatitis (RAS) is one of the most common oral mucosal lesions and affects approximately 20% of the general population (Pourahmad et al., 2010). In a study by Davatchi et al. in Tehran, out of 10,291 interviewed people, 25.2% were affected by RAS (Davatchi et al., 2008). In another study performed by Shirzaei in Zahedan, of 1105 patients examined in Zahedan Health Centres, 18% suffered from RAS.
(Shirzaei, 2011). According to these studies, prevalence of RAS is rather high in Iran.

RAS is more common in women than men and usually appears first in childhood or adolescence (Samet et al., 2007). RAS is divided, on morphological criteria, into three groups: minor ulcers, which are the most prevalent form (80% of all RAS), smaller than 1 cm in diameter and resolve within 10–14 days without scarring; major ulcers, which are characterized by painful ulcers, larger than 1 cm in diameter and lasting several weeks; and, herpetiform ulcers, a rare type of RAS with a bunch of small pinpoint ulcers (Babae et al., 2010; Chattopadhyay and Shetty, 2011; Huling et al., 2012; Liu et al., 2012; Yasui et al., 2010). While the exact cause of RAS is still unknown, some aetiological factors such as genetics, allergies, medication, menstruation period, stress, excitement, fatigue, immune system dysfunction, bacterial or viral agents, chemical agents and vitamin deficiency have been suggested (Babae et al., 2010; Chattopadhyay and Shetty, 2011; Huling et al., 2012; Kolseth et al., 2005; Liu et al., 2012; Messier et al., 2012; Wardhana and Datau, 2010). Of these factors, genetic is the most significant factor (Koybasi et al., 2006). The probability of someone suffering from RAS is 90% when both parents are affected, but only 20% when neither parent has RAS (Scully et al., 2003). Despite their self-limiting nature, many patients suffer from persistent ulcers, so that before an ulcer is healed, a new one appears. Ulcers can make speech, eating and swallowing uncomfortable for patients. Therefore may have a negative influence on patients’ quality of life (Wardhana and Datau, 2010).

Treatments suggested for RAS are often palliative to relieve pain, promote healing and prevent secondary infection. These treatments include corticosteroids, antibiotics, local anaesthetics, analgesics and immune modulators (Femiano et al., 2007; Liu et al., 2012; Messier et al., 2012). Corticosteroids such as triamcinolone are the mainstay of RAS treatment (Scully and Porter, 2008). The major concern here is adrenal suppression caused by systemic steroids and local adverse effects associated with topical therapy, including oral candidiasis (Gorsky et al., 2007). Chuanxia Liu and colleagues studied the efficacy and safety of a topical corticosteroid on RAS. In their study no important side effects were detected, except perioral rashes and burning at the site the corticosteroid was administered (Liu et al., 2012). Bakhtiari performed a study to evaluate patients’ satisfaction of medicinal plants in Isfahan. 37% of patients knew herbal drugs well and better than chemical drugs. 21% believed that chemical drugs are better and 67% did not give an opinion. In fact due to the side effects of some chemical drugs, many patients would prefer to use herbal treatment. Considering the side effects of chemical drugs and patients’ interest in using herbal medicines, medicinal plants have received increasing attention (Bakhtiari, 2010).

Some herbs like Alchemilla vulgaris, Matricaria chamomilla and Aloe barbadensis have been reported to be used in the management of RAS (Meksepralard et al., 2010). There have also been some trials on the effect of these substances on RAS, for example, in one, a paste containing Myrtus communis was compared to placebo in 45 patients with RAS and as a result the researchers declared that the herbal substance was effective in reduction of pain severity, ulcer size, erythema and exudates. They also found it effectively improved the quality of life of the patients (Babae et al., 2010).

