The therapeutic and prophylactic role of oral zinc sulfate in management of recurrent aphthous stomatitis (ras) in comparison with dapsone

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ABSTRACT

الأهداف: لتقييم الفعالية العلاجية والوقائية لكبريتات الزنك الفموية في علاج تقرحات الفم القلاعية المتكررة (RAS) بالمقارنة مع عقار الدابسون.

الطريقة: أجريت دراسة علاجية ووقائية غير معلومة الطرفين مسيطر عليها على 45 مريضاً مصاباً بتقرحات الفم القلاعية المتكررة (RAS) من الذين راجعوا العيادة الخارجية للأمراض الجلدية في مستشفى بغداد التعليمي من مايو 2005م وحتى أكتوبر 2006م. قسم المصابون إلى ثلاثة مجاميع، كل مجموعة مكونة من 15 مريضاً. مجموعة (أ) (عولجوا بكبريتات الزنك 150mg) مرتين يومياً، مجموعة (ب) (عولجوا بالدابسون 50mg) مرتين يومياً، مجموعة (ج) (عولجوا بالكلوكوز 250mg). تم تحضير العلاجات في كبسولات متشابهة وأرشد المرضى إلى استخدام الكبسولات.

النتائج: الخمسة والأربعون مريضاً الذين أدخلوا في هذه الدراسة هم 25 ذكر (55.5%) و20 أنثى (44.5%)، نسبة الإناث إلى الذكور (1.24:1)، وتتراوح أعمارهم ما بين 16–45 عاماً بمعدل(31.24±8.14). في المجموعة (أ) معدل معامل المظاهر السريرية الفموية (p=0.0001)، ومعدل أكبر قطر لكل قرحة بدأ بالإنخفاض حتى نهاية فترة العلاج وبفارق إحصائي مهم (0.0001)، بينما المجموعة (ب) كان هناك انخفاض في معدل معامل المظاهر السريرية الفموية (p=0.0001) ومعدل أكبر قطر لكل قرحة (0.001) وبفارق إحصائي مهم، ولكن بفعل بطيء واقل قوة، كما أظهرت المجموعة (ج) انخفاضاً قليلاً وبفارق إحصائي غير مهم في معدل معامل المظاهر السريرية الفموية(p=0.028) ومعدل أكبر قطر لكل قرحة (0.034). في الأسبوع السادس من العلاج كانت كبريتات الزنك أكثر فعالية من الدابسون في خفض معدل معامل المظاهر السريرية الفموية لكل قرحة (p=0.007).

خاتمة: أظهرت هذه الدراسة بأن لكل من كبريتات الزنك والدابسون أهمية علاجية وتأثير وقائي في السيطرة على القرحة القلاعية الفموية المتكررة (RAS)، لكن كبريتات الزنك كانت أكثر سرعة و فعالية ومدة عمل أطول من الدابسون.

Objective: To evaluate the therapeutic and prophylactic effectiveness of oral zinc sulfate in recurrent aphthous stomatitis (RAS) in comparison with dapsone.

Methods: A double-blind placebo controlled study, conducted in the Department of Dermatology, Baghdad Teaching Hospitals, Baghdad, Iraq between May 2005 and October 2006, in which 45 patients with RAS were recruited and divided into 3 equal groups: group A (on zinc sulfate 150 mg twice daily), group B (on dapsone 50 mg twice daily), and group C (on glucose 250 mg as placebo). The drugs were prepared in identical capsules, and the patients were instructed to take the capsules twice daily after meals (in a double-blind manner). Assessment of each patient was carried out by the Oral Clinical Manifestation Index (OCMI) and the diameter of the ulcers at day 0, day 4, and at the second, fourth, sixth, eighth, tenth, and twelfth weeks of therapy.

