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Pimecrolimus versus Placebo in Minor, Recurrent Aphthous Stomatitis: A Randomized Double-blind Controlled Trial

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ABSTRACT

Background: Oral aphthous is one of the most common oral mucosal inflammatory disorders which are very painful. There is no definite medical strategy up to now for aphthous treatment. Recently, some researchers have focused on immunomodulatory drugs such as tacrolimus and pimecrolimus in preventing aphthus recurrences. The aim of this study is to assess the effect of pimecrolimus cream against placebo in management of oral minor aphthous.

Methods: The study is a randomized clinical trial, was done in "Shariati" hospital and Isfahan Skin Research Center. 62 patients with minor aphthuos were included and divided randomly to two groups (31 in each). In experimental group, pimecrolimus cream was applied for two weeks and cold cream for the same duration in control group. Patients were followed for 3 and one week; results were assessed in recovery after drug administration. Compared variables between two groups were including: the size of lesions, the time to recovery and pain intensity.

Results: Results showed that mean size lesion in experimental and placebo group after complete recovery reduced (23.6 ±15.3 and 24.8 ±15 mm respectively) but it was not significant (P: 0.1). Mean time for recovery in both groups was 8±2.2 and 9.5±2.5 respectively which was significant in pimecrolimus treated patients (P: 0.014). Also mean degree for pain intensity measured by pain scale method was reduced significantly in test group (6 ± 1.2 before treatment and 5.3 ± 1.1 after treatment, P<0.001).

Conclusion: This study stated that pimecrolimus cream has an appropriate effect in reduction of recovery time and pain in minor aphthous compared to placebo but more clinical studies are needed to better conclusion.

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Introduction

Recurrent Aphthous Stomatitis (RAS) can be a debilitating disease characterized by shallow, extremely painful oral ulcerations (1, 2). Recurrent aphthous ulcers first described by Hippocrates in 400 B.C., the disease is named by the lay public and professionals as several term including canker sores, cold sores, aphthous stomatitis and recurrent aphthous ulcers (3). RAS is one of the most common oral ailments and affects at least 10% to 20% of the general population. Some investigators speculate the prevalence to be 50% in certain populations (4, 5).

The lesions typically embrace patients of ages 10 to 30 years and recur at varying intervals throughout life. Although recurrences happened by decreasing in frequency and severity as the patient ages (4, 6, 7).

There are 3 clinical subtypes for RAS: minor, major, and herpetiform. Minor aphthous ulcers represent by a

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painful small, round, or ovoid ulcers with circumscribed margins, erythematous haloes, and yellow or grey floors which include, 80% to 90% of RAS (8-10). Minor aphthous ulcers are less than 1 cm in size and less than 10 in number, usually between 1 and 3 and appear on the unattached oral mucosa (labial, buccal, and lingual). Ulcers heal within 7 to 10 days without any scarring.

It has been suggested that various factors precipitate outbreaks of RAS in predisposed persons, including trauma to the oral mucosa due to local anesthetic injections, dental treatments, and tooth brush injury, cigarette smoking, smokeless tobacco, certain drugs, some autoimmune inflammatory disease, anxiety or stress, hormonal changes related to the menstrual cycle, some viruses and hematinic deficiency; however, evidence to support the causative role of these factors is scarce (5).

Diagnosis is on clinical judgment alone, and must be differentiated from other causes of recurrent ulceration, particularly a systemic disorder like Behçet disease which aphthous-like ulcers are associated with genital ulceration, and eye disease (4).

The cause of RAS is still unknown but it seems that a genetic predisposition has been suggested as at least 40% of patients with RAS have a familial history (11). Also it is likely that several immunologically mediated mechanisms are involved in the pathogenesis of RAS (1).

Due to absence of a clearly defined cause, management of RAS remains unsatisfactory and aimed primarily at pain relief and the reduction of inflammation. The best guides for the treatment choices distinctive by considering the severity of the disease (the amount of pain), the frequency of ulceration, and the potential adverse effects of the medications. Some agent such as local anesthesia, topical antibacterial agents including chlorhexidine and tetracycline are sufficient for patients who experience occasional episodes of minor aphthous ulcers (4). Topical corticosteroids are considered the mainstay of therapy. Randomized, controlled trials of the interventions are limited. Some other medications such as levamisole, colchicine, azothiaprim, dapsone and pentoxifylline have been suggested for the treatment of more refractory cases, but limited data are available to support their effectiveness (2, 4, 11).

Pimecrolimus is an ascomycin macrolactam, topical calcineurin inhibitor, non-steroid, anti-inflammatory with a broad therapeutic potential for the treatment of inflammatory diseases. By considering this fact that, there is still no proper medication for advocating therapy and by new discovering of several mechanism involve d in RAS pathophysiology, new clinical researches must be done for evaluating the effects of new drugs on RAS treatment (12).

