

# Zinc Sulphate 5% Mouthwash is an Effective Therapeutic and Prophylactic Agent in Treatment of Recurrent Aphthous Ulcer (Single blind placebo controlled therapeutic study)

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## Abstract

**Background:** Recurrent aphthous ulcer (RAU) is a common disease where its exact etiology and pathogenesis are not known. There is no uniformly effective therapy for this disease. Recent study showed that oral zinc sulphate has effective therapeutic and prophylactic role in management of this disease.

**Objective:** To evaluate the therapeutic, prophylactic efficacy and safety of 5% zinc sulphate mouthwash in the management of patients with RAU.

**Patients and Methods:** This is single blind placebo controlled therapeutic study where 40 patients with early onset oral aphthosis were recruited in this work those who attended Baghdad Teaching Hospital-Department of Dermatology between April 2005- April 2006. Patients were divided into two groups: **Group A** (20 patients) were instructed to use 5% zinc sulphate mouthwash, 5 ml twice daily for three months, while 20 patients in **Group B** used placebo in a form of distilled water mouthwash and in a similar way to zinc sulphate mouthwash. A short term assessment of each patient of both groups was done to evaluate the therapeutic effect of the drug by using oral clinical manifestation index (OCMI and the mean size of the largest diameter of ulcers. A long term assessment was done for each patient to evaluate the prophylactic effect of the drug by using (OCMI) before, after 1, 2 and 3 months of therapy.

**Results:** The patient included in this study 19 males (47.5%) and 21 females (52.5%), female to male ratio was 1.1: 1. Their ages ranged between 20-60 ( $29.6 \pm 9.6$ ) years. The mean of OCMI in **Group A** started to decline directly after 4 days of therapy and went to its lower level after 8 days of therapy, and it was statistically significant (P value <0.05). The change in the mean of OCMI of **Group B** after 4 and 8 days of therapy was also statistically significant (P value <0.05). The response rate (percentage of change in the mean) after 4 days of therapy in **Group A** was 22.65% and in **Group B** was 6.44%, while the response rate after 8 days of therapy in **Group A** was 66.33% and in **Group B** was 44.98%. The difference in the response rates after 4 and 8 days between **Group A** and **B** was statistically significant (P value <0.05). The mean size of ulcers in **Group A** started to decline directly after 4 days of therapy and to its lower level after 8 days of therapy, and it was statistically significant (P value <0.05). The change in the mean size of ulcers of **Group B** after 4 and 8 days of therapy was also statistically significant (P value <0.05). The response rate after 4 days of therapy in **Group A** was 44.30% and in **Group B** was 15.08%, while the response rate after 8 days of therapy in **Group A** was 83.54% and in **Group B** was 55.36%. The difference in the response rates after 4 and 8 days between **Group A** and **B** was statistically significant (P-value <0.05). So the therapeutic effect of zinc sulphate mouth wash was statistically more significant than placebo effect. No significant side effects were noticed apart from mild irritation in two patients using zinc sulphate. Zinc sulphate mouth wash showed statistically significant prophylactic effect in comparison to placebo after 1, 2 & 3 months from starting therapy using the oral clinical manifestation index.

**Conclusions:** Zinc sulphate 5% mouthwash is a new, safe effective therapeutic and prophylactic remedy in management of RAU. The mechanism of action could be related to its immunomodulatory, antimicrobial, antioxidant actions and effects on wound healing.

**Keywords:** zinc sulphate, RAU, mouthwash.

## Introduction

Recurrent aphthous ulcer (RAU) is a common disease that probably afflicts at least 20% of the population<sup>(1)</sup>. It is the most common oral mucosal disease in adolescent and adult; characteristically begins in childhood or early adulthood in more than 50% of the patients, the onset of the disease occurred between age 10-30 years, also it rarely occurred for the first time after the age of 50<sup>(2,3)</sup>. RAU characterized by recurring episodes of ulcers, each lasting from 1 to about 4 weeks before healing, aphthae typically are multiple round or ovoid ulcer with circumscribed margin, erythematous halo and a yellow or grey floor<sup>(1)</sup>.