Results: Forty-five patients were included in the study (25 males and 20 females), and their ages ranged between 16-45 years (mean±SD 31.24±8.14). In group A, the mean of OCMI and diameter of ulcers improved, with a p=0.0001 for OCMI, and 0.0001 for the diameter for ulcers at the end of the twelfth week of therapy, which was statistically significant. Group B, also showed significant improvement, however, the action was lower and slower (p=0.0001 for OCMI, and 0.001 for the diameter for ulcers). Group C revealed slight non-significant improvement (p=0.028 for OCMI, and 0.034 for the diameter of ulcers). In the sixth week of therapy, zinc sulfate was more effective than dapsone in reducing the OCMI of the ulcers (p=0.007).

Conclusion: The present study showed that both zinc sulfate and dapsone had significant therapeutic and prophylactic effects in controlling RAS, however, zinc sulfate had much more rapid and sustained action.

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Recurrent aphthous stomatitis (RAS) constitutes the most common oral mucosal disease and affects approximately 10-25% of the population.[1] The etiology of the disease is still not well elucidated, although many theories have been raised to explain the etiopathogenesis, such as, genetic factors, trauma, infections, gastrointestinal diseases,[1] immunological abnormalities,[1-3] hematological deficiencies,[2,4,5] hormonal factors,[1,5] and allergies to food.[1] There are many therapies that have been suggested to treat the disease, which mostly work through shortening the duration and symptoms of RAS, such as, corticosteroids,[1,6] lidocaine solution,[6] sucralfate suspension,[6] Nigella sativa oil,[7] and antibacterial agents such as chlorhexidine,[8] topical honey,[9] colchicines,[10] and thalidomide.[11] Zinc sulfate is an important trace element as it is involved in more than 300 metaloenzymes,[12] and has immunomodulatory,[13,14] antibacterial,[15,16] and antioxidant actions,[17] as well as accelerate wound healing.[18] Zinc sulfate[19] and dapsone[20] have been tried in Behçet's disease and proved to have effective therapeutic and prophylactic actions, especially against oral ulcers. These results encouraged us to conduct the present work by using zinc sulfate and dapsone in the treatment of RAS. Therefore, the aim of the present work is to determine the therapeutic and prophylactic effectiveness of oral zinc sulfate in RAS in comparison with dapsone.

Methods. After approval from the Scientific Committee of the Scientific Council of Dermatology and Venereology, this double-blind placebo controlled study was conducted in the Department of Dermatology and Venereology, Baghdad and Al-Kadhimyia Teaching Hospitals, Baghdad, Iraq between May 2005 and October 2006. Forty-five patients were enrolled in this work who had recurrent oral aphthous ulcers at least one attack per month and had little benefit from other therapies. Complete history was taken from each patient regarding age, gender, duration of the disease, recurrence rates, severity, effect of ulcer on feeding, duration of each attack and history of previous therapies. Examination was carried out for all patients including: size, shape, number, and site of the lesion. Complete blood picture, erythrocyte sedimentation rate, and human leukocyte antigen (HLA-B5, HLA-B51, and HLA-B27), pathergy test and ophthalmological consultation was carried out to exclude Behçet's disease and other known causes of oral ulcers. All patients included in the present work had no history of any systemic or oral therapy intake at least 3 months before the start of this study, also other causes of oral aphthosis such as inflammatory bowel diseases, and so forth. Formal consent was taken from each patient before using the remedy, after a full explanation including: method of application, duration of therapy, and follow up. Drugs were prepared in identical capsule forms (zinc sulfate 150 mg, dapsone 50 mg, glucose 250 mg as placebo). Patients were divided into 3 equal groups according to therapy received: group A (on zinc sulfate), group B (on dapsone), and group C (on glucose), drugs were given in a double-blind manner, 2 times daily after meals for 3 months. Patients were instructed not to take any other drug for their disease during the study, and to return if they developed any cutaneous and systemic side effects from the drugs, such as weakness, red discoloration of urine, blue discoloration of skin or lips, and others. An oral clinical manifestation index (OCMI)[20] (**Table 1**) and measurement of the diameter of the oral aphthous ulcer was performed before treatment, at the fourth day, second, fourth, sixth, eighth, tenth, and twelfth week of therapy. In addition to the complete history, physical examination, and necessary investigations were undertaken at each visit.