The aim of this study was to discover if local treatment with pimecrolimus could accelerate the healing of RAS. The study was designed at the Dermatology Research Center, Isfahan University for Medical Sciences, Isfahan, Iran.

Patients and Methods

Study was done on patients visiting "Shariati" hospital clinic or Skin Research Center (Isfahan University of Medical Sciences, Isfahan-Iran) from April 2012 till July 2013. 62 patients aged between 10 and 60 years with newly diagnosed minor recurrent aphthous and singular or multiple lesions on their buccal mucosa and mucosal zone of the lips (after a medical diagnosis of RAS minor). Only patients without any other medical complications who had noticed oral lesions during the last two days were included and randomly assigned to receive either pimecrolimus cream or placebo. Written consent had given to participant before entering to trial and this study was conducted under the Isfahan Azad University of Medical Sciences' Ethics Committee approval.

In the patient group (N = 31), pimecrolimus cream (Elidel®, Novartis, Swiss) was applied twice daily for a maximum of two weeks and cold cream as placebo was used for the same duration in the control group. Elidel topical cream was used before in oral cavity by other researcher, they introduced it as a safe and applicable cream for oral cavity and we did not worry about their oral limitation (12).

Two dermatologists followed the patients; one was blind to the treatment, and the other one recruited patients and assigned them to one of the groups, according to computer generated random numbers.

Patients with systemic diseases, major aphthous lesions in the oral cavity, RAS lesions other than those located on the buccal mucosa and mucosal zone of the lips, allergy history, systemic diseases, pregnant mothers and smokers were excluded from the study.

Patients' oral lesions were clinically observed at days 0 (just before entering the study), 3, 7 and until complete recovery. Using a metal caliper, the lesions' diameters and their inflammatory zone were measured. If more than one ulcer existed, the size of the largest one was calculated. The mean healing time was also calculated for patients.

Also, patients were trained to record their orange juice-stimulated pain score (using Visual Analogue Scale [VAS]) every day for 10 days. Patients with stimulated pain score of 1 and lesion diameter less than 1mm were considered healed.

Side-effects with pimecrolimus and placebo cream were noted. The primary outcome was the healing time up to 7 days.

Statistical analysis

All data were expressed as mean ± standard deviation of mean. After decoding the containers at the end of the study, the comparison of the entry data and the results was done by T-test in paired samples. For the comparison

Table1. Patients' charactristics.

Group	Pimecrolimus	Placebo	P value
Age	33.1	31.9	0.663
Gender	31 (16male, 15 female)	31 (16 male, 15 female)	0.99

of pimecrolimus and placebo, the Chi-square test, and Analysis of Variance (ANOVA) were used. The statistical software was SPSS 20 (SPSS Inc., Chicago, IL, USA). All tests reported a 2-sided *P* value with the level of significance set at 0.05.

Results

This study was a double blind randomized control trial, 62 newly diagnosed patients with RAS were assigned to conduct the study. 32 patients were male and 30 were female. The age of participant ranged from 10-60 years old.

The mean size of aphthous before applying treatment in pimecrolimus and control group was 36.3 ± 16.4 and 34.4 ± 16.7 mm respectively. It was not statistically significant (P: 0.66). After 3 days of treatment, mean aphthous size in pimecrolimus and control group was 23.6 ± 15.7 and 24.8±15 mm respectively and it was not statistically significant too (P: 0.66). Data analysis obtained from 7 days treatment showed that mean size of lesions in pimecrolimus and control group was 5.3 ± 6.2 and 8.3 ± 7.9 mm and it wasn't significantly difference (P: 0.1) (Table 2).

In the pimecrolimus group, the mean pain before the treatment was 6.2 ± 1.1. For the placebo group, the mean was 6 ±1.2 (Table 3). The difference between the two groups was not significant (P: 0.51).

In the pimecrolimus group, the mean pain after 7days treatment was 4.4 ± 1.4. For the placebo group, the mean was 5.3 ± 1.1 (Table 2). The difference between the two groups was not significant (P: 0.001).Mean pain differences in two group of intervention and control was 1.8 ± 1.1and 0.71 ± 0.64 respectively which was significant (P < 0.001).

The mean size of ulcer after 3 days of treatment in pimecrolimus group and control group was 23.6 ± 15.7 and 24.8 ± 15 millimeter respectively but the differences were not significant (P: 0.76). After 7 days of treatment the mean size of ulcer was 5.3 ± 6.2 and 8.3 ± 7.9 millimeter and it was not significant too (P: 0.1). Even λ^2 test cannot prove significance between two groups (P: 0.81).

In the pimecrolimus group, the mean time to healing was 8 ± 2.2 days. In the placebo group, the mean was 9.5 ± 2.5 days. By ANOVA, the difference between the pimecrolimus group and the placebo group was significant (P: 0.014). By considering complete healing after 7 days of assessment we found that 13 patients in pimecrolimus and 6 patients in control group have been completely recovered (41.9% against 19.4%).