The etiology of RAS is not clear, multifactorial etiopathogenesis has been suggested to explain the cause of lesions of RAU, including: genetic predisposition, trauma, infectious agents and

immunological dysfunction. It is likely that immune-mediated destruction of the epithelium is the final common pathway in RAU pathogenesis<sup>(4)</sup>; accordingly there is no uniform effective therapy for this disease.

A large number of therapies both topical and systemic have been used in treatment of RAU, including: chlorohexidine<sup>(5)</sup>, tetracycline<sup>(1)</sup>, honey<sup>(6)</sup>, benodryl and maalox, sucroflate<sup>(2)</sup>, zinc sulphate<sup>(7)</sup>, topical, intra-lesion and oral steroids<sup>(2)</sup>, dapsone<sup>(2)</sup>, colchicine<sup>(4)</sup>, pentoxifylline<sup>(8)</sup>, thalidomide<sup>(4)</sup>, low intensity ultrasound<sup>(9)</sup> and BCG<sup>(10)</sup>. These therapies act through different mechanisms with variable success rates and most of them were associated with a variety of side effects.

Zinc is one of the essential trace elements<sup>(11)</sup> and zinc sulphate has been used in many medical conditions especially skin diseases as a topical or

systemic oral; it is used topically in treatment of severe herpes simplex infection<sup>(12)</sup>, plane warts<sup>(13)</sup>, melasma<sup>(14)</sup>, superficial fungal infection<sup>(15)</sup> and provide antioxidant photo protection for the skin<sup>(16)</sup>. Intra-lesional zinc sulphate is found to be an effective therapy for cutaneous leishmaniasis<sup>(17)</sup>, basal cell carcinoma<sup>(18)</sup> and in treatment of viral warts<sup>(19)</sup>.

Oral zinc sulphate is used in treatment of cutaneous leishmaniasis<sup>(20)</sup>, viral warts<sup>(21)</sup>, psoriatic arthritis<sup>(22)</sup>, Behcet's disease<sup>(23)</sup>, rosacea<sup>(24)</sup>, Nigella sativa oil<sup>(25)</sup> and recently an Iraqi study proved that oral zinc sulphate is an effective therapeutic and prophylactic agent in treatment of RAUs<sup>(7)</sup>.

So, the aim of the present work is to evaluate the effectiveness of 5% zinc sulphate mouthwash in treatment of RAU.

### Patients and Methods

This is a single blind placebo controlled study to evaluate the therapeutic and prophylactic efficacy of 5% zinc sulphate mouth wash in patients with RAU. This study was conducted at Baghdad Teaching Hospital - Department of Dermatology & Venereology in the period between April 2005 and April 2006.

Patients with RAUs included in this study were those with ulcerations of early onset (less than 3 days duration) and had little or no benefit from other conventional therapies in the previous attacks. Patients were requested to avoid the use of any medicaments throughout the trial.

The diagnosis of RAU was based on history and clinical examination. Detailed history including: age, gender, occupation, history of disease, the recurrence rate, their general health and previous medical history and family history of the same condition. Also, they were asked about any aggravating factors including food, stress, trauma and smoking or associated symptoms. All patients were fully examined regarding: shape, size and number of the lesions.

Investigations were done for all patients including: pathergy test, complete blood picture, ESR and HLA typing for HLA-B5, 51 and HLA-B27 to exclude patients with Behcet's disease and other internal causes of oral ulcerations.

All patients were seen by ophthalmologists to exclude findings suggestive for Behcet's disease.

The nature of this trial was explained to each patient and formal consent was taken before starting the therapy, after full explanation about the nature of the disease, course, procedures of treatment, and follow up, prognosis. Also, the ethical approval was performed by the scientific committee of the Scientific Council of Dermatology and Venereology-Iraqi Board for Medical Specializations. Forty patients with early onset oral ulcerations were included in this study. The patients were divided into two groups:-

**Group A** on 5% zinc sulphate ( $ZnSO_4 \cdot 7H_2O=287.54$  from MERK, France) mouth wash while **Group B** on distilled water mouth wash as a placebo control group. Patients in **Group A** and **B** were instructed to use medication as 5 ml of mouths wash two times daily for 3 months.

