

# The Effect of Topical Sucralfate Suspension on Oral Aphthae

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## Abstract:

**Objectives:** The purpose of this study was to determine the efficacy of oral sucralfate suspension (1gr/10ml) in the treatment of recurrent aphthous stomatitis (RAS).

**Materials and Methods:** Fifty-five patients with oral aphthae were included in this randomized, double-blind, placebo-controlled clinical trial conducted in the Department of Oral Medicine, School of Dentistry, Mashhad University of Medical Sciences. In the first part of the study, all subjects were instructed to rinse with a 10% suspension of sucralfate or placebo, 4 times a day for 2 weeks. Clinical examination was performed two times a week. The second part consisted of topical use of sucralfate or placebo 2 times a day for 4 weeks, followed by biweekly inspections for 6 months.

The size and number of the ulcers along with pain severity were assessed in the course of the pretreatment and treatment phases. Recurrence was evaluated during the follow up period. Pearson,  $\chi^2$ , and Fisher's exact tests were used for statistical analysis.

**Results:** On the fourth day of the study, pain relief was encountered in 59% and 14% of the case and control patients, respectively. Also, 63% of the ulcers in the sucralfate group and 71% in the placebo group showed size-reduction on the first visit. During the first 7 days of treatment, the number of ulcers showed reduction in both groups, which was significantly larger in the case group.

**Conclusion:** A 10% suspension of sucralfate accelerated pain relief in aphthous patients and its use is recommended as an adjunct for the treatment of RAS.

**Key Words:** Oral Aphthae; Sucralfate; Topical; Treatment

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## INTRODUCTION

Recurrent aphthous stomatitis (RAS) is a common lesion, manifesting as painful recurrent ulcers limited to the oral cavity [1-4]. Most people have experienced at least one episode of aphthous ulceration in their mouth [4,5]. Due to severe pain and multiple recurrences, some patients may feel the need to seek professional help. Although the exact cause of aphthous stomatitis remains unclear, dysregulation of the cellular immune system

appears to play an essential role in its pathogenesis [6-9].

Based on the immune pathogenesis of RAS, different methods have been proposed for the treatment of aphthous ulcers using drugs with anti-inflammatory effects [6,8]. Systemic corticosteroids are considered as the mainstay of therapy, but exhibit numerous side effects. Hypertension, diabetes mellitus, mood changes and peptic ulcers are a few examples of the adverse effects of systemic and long-time use

of these drugs [4-8,10,11]. Topical application of corticosteroids can raise the risk of secondary infections and increase the possibility of recurrences, even after discontinuation of the drug, and indefinite levels of systemic absorption may occur [10,12]. In addition, topical corticosteroids can be difficult to apply especially in large posterior lesions. Normal Salivary flow and mouth movements can rinse and displace the medicament.

Sucralfate was first introduced for treatment of duodenal ulcers in 1968 and is a basic salt complex of sucrose sulfate and aluminum hydroxide. It has topical effects and is considered as a mucoprotective agent with low systemic absorption [13-15].

The negatively charged sucralfate molecule binds to the positive charge of mucosal proteins and white blood cells present in the base of the ulcers [15]. Attachment of Sucralfate to ulcerative mucosa is stronger than normal mucosa [16].

The main mucoprotective effect of this drug is because of its ability to increase the activity of topical prostaglandins by augmentation of mucosal cyclooxygenase activity and direct prostaglandin release from mucosa. It can also affect fibroblast growth factor and increase mucosal blood circulation [13].

Sucralfate could relieve peptic and duodenal ulcers through several mechanisms like: inactivating pepsin, producing a physical barrier on the ulcerative region, changing the composition of peptic mucus, increasing the secretion of bicarbonate from peptic mucosa and inducing the local production of epithelial growth factor [11,13].

In healthy subjects, sucralfate increases the production and secretion of PGE<sub>2</sub> and 6 keto-PGF<sub>1</sub> $\alpha$  in the GI tract and decreases TXB<sub>2</sub> [15]. Slomiany et al [17] suggested that the main cause of accelerated ulcer relief was the prompt production of mucosal interleukin (IL-4), which could block apoptosis. Down regulation of IL-4 at the onset of ulceration, may

dysregulate the production of endothelin-1 (ET-1) and can induce TNF-alpha in addition to affecting mucosal repair by initiation of apoptosis.

Sucralfate has been used for the treatment of chemotherapy-induced mucositis [18-20]. A number of studies have also been conducted on the use of this drug in the treatment of oral ulcers in Behcet's syndrome and the reduction of their recurrences [21].

The purpose of this study was to evaluate the efficacy of topical sucralfate suspension on oral aphthous lesions. In this order, its effect on the number, size, healing time and pain of aphthous ulcers as well as its efficiency in the prevention of their recurrences has been investigated. The possibility of the application of sucralfate as an alternative treatment of aphthous ulcers has also been explored.