Statistical analysis. The ANOVA test was used to compare the means of OCMI and the diameters of the ulcers according to weeks of treatment. Student's T test was used to compare the OCMI and the diameters of the oral aphthous ulcer between the 3 groups. A p-value <0.05 was considered to be statistically significant.

Results. Forty-five patients were included in this study, 25 males and 20 females with a female to male ratio of 1:1.24, their ages ranged between 16-45 years with a mean±SD of 31.24±8.14 years. Duration of their disease ranged between 6 months and 2 years.

The effect of the drugs on OCMI. Group A (zinc sulfate). The OCMI before therapy ranged between 11-16 with a mean±SD of 11.93+1.39, the mean started to decline significantly to a lower level within the first 4 days, and continued to decline until the end of the course of therapy, p=0.0001 (**Table 2**).

Group B (Dapsone). The OCMI before therapy ranged between 8-14 with a mean±SD of 10.87±1.41, the mean started to decline significantly to a lower level within the first 4 days, and continued to decline until the second week, remained stable until the 10th week, and then showed another decline from the tenth to twelfth weeks, p=0.0001 (**Table 2**).

Group C (Placebo). The OCMI before therapy ranged between 9-14 with a mean±SD of 10.80±1.42, the mean showed a slight statistically significant decline initially, and reached a stable level at the second week until the end of the course of therapy, p=0.028 (**Table 2**).

The effect of the drugs on the diameter of the ulcers. Group A (zinc sulfate). The diameter of ulcers in this group before therapy ranged between 3-15 mm with a mean±SD of 8.07+4.57 mm, the mean started to decline significantly to a lower level within the first

Table 1 - Oral clinical manifestation index.

Characteristics	Score
Type	
Minor ulcer	1
Major ulcer	2
Herpitiform ulcer	3
Number of ulcers/attack	
1-3	1
4-6	2
7-9	3
9-12	4
More than 12	5
Duration of the attack	
1-4 days	1
5-8 days	2
9-12 days	3
More than 12 days	4
Frequency (attack/date)	
0-2 weeks	5
3-4 weeks	4
5-6 weeks	3
7-8 weeks	2
More than 8 weeks	1
Associated symptoms	
Uncomfortable	1
Painful but not interfere with eating or swallowing	2
Interfere with solid feeding	3
Interfere with liquid feeding	4

4 days, and continued to decline until the end of the course of therapy, p=0.0001. (**Table 3**).

Group B (Dapsone). The diameter of ulcers in this group before therapy ranged between 3-20 mm with a mean±SD of 7.27±4.04 mm, the mean started to decline significantly to a lower level within the first 4 days, continued to decline until the second week, remained stable until the 10th week, and then showed another decline from the 10th to 12th weeks, p=0.001 (**Table 3**).

Group C (placebo). The diameter of ulcers in this group before therapy ranged between 3-15 mm with a mean±SD of 8.13±4.03 mm, the mean showed a slight statistically significant decline initially, and reached a stable level at the second week until the end of the course of therapy, p=0.034 (**Table 3**).

The therapeutic and prophylactic role of zinc sulfate continued until the end of the course of therapy (p=0.0001 for OCMI, and 0.0001 for the diameter of ulcers), while in dapsone there was decline in OCMI and size of the ulcer significantly to a lower level within the first 4 days, continued to decline until the second week, remained stable until the tenth week, and then showed another decline from the tenth to twelfth weeks (p=0.0001 for OCMI, and 0.001 for the diameter for ulcers). For glucose, there was a slight insignificant decline in the OCMI and size of the ulcer during the first 4 days (p=0.084 for OCMI, and 0.104 for the diameter of ulcers), became slightly significant at the

Table 2 - The effect of zinc sulfate, dapsone, and placebo glucose on OCMI of the ulcers.