Chamomile is a widely available herb with diverse therapeutic uses that has been used for centuries as a medicinal plant (Srivastava et al., 2010). The components of the essential oil extracted from chamomile flowers possess anti-inflammatory, anti-allergic, anti-spasmodic, anti-bacterial, anti- pyretic, ulcer-protective, anti-fungal, sedative, analgesic and anti-oxidant properties (Ghavimi et al., 2012; Shrafzadeh and Alizadeh, 2011; Srivastava et al., 2010; Srivastava and Gupta, 2009; Zeggagh et al., 2009). Some of these principle components are terpenoids, flavonoids, bisabolol and chamazulene (Shrafzadeh and Alizadeh, 2011; Srivastava and Gupta, 2009). Cimen et al. studied oxidant/antioxidant status in patients with RAS; they demonstrated that enzymatic and non-enzymatic antioxidant defence systems are impaired in patients with RAS (Cimen et al., 2003). Holbrook et al. demonstrated that the amount of antioxidant vitamins such as A, C and E is decreased in the saliva and serum of RAS patients (Holbrook et al., 1998). Therefore, the antioxidant potential of chamomile may promote healing of the ulcers. Hamalainen et al. demonstrated the inhibitory effect of kaempferol, daidzein, genistein and quercetin on STAT-1 and NF-κB, while naringenin, flavone and isorhamnetin inhibited only NF-κB activation and inducible nitric oxide synthase (iNOS) expression. While nitric oxide (NO) is induced in inflammatory processes, compounds that have an inhibitory effect on NO production can have an anti-inflammatory effect (Hamalainen et al., 2007). According to these studies, the anti-inflammatory mechanisms of the flavonoids in chamomile can play a role in healing of the ulcers. Chamomile tea has been recommended for mouth inflammation (Srivastava et al., 2010). In folk medicine, chamomile has been suggested for mouth ulcers (Amin et al., 2011). To our knowledge, there is one study about the effect of chamomile extract on aphthous ulcers. Ramos-e-Silva et al. evaluated the safety and effectiveness of a fluid extract of chamomile on pain relief in RAS. They evaluated two parameters, analgesic effect and tolerance. The analgesic effect was considered excellent by 82% and good by 18% of patients. Tolerance was excellent according to 97% and good by 3% of the participants (Ramos-e-Silva et al., 2006). In order to determine the efficacy of chamomile extract when applied topically for the treatment of RAS, a new Orabase containing chamomile extract was developed and a randomized, double-blind, placebo-controlled clinical trial was performed. The purpose of this study was to assess the clinical efficacy of Orabase containing Chamomile extract in treating RAS.

2. Materials and methods

The study was a randomized, double-blind, placebo-controlled clinical trial and was conducted at Shiraz University of Medical Science in Iran. 45 patients of both genders were enrolled for participation in the study. Patients were selected from September 2012 till May 2013. The inclusion criteria were that patients should have a clear history of RAS, be aged 18–60 years, have adequate motivation and understanding to participate in the study, and provide informed consent. The patients also had had only one minor aphthous stomata, initiated in
the last 48h. Exclusion criteria were: presence of any systemic haematological or immunological problems, drug or alcohol abuse, taking treatment for lesions within 1 month prior to the study, pregnancy or allergy to chamomile or triamcinolone. Patients whose ulcer was not easily accessible were also excluded from the study.

Individuals were divided into three groups, using a block randomization method. The group treated with Orabase only as placebo was named “0” group, the group treated with triamcinolone in Orabase was named “T” group and the last group treated with chamomile in Orabase was called “C” group. The pastes were prepared in similar tubes by a pharmaceutical company. Participants signed an informed consent form. A nurse was responsible for distribution of the medications to patients according to their codes. The patients and the investigator evaluating variables of the study were blind to the medications. All participants were assessed three times during the treatment period (on days 1, 3 and 6). Four variables were evaluated in this study: pain intensity, size of ulcer, days to complete resolving of the ulcer and satisfaction of patients. Pain intensity is difficult to evaluate because it is subjective. One method for pain evaluation is the 10-point VAS system in which “0” means mildest pain and “10” means worst pain. This system is an easily understandable scale for patients to evaluate pain. The size of ulcer was measured by a sterile calliper. Patients’ satisfaction of their treatment was evaluated by three descriptions: quite satisfied, satisfied and dissatisfied.

We asked patients to use their preparation four times a day, after eating and performing oral hygiene and to continue till complete resolution. They were examined each session for any unwanted side effects such as hypersensitivity and infection. A phone number was also available for any questions. The collected data were analyzed using SPSS version 17. We had three variables including pain intensity, size of the ulcers and days required to complete resolution of the ulcers, which were compared across the three groups using the Mann–Whitney test. The Chi-square test was used to analyze gender and location of the ulcers and Repeated measures ANOVA was used for comparison of age between patients.

