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# Activity of Zinc Oral Dispersible Tablet on Marjory Clinical Type of Recurrent Aphthous Stomatitis Ulceration, a Clinical Trial Human Study

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## Abstract

**Introduction:** Oral recurrent aphthous stomatitis is the most common disease of the oral cavity. The underlying etiology remains unclear, and no curative treatment is available. Zinc is essential and useful for normal growth and tissue repair, zinc acts as an integral part of several enzymes important to protein and carbohydrate metabolism.

**Aim:** The present study aimed to use systemic drug used zinc oral dispersible tablet (20 mg). Illnesses related to the oral cavity by studying its effects in oral recurrent aphthous stomatitis major clinical type (ORAS), this systemic therapy is not indicated in such situations among other drugs.

**Subjects, Materials and Methods:** In this study patients presented with (ORAS) ulceration lesions were treated with zinc oral dispersible tablet (20 mg) administered orally once daily after meal. The dispersible tablet was administered orally once daily for 14 days, 52 patients (36 males and 16 females aged between 28 - 30) with biopsy-confirmed aphthous ulceration of the lesions area, divided into two groups; group A, 28 patients were randomly assigned to receive zinc oral dispersible tablet, 20 mg/day once per day, and group B; 24 patients with oral placebo daily for 14 days.

**Results:** The results showed that administering of zinc oral dispersible tablet once per day accelerated the healing process within a short time period (8 days) without complications or disfigurement in all patients. Group A, 22 patients, (the healing rate were 0.66%) of 28 patients were used zinc oral dispersible tablet (20 mg) doses administered orally had complete healing of aphthous ulcers at period time eight days of clinical investigation evaluation and weight increase rate by 0.32% kg during the time period of the study, compared with group B, only 8 patients (the healing rate were 0.21%) of 24 placebo-randomized patients eating ability caused by oral cavity aphthous ulceration were improved markedly and had a weight loss rate by 0.53% kg.

**Conclusion:** In this study showed that, the zinc oral dispersible tablet treatment was effective in healing of the major type aphthous ulceration and the end-points of the study were complete healing and absence of any discomfort pain while eating within a short period of treatment.

***Keywords:*** *Zinc; Recurrent Aphthous Stomatitis; Treatment; Clinical Management; Zinc Oral Dispersible Tablet*

## Introduction

Oral recurrent aphthous stomatitis is the most common chronic disease of the oral cavity, affecting about 17% of the population [1,2]. Recurrent aphthous stomatitis is a very common oral condition that remains incompletely understood [3,4]. Presentation has been well-classified into minor, major or herpetic-form subcategories based on clinical features, but exact etiology is unknown and

unclear, treatments are primarily empiric and aimed at symptom reduction rather than prevention or cure. However, there are several methods, both topical and systemic, that can be easily and affordably utilized in the primary care setting [5,6]. ORAS is characterized by the appearance of initially necrotic ulcers, with well-defined limits surrounded by an erythematous halo. The lesions are located on the oral mucosa, but are infrequent on the gums [7,8]. The disease manifests in the form of outbreaks, with a chronic and self-limiting course in most cases [9,10]. ORAS is the most frequent chronic disease of the oral cavity, affecting 5 - 25% of the population [9,11,12]. It is more common in patients between 10 - 40 years of age, and predominantly affects women and individuals of higher socioeconomic levels [7,9,13]. The underlying etiology is not clear, though a series of factors are known to predispose to the appearance of oral aphthae, including genetic factors, food allergens, local trauma, endocrine alterations (menstrual cycle), stress and anxiety, smoking cessation, certain chemical products and microbial agents [8,11,14,15].