OCMI Score	Zinc sulfate	Dapsone	Glucose	*P*-value
	Mean±SD (Min-Max)			
At day 0	11.93±1.39 (11-16)	10.87±1.41 (8-14)	10.80±1.42 (9-14)	0.057
At day 4	10.60±1.18 (9-12)	9.87±1.19 (8-11)	8.73±4.71 (0-14)	0.216
At week 2	6.07±5.31 (0-12)	3.73±4.79 (0-11)	7.60±5.15 (0-14)	0.124
At week 4	1.73±3.63 (0-10)	4.40±5.01 (0-13)	9.20±3.30 (0-14)	0.0001*
At week 6	1.07±2.81 (0-8)	4.93±4.28 (0-11)	9.13±3.29 (0-14)	0.0001*
At week 8	2.80±3.61 (0-8)	4.27±4.18 (0-9)	7.27±5.47 (0-14)	0.029*
At week 10	0.93±2.46 (0-7)	2.33±4.06 (0-10)	7.40±5.55 (0-14)	0.0001*
At week 12	0.93±2.46 (0-7)	2.80±4.18 (0-10)	8.67±4.20 (0-14)	0.0001*

OCMI - oral clinical manifestation index, *Significant difference using ANOVA test (F-test)

Table 3 - The effect of zinc sulfate, dapsone and glucose on the diameter of the ulcers.

Size (largest diameter)	Zinc sulfate	Dapsone	Glucose	*p*-value
	Mean±SD (Min-Max)			
At day 0	8.07±4.57 (3-15)	7.27±4.04 (3-20)	8.13±4.03 (3-15)	0.823
At day 4	4.73±4.25 (2-15)	5.27±3.08 (2-15)	6.20±4.78 (0-15)	0.615
At week 2	3.40±4.27 (0-15)	2.80±4.33 (0-15)	5.53±4.91 (0-15)	0.231
At week 4	1.53±3.52 (0-10)	2.93±4.10 (0-13)	6.07±3.37 (0-15)	0.005*
At week 6	1.00±2.80 (0-10)	2.73±2.40 (0-5)	5.53±3.64 (0-15)	0.001*
At week 8	1.80±2.34 (0-5)	2.20±2.34 (0-6)	4.87±4.16 (0-15)	0.018*
At week 10	0.87±2.36 (0-8)	1.27±2.25 (0-6)	5.07±4.53 (0-15)	0.001*
At week 12	0.87±2.36 (0-8)	1.80±2.40 (0-6)	5.60±3.96 (0-15)	0.0001*

*Significant difference using ANOVA test (F-test).

Table 4 - The comparison of response rates in OCMI between the different groups.

T-test for equality of means	Zinc comapared with dapsone	Zinc comapared with glucose	Dapsone comapared with glucose
OCMI score at day 0	0.046*	0.036*	0.898
OCMI score at day 4	0.101	0.148	0.374
OCMI score at week 2	0.217	0.429	0.042*
OCMI score at week 4	0.106	0.0001*	0.004*
OCMI score at week 6	0.007*	0.0001*	0.005*
OCMI score at week 8	0.313	0.013*	0.103
OCMI score at week 10	0.264	0.0001*	0.008*
OCMI score at week 12	0.147	0.0001*	0.001*

OCMI - oral clinical manifestation index, *Significant difference using t-test for 2 independent means.

Table 5 - The comparison of response rates in the diameter of ulcers between the different groups.