3. Results

There were 45 patients of both genders. Two patients (4.4%) discontinued the study and were dropped from the study due to lack of cooperation. One of them was in the group treated with triamcinolone in Orabase and another in the group treated with chamomile in Orabase. Overall 15 patients received placebo (Orabase alone) as the negative control group (group O), 14 patients received triamcinolone in Orabase as the positive control group (group T) and 14 patients received chamomile in Orabase as the test group (group C). Group O consisted of 5 (33.3%) males and 10 (66.7%) females, with a mean age of 28.93 ± 7.294 (20–46 years). Group T consisted of 9 (64.3%) males and 5 (35.7%) females, with a mean age of 30.86 ± 4.786 (22–40 years). Group C consisted of 4 (28.6%) males and 10 (71.4%) females, with mean age of 28.29 ± 7.488 (19–43 years). There was no statistical difference between the groups in age (p=0.571) or gender (p=0.113). Most of the ulcers were located on buccal mucosa and there was no statistical significant difference between groups in location of the ulcers (p=1). Ulcer size and pain intensity had no statistically significant differences between the three groups at the beginning, but after using the remedies for 3 days, there were significant differences. In groups T and C, the ulcer size and pain intensity, were significantly less than in group O. On the other hand there was no statistically significant difference between group T and C in these two variables (p>0.05; Tables 1 and 2). After 6 days, in group T the decrease in ulcer size was significantly greater than groups O and C. There was no significant difference between groups O and C in the decrease in ulcer size on day 6 (p=0.343; Table 1). Groups T and C had statistically significant differences from group O in pain intensity at the last visit, which means that application of triamcinolone and chamomile on RAS ulcers significantly lowered the pain intensity in comparison with placebo (Table 2).

Another parameter that we evaluated was the time to complete resolution of symptoms, which was statistically significantly shorter in group T than in groups O and C (Fig. 1). The last parameter was patient’s satisfaction of their treatment. Of the 15 patients in group O, 9 people were dissatisfied with their treatment; on the other hand, in group T 10 out of 14 participants were quite satisfied and 9 out of 14 patients in group C were quite satisfied (Table 3).

4. Discussion

RAS is a self-limiting lesion, but repeated ulceration has a negative effect on patients’ quality of life (Messadi and Younai, 2010). Currently, there is no known aetiology for the ulcers, nor is there a treatment that can safely and conclusively treat ulcers. Different treatments are recommended for RAS. Corticosteroids are the most important treatment. The side effects of using drugs such as corticosteroids, and greater interest in herbal drugs, led us to find a herbal substitute for conventional treatment. The herb chosen to evaluate its effects on RAS in this study was chamomile, due to components, such as terpenoids, bisabolol, chamazulene and flavonoids.
Table 1 – Size of the ulcers at three sessions in groups O, T and C. (Group O = placebo, Group T = triamcinolone, Group C = chamomile).

<table>
<thead>
<tr>
<th>Time/size of the ulcer</th>
<th>Comparing groups O and T</th>
<th></th>
<th></th>
<th></th>
<th>Comparing groups O and C</th>
<th></th>
<th></th>
<th></th>
<th>Comparing groups T and C</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>P value</td>
<td>Mean ± SD</td>
<td>P value</td>
<td>Mean ± SD</td>
<td>P value</td>
<td>Mean ± SD</td>
<td>P value</td>
<td>Mean ± SD</td>
<td>P value</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Group O</td>
<td>Group T</td>
<td></td>
<td></td>
<td>Group O</td>
<td>Group C</td>
<td></td>
<td></td>
<td>Group T</td>
<td>Group C</td>
<td></td>
</tr>
<tr>
<td>Size at the first visit</td>
<td>2.700 ± 0.9783</td>
<td>2.536 ± 0.9500</td>
<td>0.699</td>
<td></td>
<td>2.700 ± 0.9783</td>
<td>2.643 ± 0.7703</td>
<td>0.852</td>
<td></td>
<td>2.536 ± 0.9500</td>
<td>2.643 ± 0.7703</td>
<td>0.584</td>
</tr>
<tr>
<td>Size at the second visit (day3)</td>
<td>3.000 ± 0.6268</td>
<td>1.179 ± 0.3725</td>
<td>0.000</td>
<td></td>
<td>3.000 ± 0.6268</td>
<td>1.429 ± 0.9778</td>
<td>0.000</td>
<td></td>
<td>1.179 ± 0.3725</td>
<td>1.429 ± 0.9778</td>
<td>0.220</td>
</tr>
<tr>
<td>Size at the last visit (day6)</td>
<td>1.667 ± 0.9386</td>
<td>0.214 ± 0.4258</td>
<td>0.000</td>
<td></td>
<td>1.667 ± 0.9386</td>
<td>1.357 ± 0.9493</td>
<td>0.343</td>
<td></td>
<td>0.214 ± 0.4258</td>
<td>1.357 ± 0.9493</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Table 2 – Pain intensity at three sessions in groups O, T and C. (Group O = placebo, Group T = Triamcinolone, Group C = Chamomile).