An oral clinical manifestations index (OCMI)<sup>(10, 25)</sup> (Table-1) was calculated for each patient in both groups was calculated before therapy and during the course of treatment.

Patients were assessed on short term assessment base (therapeutic effect) and on long term base (prophylactic effect).

### \* Short term assessment (The therapeutic effect of drugs):

An assessment was performed for each patient on day 4 and 8 from starting therapy using OCMI with exclusion of the score of frequency of attacks since we are trying to evaluate the therapeutic efficacy of the therapies used in the trial in short time. Also on each visit, the size of each oral ulcer depending on the largest diameter was recorded before starting therapy and on day 4 and 8 after on therapy, then mean size of ulcers was calculated for each patient on each visit.

### \* Long term assessment (The prophylactic effect of drugs):

The OCMI score was recalculated for each patient monthly for 3 months after starting the therapy to evaluate the prophylactic efficacy of each therapy used in the study. The data were analyzed, and the paired t-test was used to compare the means of OCMI before, after 4 days and after 8 days of therapy of both groups. The response rate was estimated by calculating the percentage of change in the means of OCMI after 4 and 8 days of treatment from the baseline of mean of OCMI before treatment.

Also paired t- test was used to compare the response rates after 4 and 8 days of therapy between the two groups included in this study.

P-value of less than 0.05 was considered to be statistically significant. ANOVA test was used to compare the mean of OCMI, the mean size of ulcer and symptoms after treatment between these two groups.

**Table-1: Oral Clinical Manifestation index.**

|  |   |
|--|---|
| Minor ulcer  | 1 |
| Herpetiform  | 2 |
| Major ulcer  | 3 |
|  |   |
| 1-3  | 1 |
| 4-6  | 2 |
| 7-9  | 3 |
| 9-12   | 4 |
| More than 12   | 5 |
|  |   |
| 1-4 days   | 1 |
| 5-8 days   | 2 |
| 9-12 days  | 3 |
| More than 12 days                                    | 4 |
|  |   |
| 0-2 weeks  | 5 |
| 3-4 weeks  | 4 |
| 5-6 weeks  | 3 |
| 7-8 weeks  | 2 |
| More than 8 weeks                                    | 1 |
|  |   |
| Uncomfortable  | 1 |
| Painful, but not interfere with eating or swallowing | 2 |
| Interfere with solid feeding                         | 3 |
| Interfere with liquid eating                         | 4 |

## Results

Forty patients were included in this study; 19 males (47.5%) and 21 females (52.5%), female to male ratio was 1.1: 1. Their ages ranged between 20-60 years with a mean  $\pm$  SD of  $29.6 \pm 9.6$  years. All investigations were negative.

### The therapeutic effect of drugs:

#### ► The effect on OCMI scores:

##### 1- Group A (5% zinc sulphate mouth wash):

In this group (20 patients), 11 males and 9 females; their ages ranged between 16-58 years with a mean  $\pm$  SD of  $37.75 \pm 11.97$  the OCMI before therapy ranged between 10 and 21 with a mean  $\pm$  SD  $15.45 \pm 3.4$ , the mean started to decline significantly to a lower level within 4 days of treatment to be  $12.0 \pm 3.63$ . While after 8 days of treatment a significant lower level of data was recorded, the mean was:  $5.55 \pm 5.76$  with a  $P < 0.05$  which was statistically significant (Table- 2).

The response rate was estimated by calculating the percentage of change in the mean of OCMI after 4 and 8 days of treatment from the baseline of mean before treatment, it was  $22.65 \pm 21.43$  after 4 days of treatment and  $66.33 \pm 35.24$  after 8 days of treatment.

##### 2- Group B (Distilled water mouth wash):

In this group (20 patients), 7 males and 13 females; their ages ranged between 20-58 years with a mean  $\pm$  SD of  $38.55 \pm 10.71$ , the OCMI before therapy ranged between 10 and 21 with a mean  $\pm$  SD  $14.6 \pm 3.23$ , the mean started to decline significantly to a lower level within 4 days of treatment to be

$13.5 \pm 2.42$ . While after 8 days of treatment a significant lower level of data was recorded, the mean was  $8.30 \pm 5.83$  with a  $P < 0.05$  which was statistically significant (Table- 2).