T-test for equality of means	Zinc comapared with dapsone	Zinc comapared with glucose	Dapsone comapared with glucose
Size (largest diameter) at day 0	0.616	0.967	0.561
Size (largest diameter) at day 4	0.697	0.382	0.530
Size (largest diameter) at week 2	0.705	0.215	0.117
Size (largest diameter) at week 4	0.324	0.001*	0.030*
Size (largest diameter) at week 6	0.080	0.001*	0.019*
Size (largest diameter) at week 8	0.643	0.019*	0.039*
Size (largest diameter) at week 10	0.638	0.004*	0.007*
Size (largest diameter) at week 12	0.291	0.0001*	0.004*

*Significant difference using t-test for 2 independent means.

second week (p=0.014 for OCMI, and 0.042 for the diameter of ulcers) then reached almost a steady state during the course of therapy (p=0.028 for OCMI, and 0.034 for the largest diameter of ulcers). **Table 4** showed that in the sixth week of therapy, zinc sulfate was slightly more effective than dapsone in reducing the OCMI and the ulcers (p=0.007). While in most of the stages of therapy there were significant differences in response rates according to OCMI and diameter of ulcers between zinc sulfate and glucose, also between dapsone and glucose (**Table 4 & 5**). No side effects were recorded in the 3 groups of therapy.

Investigations. Pathergy test was negative in all patients, while HLA-B5, HLA-B51, and HLA-B27 were absent. The blood picture and erythrocyte sedimentation rate were within normal range during the course of therapy.

Discussion. Recurrent aphthous stomatitis (RAS) is a major health problem and accounts for 10-25% of the general population.[1] The etiology is still not well understood, however, many theories have been raised, such as, genetic factors, trauma, infections, gastrointestinal diseases, allergies to food,[1] immunological abnormalities,[1-3] hematological deficiencies,[2,4,5] and hormonal factors.[1,5] The disease is a self-limiting one, takes 1-2 weeks for full recovery, however, the problem of recurrence is high, so the aim of therapy has 2 roles: to shorten the duration and symptoms of the episode of the disease, and to decrease further episodes of recurrence.[6] A large number of therapies have been used in the treatment of RAS, most were associated with a variety of side effects, and are mostly used only to shorten the duration and symptoms of the illness, for example, corticosteroids,[1,6] lidocaine solution,[6] sucralfate suspension,[6] and antibacterial agents.[7] Colchicine[10] and

thalidomide[11] were reported to decrease the recurrence of the disease, however, it might be associated with many side effects. Most recently, an Iraqi study showed that bacille Calmette-Guerin (BCG) is an effective mode of therapy as a therapeutic and prophylactic agent in the treatment of RAS.[21] Daspone[20] and zinc sulfate[19] has a therapeutic and prophylactic role in the management of patients with Behçet's disease, especially on oral ulceration, and these results encouraged us to conduct the present work.

The results of the present work showed that both zinc sulfate and dapsone were effective agents as therapeutic and prophylactic drugs in controlling oral aphthous. Although, the limited period of follow up, which was 3 months, however, many of these treated patients were followed up for longer time extended to one year, and continued to show this effective prophylactic action of these drugs. Accordingly, we are planning to carry out further studies for patients with RAS, and the duration of the study will be at least one year to confirm the results of the present work. Also, the levels of trace elements like zinc, copper, selenium, and so forth, will be measured before, during therapy, and the follow up period. In addition, the effect of these drugs on oxidative stress in these patients with RAS will be evaluated.

Zinc sulfate was slightly better than dapsone especially at week 6 of therapy, and much safer as it is a trace nutrient element and could be given even during pregnancy. The possible mechanisms of action of zinc sulfate in RAS might be through its immunomodulatory,[13,14] antimicrobial,[15,16] and antioxidant actions,[17] and zinc sulfate accelerates wound healing.[18] The mechanism of action of dapsone in RAS might be attributed to its anti-neutrophil effect, as it decreases neutrophil chemotaxis in addition to its anti-inflammatory effect and antibacterial action on oral microbial flora especially *Streptococcus sanguis*.[22]

In conclusion, the present study showed that zinc sulfate and dapsone were effective drugs in controlling RAS, with both therapeutic and prophylactic roles, however, zinc sulfate is safer and slightly more effective than dapsone.

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