<table>
<thead>
<tr>
<th>Time/pain intensity</th>
<th>Comparing groups O and T</th>
<th></th>
<th></th>
<th></th>
<th>Comparing groups O and C</th>
<th></th>
<th></th>
<th></th>
<th>Comparing groups T and C</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>P value</td>
<td>Mean ± SD</td>
<td>P value</td>
<td>Mean ± SD</td>
<td>P value</td>
<td>Mean ± SD</td>
<td>P value</td>
<td>Mean ± SD</td>
<td>P value</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Group O</td>
<td>Group T</td>
<td></td>
<td></td>
<td>Group O</td>
<td>Group C</td>
<td></td>
<td></td>
<td>Group T</td>
<td>Group C</td>
<td></td>
</tr>
<tr>
<td>Pain intensity at the first visit</td>
<td>3.80 ± 2.077</td>
<td>4.14 ± 1.351</td>
<td>0.464</td>
<td></td>
<td>3.80 ± 2.077</td>
<td>3.92 ± 1.592</td>
<td>0.689</td>
<td></td>
<td>4.14 ± 1.351</td>
<td>3.92 ± 1.592</td>
<td>0.673</td>
</tr>
<tr>
<td>Pain intensity at the second visit (day3)</td>
<td>4.47 ± 1.457</td>
<td>1.71 ± 0.611</td>
<td>0.000</td>
<td></td>
<td>4.47 ± 1.457</td>
<td>2.36 ± 2.240</td>
<td>0.011</td>
<td></td>
<td>1.71 ± 0.611</td>
<td>2.36 ± 2.240</td>
<td>0.603</td>
</tr>
<tr>
<td>Pain intensity at the last visit (day6)</td>
<td>2.40 ± 1.502</td>
<td>0.43 ± 0.852</td>
<td>0.01</td>
<td></td>
<td>2.40 ± 1.502</td>
<td>0.71 ± 0.611</td>
<td>0.02</td>
<td></td>
<td>0.43 ± 0.852</td>
<td>0.71 ± 0.611</td>
<td>0.097</td>
</tr>
</tbody>
</table>
and its anti-inflammatory, anti-allergic, anti-spasmodic, antibacterial, anti-pyretic, ulcer-protective, anti-fungal, sedative, analgesic and antioxidant properties (McKay and Blumberg, 2006). According to the results of the study, chamomile in Orabase could reduce pain of the ulcers similar to triamcinolone in Orabase with a significant difference to the control group on days 3 and 6. Therefore Chamomile in Orabase is as effective as triamcinolone in Orabase at reducing pain of the ulcers. This finding corroborates the findings of Ramos-e-Silva et al., who found that an extract of Chamomilla was effective in 100% of the patients at reducing pain of the ulcers (Ramos-e-Silva et al., 2006).

There were differences between triamcinolone and chamomile with regards to size of the ulcers on days 3 and 6. At day 3, chamomile reduced ulcer size similarly to triamcinolone with a significant difference from the placebo group. But on day 6 (the last visit) triamcinolone was superior to chamomile and the placebo group for reducing size of the ulcers. Therefore triamcinolone caused complete resolution of symptoms earlier than chamomile and placebo. Patients’ satisfaction with triamcinolone and chamomile in Orabase was nearly the same; 10 out of 14 patients from the triamcinolone group and 9 out of 14 from the chamomile group were quite satisfied with their remedies. This finding is similar to the results of Ramos-e-Silva et al.; 97% patients in their study judged the tolerance and safety of chamomile extract as excellent (Ramos-e-Silva et al., 2006).

5. Conclusion

Chamomile could not completely resolve symptoms as early as triamcinolone, but could reduce pain intensity and provide patient satisfaction similar to triamcinolone.

Conflict of interest

The authors declare that there was no conflict of interest in the study.

Acknowledgements

The authors thank the vice-chancellor of Shiraz University of Medical Sciences, for supporting the research (Grant #6653). This manuscript relevant thesis of Dr. Zohrehjahpour. Also the authors thank Dr. M. Vossoughi from the Dental Research Development Centre, for the statistical analysis. The Barij-essence pharmaceutical company, Kashan-Iran is acknowledged for producing medications.

Table 3 – Patients’ satisfaction in groups O, T and C. (Group O= placebo, Group T = triamcinolone, Group C= chamomile).

<table>
<thead>
<tr>
<th></th>
<th>Quite satisfied</th>
<th>Satisfied</th>
<th>Dissatisfied</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group O</td>
<td>1</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Group T</td>
<td>10</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Group C</td>
<td>9</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

REFERENCES