The response rate was  $6.44 \pm 7.81$  after 4 days of treatment and  $44.98 \pm 38.05$  after 8 days of treatment.

The difference in response rate between both groups was statistically significant (Table-3).

#### ► The effect on mean size of ulcers:

##### 1. Group A (5% zinc sulphate mouth wash):

The mean size of oral aphthous ulcers in this group before therapy ranged between 3-10 mm with a mean  $\pm$ SD of  $6.35 \pm 1.76$ , the mean started to decline significantly to a lower level within 4 days of therapy to be  $3.58 \pm 1.48$  and continued to decline till the 8<sup>th</sup> day of the course of therapy to be  $1.20 \pm 1.58$  with a  $P < 0.05$  (Table- 4).

The response rate was  $44.30 \pm 21.66$  after 4 days of treatment and  $83.54 \pm 21.80$  after 8 days of treatment.

##### 2- Group B (distilled water mouth wash):

The mean size of oral aphthous ulcers in this group before therapy ranged between 3-10 mm with a mean  $\pm$ SD of  $5.67 \pm 2.23$ , the mean started to decline significantly to a lower level within days of therapy to be  $4.82 \pm 1.98$  and continued to decline till the 8<sup>th</sup> day of the course of therapy to be  $3.00 \pm 2.40$  with a  $P < 0.05$  (Table- 4).

The response rate was  $15.08 \pm 13.12$  after 4 days of treatment and  $55.36 \pm 31.48$  after 8 days of treatment. The difference in response rate between both groups was statistically significant (Table-5).

**Table-2: The effect of zinc sulphate and placebo on OCMI of the ulcers.**

| OCMI score | Zinc Sulphate MW             | Placebo                      |
|------------|------------------------------|------------------------------|
|            | Mean $\pm$ SD<br>Min-Max     | Mean $\pm$ SD<br>Min-Max     |
| At day 0   | $15.45 \pm 3.4$<br>10.0-21.0 | $14.6 \pm 3.23$<br>10.0-21.0 |
| At day 4   | $12.0 \pm 3.63$<br>0-18.0    | $13.5 \pm 2.42$<br>10.0-18.0 |
| At day 8   | $5.55 \pm 5.76$<br>0-13.0    | $8.30 \pm 5.83$<br>0-16.0    |
| P value    | 0.000001                     | 0.000007                     |

**Table-3: The significance of response rates on OCMI between both groups.**

|                           | Zinc sulphate x Placebo |
|---------------------------|-------------------------|
| Difference in score 0 & 4 | 0.003*                  |
| Difference in score 0 & 8 | 0.073                   |
| Difference in score 4 & 8 | 0.280                   |

\*Significant difference between groups using independent t test ( $P < 0.05$ )

**Table-4: The effect of zinc sulphate and placebo on the mean size of largest diameter of ulcers.**

| Mean size of ulcers | Zinc sulphate MW            | Placebo                     |
|---------------------|-----------------------------|-----------------------------|
|                     | Mean $\pm$ SD<br>Min-Max    | Mean $\pm$ SD<br>Min-Max    |
| At day 0            | 6.35 $\pm$ 1.76<br>3.0-10.0 | 5.67 $\pm$ 2.23<br>3.0-10.0 |
| At day 4            | 3.58 $\pm$ 1.48<br>0-6.0    | 4.82 $\pm$ 1.98<br>2.0-8.0  |
| At day 8            | 1.20 $\pm$ 1.58<br>0-4.0    | 3.00 $\pm$ 2.40<br>0-7.0    |
| P value             | 0.0000001                   | 0.0003                      |

**Table-5: The significance of response rates on the mean of largest diameter of ulcers between both groups.**

|                          | Zinc sulphate x Placebo |
|--------------------------|-------------------------|
| Difference in size 0 & 4 | 0.0001*                 |
| Difference in size 0 & 8 | 0.002*                  |
| Difference in size 4 & 8 | 0.037*                  |

\*Significant difference between groups using independent t test (P<0.05)

#### The prophylactic effect of drugs:

Both groups showed statistically significant effect on the OCMI of ulcers after 1, 2 and 3 months from starting therapy (Table-6).