## MATERIALS AND METHODS

This study was a randomized, double-blind, placebo-controlled clinical trial carried out from October 2002 to June 2003. The patients were selected from those referred to Department of Oral Medicine, School of Dentistry, Mashhad University of Medical Sciences. All subjects had a history of recurrent aphthous ulcers (RAU) limited to the oral cavity which was confirmed by their clinical features. In order to rule out "aphthous-like" lesions, laboratory tests including complete blood cell count (CBC), serum iron (SI) and total iron binding capacity (TIBC) were performed for all subjects [22-26].

Inclusion criteria consisted of a history of 3 or more RAUs in one year; limitation of ulcers to the oral cavity and the presence of new ulcers with less than three days duration. Exclusion criteria included pregnancy, breast feeding or under eight years of age; treatment of the aphthous ulcers with any kind of oral or topical medication in the past two weeks; blood disorders detected by laboratory tests and presence of "aphthous-like" lesions.

A total of 69 patients presented with RAU, but eight subjects did not fulfill the inclusion criteria and six were excluded due to poor compliance. Using the simple random sampling method, the rest were randomly divided into treatment and placebo groups consisting of 27 and 28 cases, respectively. The two groups were matched according to age, gender, number of aphthous ulcers, the level of perceived pain and ulcer duration, size, and location. Informed consents were obtained from all patients after explaining the treatment process. The study protocol was approved by the Ethical Committee of Mashhad University of Medical Sciences.

Demographic data were collected and all patients were examined by two investigators. Information including location, number, size and duration of ulcers as well as pain score, recurrence time, history of any other treatment and past medical history were recorded. Ulcer size was measured in millimeters by a caliper and pain assessment was performed using a 4 point perceived pain rating scale as follows [14]:

0: No pain; 1: (Slight) Minimal discomfort and capable of eating; 2: (Moderate) Significant discomfort but still capable of eating more than half of meals; 3: (Severe) Extreme discomfort and difficulty to eat.

A 10% suspension of sucralfate and placebo was prepared by a pharmacologist in School of Pharmacy, Mashhad University of Medical Sciences, filled in identical bottles and coded as A or B. The only difference between two groups was their active ingredient which was powder of sucralfate tablet and Tri basic calcium phosphate powder in sucralfate suspension and placebo respectively.

The experiment was carried out in two stages. In the first stage the patients were given sucralfate or placebo for two weeks (1 gram, four times a day), according to their group allocation. They were asked to rinse their mouths with water followed by rinsing with the sus-

pension for two to three minutes. All subjects were instructed to avoid eating or drinking for at least half an hour after oral administration of the mouth rinse.

The purpose of the first stage was to determine the effects of sucralfate on pain relief and decreasing the number, size and healing time of the ulcers. The mean expected healing time of RAU (excluding major aphthous ulcers) is considered as two weeks [7], therefore the patients were examined two times a week for two weeks on the fourth, seventh, eleventh and fourteenth days. In every visit, the number, location, and size of the ulcers were assessed. In addition any change in pain severity, formation of new ulcers and possible side effects of the drug were evaluated. Ulcer size-decrease was defined as a reduction of two millimeters or more in diameter.

An exact definition for "healing" of aphthous lesions has not been presented in previous studies. A number of investigations consider "reduction of healing time", "decrease in the number and size of the ulcer" and "pain reduction" as healing, but the duration of these changes, despite its importance in the healing process of the ulcer, has been overlooked [3,9]. Thus we decided to determine the effects of sucralfate and placebo on the duration of pain reduction and decrease in ulcer size and number in the course of treatment.

In the second stage, the effect(s) of sucralfate on the prevention of recurrence was evaluated. All patients were instructed to take the drug or placebo for another four weeks similar to the first stage. The two-week visits were performed for six months and in every visit, the aforementioned criteria were assessed.

From the 55 subjects who completed the first stage, only 15 took sucralfate suspension or placebo for one month twice a day. In other words only 15 patients completed the six-month period of the second stage.

Pearson-,  $\chi^2$ -, Fisher's exact and log-Rank (Kaplan-Meier) tests in cross tabulation and

longitudinal data analysis were applied using SA S8.2, SPSS 10 and Excel softwares. The level of significance was set at 95%.

The suspensions were unveiled and drugs A and B turned out to be placebo and sucralfate, respectively.

## RESULTS

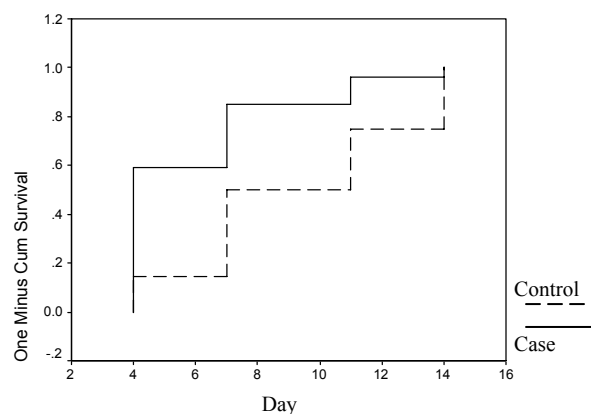
In the control group, 39.3% of the patients were men and 60.7% were women; likewise, there were 44.4% men and 55.6% women in the case group. According to Fisher's Exact test, the two groups matched in sex distribution ( $P > 0.05$ ). The age of the subjects ranged from 13-45 years and matching was confirmed by  $\chi^2$  test.