No major side effects were noted with pimecrolimus. Pimecrolimus ointment was tolerated well with no signs of itching or burning. No patients complained about the reduced adherence properties of the cream.

Discussion

Although the main cause of RAS is still unknown, there is some evidence in favor of infiltration of the epithelium by mononuclear (lymphocytic) cells and generation of tumor necrosis factor alpha (TNF-α) and other cytokines from these and other leucocytes (macrophages and mast cells) (13, 14).

Pimecrolimus belongs to a new class of topical immune modulators or non-steroidal anti-inflammatory agent and was approved by the Food and Drug Administration (FDA) in 2001. It inhibits calcineurin, a protein phosphatase known as protein phosphatase 2 B (PP2B), activates the transcription of interleukin-2 (IL-2) by dephosphorylating NFATc, a transcription factor that activates in the nucleus the genes involved in IL-2 synthesis. Once released, IL-2 stimulates the growth, differentiation and activation of T-cells. Pimecrolimus inhibits T cell activation by inhibiting the synthesis and release of cytokines from T cells and inhibitions of calcineurin. Pimecrolimus also prevents the release of inflammatory cytokines and mediators from mast cells after stimulation by antigens or IgE (15).

At first, pimecrolimus was presented as a safe and effective second-line treatment in atopic dermatitis (16), but gradually was used in other dermatosis-like conditions, such as psoriasis, vitiligo, lupus erythematosus, seborrheic dermatitis, chronic vulvar pruritus and allergic contact dermatitis of the vulva, anogenitallichen sclerosus,

Table 2. Size of aphthous lesion.

Group	Day 0	Day 3	Day 7
	Lesions diameter	Lesions diameter	Lesions diameter
Pimecrolimus	36.3 ± 16.4	23.6 ± 15.7	5.3 ± 6.2
Placebo	34.4 ± 16.7	24.8 ± 15	8.3 ±7.9
P-value	0.66	0.76	0.1

All diameters are based on mm^2

Table 3. Pain of aphthous lesion using Visual Analog Scale (VAS) score.

Group	Day 0	Day 7
	Pain	Pain
Pimecrolimus	6.2 ± 1.1	4.4 ± 1.4
Placebo	6 ± 1.2	5.3 ± 1.1
P-value	0.57	0.008

genital lichen planus, vulvar pruritus simplex chronicus, and related pruritic vulvar dermatosis (17, 18).

Since, RAS is a very common disorder but there is no curative treatment for it, it is likely to evaluate new agents in RAS management, the available data suggest that topical calcineurin inhibitors may be effective and are well-tolerated in this vulvar dermatosis and other mentioned disorder, it seems that topical calcineurin inhibitors are safe become an effective option for RAS treatment (1, 2).

There is paucity of data in evaluating the effect of pimecrolimus in aphthous disorder. Chams-Davatchi et al., evaluated the effects of local treatment with pimecrolimus on the healing of genital ulcers and found that pimecrolimus is safe and efficient in the treatment of behcet's genital ulcers, by accelerating the healing process. They declared that the mean time for healing was significantly shorter and the pain significantly less in the pimecrolimus group (19). Kose and colleagues evaluated the effects of pimecrolimus cream with oral colchicine against colchicines alone and assessed pain and healing time. They found an improvement in pain but not in healing time (20).

In this randomized double-blind trial, pimecrolimus cream was compared to placebo cream applied onto the RAS lesion. As shown in the results, the pimecrolimus group and the placebo group were similar regarding gender, age, the size of ulcers, and the intensity of pain. Results showed that pimecrolimus improved mean time for healing and pain significantly in comparison to placebo. Pimecrolimus improved ulcers significantly in comparison to placebo by more positive results (healing in 7 days or less).The mean time for healing was significantly shorter and the pain significantly less in the pimecrolimus group. These results are similar to two mentioned published study on genital lesions (19, 20).

To our knowledge, there aren't any published articles assessing the effect of pimecrolimus cream on RAS. This article declared that pimecrolimus has a positive effects on RAS treatment.

Because patients were randomly allocated in either the test or the control group, their mean age and the female to male ratios, which might be two important factors affecting pain perception and RAS healing process, were not significantly different.

The lower VAS scores in the pimecrolimus-treated patients, which were observable just a few days after the treatment, might be attributed to the anti-inflammatory properties of pimecrolimus. Using anti-inflammatory medications in oral cavity disorders, including RAS, has a well-established basis in dentistry. The immunomodulatory role of pimecrolimus is another possible mechanism involved in its anti-inflammatory properties that could facilitate the wound healing process as well.

In this clinical trial, we have studied the therapeutic effects of pimecrolimus cream on RAS lesions, which were shown to be effective in terms of alleviating the patient's pain score and healing time compared with the control group (placebo).

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