But, using the independent t test, zinc sulphate mouth wash showed statistically significant prophylactic effect in comparison to placebo after 1, 2 & 3 months from starting therapy (Table-7).

**Table-6: The prophylactic effect of zinc sulphate and placebo on OCMI score.**

| OCMI score | Zinc Sulphate MW              | Placebo                       |
|------------|-------------------------------|-------------------------------|
|            | Mean $\pm$ SD<br>Min-Max      | Mean $\pm$ SD<br>Min-Max      |
| At day 0   | 15.45 $\pm$ 3.43<br>10.0-21.0 | 14.60 $\pm$ 3.23<br>10.0-21.0 |
| At month 1 | 9.45 $\pm$ 5.42<br>0-16.0     | 13.50 $\pm$ 2.95<br>10.0-18.0 |
| At month 2 | 3.15 $\pm$ 5.04<br>0-13.0     | 10.90 $\pm$ 6.30<br>0-20.0    |
| At month 3 | 4.00 $\pm$ 4.66<br>0-11.0     | 8.35 $\pm$ 6.46<br>0-16.0     |
| P value    | 0.00001                       | 0.00039                       |

**Table-7: The significance of prophylactic effect on OCMI scores between both groups.**

| OCMI Score | Zinc sulphate x Placebo |
|------------|-------------------------|
| At day 0   | 0.425                   |
| At month 1 | 0.006*                  |
| At month 2 | 0.0001*                 |
| At month 3 | 0.019*                  |

\*Significant difference between groups using independent t test (P<0.05)

#### Discussion

The etiology of RAU is not well understood although multiple factors are incriminated singly or in combinations like genetic predisposition, trauma, infectious agents and immune dysregulation. All these factors might lead into immune mediated destruction of oral mucosa<sup>(4)</sup>.

There is no curative therapy although RAU might burn itself over time and with increasing age as RAU is a disease of young people and rarely affects young children and elderly. Still RAU is troublesome condition and interfere with health and social activity of the affected individuals<sup>(2, 3)</sup>. So many treatments have been used to control complains of patients as topical therapy like honey<sup>(6)</sup>, benodryl and Maalox, sucrofolate<sup>(2)</sup> and topical or intra-lesional steroids or as oral therapy like oral steroids<sup>(2)</sup>, dapsone<sup>(2)</sup>, colchicine<sup>(4)</sup>, pentifylline<sup>(8)</sup>, thalidomide<sup>(4)</sup> and others.

Zinc is one of the essential elements that are involved in more than 300 enzymes. Zinc sulphate has many actions like antioxidant, antimicrobial, immunomodulating agent and helps in wound healing. For these reasons, zinc sulphate has been used in the treatment of many medical problems especially in skin diseased as a topical therapy like in treatment of severe herpes simplex infection<sup>(12)</sup>, plane warts<sup>(13)</sup> and melasma<sup>(14)</sup> or as an oral therapy like in treatment of cutaneous leishmaniasis<sup>(20)</sup>, viral warts<sup>(21)</sup>, psoriatic arthritis<sup>(22)</sup>, Behcet's disease<sup>(23)</sup> and rosacea<sup>(24)</sup>, Nigella sativa oil<sup>(25)</sup>.

Recently oral zinc sulphate has been used in double blind controlled study as effective therapeutic and prophylactic drug in management of RAU<sup>(7)</sup>. Also, zinc sulphate was superior to oral dapsone in oral treatment of RAU<sup>(7)</sup>.

This study encouraged us to conduct the present work using 5% zinc sulphate oral wash. The results were very interesting as this mouth wash had both therapeutic and prophylactic actions which could be compared to the effectiveness of oral zinc sulphate in treatment of RAU.

Accordingly patients can use zinc sulphate both as oral drug and as mouth wash singly or in combinations and in both conditions the drug is safe and lacking side effects.

So in conclusion, zinc sulphate mouth wash is effective safe therapeutic and prophylactic drug used in management of RAU.

**Running title:** Zinc sulphate 5% mouthwash in recurrent aphthous ulcer *Sharquie...etal.*

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