Minor aphthous was the most prevalent type of RAU in the two groups (92.6% in the case and 92.9% in control groups), but no significant difference in ulcer type was observed (Pearson, chi-square test,  $P > 0.05$ ). Most subjects in the case group had two ulcers (33.3%), but there was no significant difference in the total number of ulcers between the study groups.

The number of patients in the case group reporting pain relief on the fourth, seventh, eleventh and fourteenth day of the study, was significantly larger (Log rank test:  $\chi^2 = 12.39$ ,  $P = 0.0004$ ) than those in the control group (Fig 1). On the fourth day, 59% of the subjects in the treatment group and 14% in the placebo group demonstrated pain relief. This percentage decreased to 16% in the case group and increased to 75% in the control group on the eleventh day of the investigation.

On the fourth day, reduction in ulcer size was observed in 63% and 71% of the patients in the treatment and placebo groups, respectively (Table I). This decrease took longer in the case group as compared to the control group ( $P < 0.05$ ). Reduction in the number of ulcers was significantly greater ( $P < 0.05$ ) in the case- (51.9%) compared to the control group (3.6%) in the first week of treatment (Table II).

Most of the patients were lost to follow up in



**Fig 1:** Pain relief probability according to time (day) in the case and control groups.

the second stage of the investigation. Only 15 patients (11 cases and 4 controls) completed the six-month study period. Using Fisher's test, no significant difference in ulcer recurrence was detected between the two groups; however, the effect of sucralfate on ulcer recurrence could not be evaluated due to the small sample size.

No subject experienced side effects of sucralfate or placebo throughout the duration of the investigation.

## DISCUSSION

Sucralfate is a medicament with mucoprotective effects used in the treatment of peptic ulcers. Oral application of this drug is limited to oral ulcers of Behcet's syndrome, oral aphthous ulcerations and mucositis induced by chemotherapy and especially radiotherapy. Only a few studies have evaluated the effects of sucralfate on oral lesion [3,16-20].

According to the results obtained in the present study, sucralfate was effective in reducing the duration of pain in oral aphthous ulcers. These findings are in agreement with those reported by Rattan et al [3] and Alpsoy et al [21]. They evaluated the effect of sucralfate on the time of pain relief, remission and healing time, but there was no definition for the term "healing". Unlike our study, other investigations [3,9] considered pain reduction

**Table I:** Frequency distribution of cases according to onset of lesional size reduction in the treatment and placebo groups.

	Control	Case
	Number (%)	Number (%)
First visit	2 (7.1)	17 (63.0)
Second visit	14 (50.0)	6 (22.2)
Third visit	9 (32.1)	4 (14.8)
Fourth visit	3 (10.7)	0 (0)
Total	28 (100)	27 (100)

or ulcer size and number as healing criteria; however there was no definitive measure or statistical analysis for healing.

The sample size in the second stage of our study was insufficient due to the patients' poor compliance; therefore the effect of sucralfate in the prevention of ulcer recurrence was not fully explored. Rattan et al [3] administered sucralfate, antacid and placebo to RAS patients and followed them for two years. They showed that sucralfate prevented the recurrence of aphtous lesions in 85% of their patients. According to Alpsy et al [21], sucralfate could significantly reduce the frequency of pain and healing time in patients with Behcet's syndrome. Similar to previous studies, no side effects were found during the treatment period in patients receiving this drug [16,19, 20].

Cengiz et al [22] demonstrated that oral rinsing with sucralfate was beneficial in decreasing the intensity of radiation-induced mucositis and oral discomfort. In their study, twenty-eight patients with head and neck cancer were randomized to use either sucralfate (n=18) or placebo (n=10). Subjects in the sucralfate group experienced significantly lower degrees of mucositis than the placebo group (P<0.05).

Marini and Vecchiet [23] evaluated the efficacy of sucralfate in decreasing pain and reducing the number of vesiculobullous lesions in patients with epidermolysis bullosa. The results indicated that oral prophylaxis with sucralfate prevented oral blisters and discom-

**Table II:** Frequency distribution of cases according to number of lesions after seven days of treatment in the case and control groups.

	Control	Case
	Number (%)	Number (%)
Decreased in the number of ulcers	1 (3.6)	14 (51.9)
Without changes in the number of ulcers	23 (82.1)	12 (44.4)
Increased in the number of ulcers	4 (14.3)	1 (3.7)
Total	28 (100)	27 (100)

fort in these patients.

In a double-blind investigation, Ricer [24] failed to show improvement in aphtous ulcers following the use of sucralfate in the form of a powdered spray.

Previous studies have suggested that the improvement encountered in oral aphtous ulcerations may be because of a mucoprotective mechanism comparable to that occurring in peptic ulcers [25].

## CONCLUSION

The findings obtained in the present investigation indicated that oral rinsing with sucralfate in RAS patients could accelerate pain relief and healing time and also reduce the size and number of ulcerations, without any side effects.

Considering that pain is usually the chief complaint in patients with aphtous lesions the use of sucralfate is recommended for the treatment of aphtous ulcers.

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