Zinc is a mineral. It is called an "essential trace element" because very small amounts of zinc are necessary for human health. Since the human body does not store excess zinc, it must be consumed regularly as part of the diet. Common dietary sources of zinc include red meat, poultry, and fish. Zinc deficiency can cause short stature, reduced ability to taste food, and the inability of testes and ovaries to function properly. Zinc is needed for the proper growth and maintenance of the human body. It is found in several systems and biological reactions, and it is needed for immune function, wound healing, blood clotting, thyroid function, and much more. Meats, seafood, dairy products, nuts, legumes, and whole grains offer relatively high levels of zinc. Zinc citrate is used in toothpaste and mouthwash to prevent dental plaque formation and gingivitis. Zinc is also used in chew gum, candies, and mouth rinses to treat bad breath. Inc is also applied to the skin for treating acne, foot ulcers. Blood tests may be taken to see if you are deficient in iron, vitamin B12 and folate as being low in these vitamins and minerals will make your ulcers worse [16].

Immune alterations have been observed, beginning with an unknown antigenic stimulation of the keratinocytes, and resulting in the activation of T lymphocytes, cytokine secretion (including tumor necrosis factor-alpha (TNF-α)), and leukocyte chemotaxis. TNF-α is believed to play an important role in the development of new ORAS lesions and has been found to be increased 2- to 5-fold in the saliva of affected patients [17]. Changes have also been reported in elements of the salivary defense system, such as the enzyme superoxide dismutase (SOD), which participates in the inflammatory response of ORAS [18]. An increase is moreover observed in the expression of vascular and keratinocyte adhesion molecules. This gives rise to the accumulation of lymphocytes and lymphocyte infiltration of the epithelium, with the induction of ulcer formation [9,10]. On the other hand, many systemic diseases are known to be associated with oral aphthae, including Bechet's syndrome, hematological disorders, vitamin deficiencies, gastrointestinal diseases, cyclic neutropenia, Reiter syndrome, Magic syndrome, PFAPA (periodic fever, aphthous pharyngitis and cervical adenopathy), Sweet syndrome and immune deficiencies [7,20]. As regards the clinical manifestations, the basic lesion is a recurrent, painful, rounded or oval ulcer with a necrotic base. Three clinical subtypes of ORAS have been established according to the magnitude, number and duration of the outbreaks [19].

**Major ORAS:** Are larger recurrent ulcers of unknown cause appearing as deep, painful areas in the mouth that leave scars on healing. They last longer than minor aphthae. This is the most severe presentation of the disease, representing 10% of all cases. Aphthous stomatitis may affect anyone at any age [9,11,13,15]. Young adults are most commonly affected. The disorder starts with the development of one to several painful ulcers. The ulcers are yellowish-white and are surrounded by a red ring of inflamed mucosa. The ulcers are usually located on moveable lining mucosa rather than palate or gums, although major ulcers may also appear in the throat. Some patients experience a tingling feeling in the area that a subsequent ulcer develops. Aphthous ulcers cannot be transmitted, the ulcers measure over 1 cm in size and tend to appear on the lips, soft palate and pharynx, and the lesions persist for over 6 weeks and can leave scars.

The subtype Herpetiform ORAS accounts for 1 - 10% of all cases and is characterized by recurrent outbreaks of small, deep and painful ulcers. Up to 100 aphthae can develop simultaneously, measuring 2 - 3 mm in size, though they tend to merge to form larger ulcerations with an irregular contour. This presentation is more often seen in women and in patients of older age [9,10,15,19].

The diagnosis of ORAS is based on the patient anamnesis and clinical manifestations. There is no specific diagnostic test, though it is essential to discard possible underlying systemic causes - particularly in the case of adults who suffer sudden outbreaks of ORAS. It is advisable to request a complete series of laboratory tests, including a complete blood count, and evaluations of iron, vitamin B12 and

folic acid. A biopsy of the lesions is only recommended in the case of diagnostic uncertainty, since the findings only indicate a simple nonspecific inflammatory lesion [9,10,19]. Since the cause of the disease is not known, many drugs have been evaluated in an attempt to palliate the symptoms.

Treatment used is multifocal and varies according to the predisposing factors. In all cases management is symptomatic and seeks to reduce inflammation of the aphthae and afford pain relief by administering topical or systemic treatments [7,8]. The present study treatments for ORAS with use systemic drug zinc oral dispersible tablet (20 mg) doses administered orally once daily after meal.

## Methods

### Study population

From 60 Patients complain from oral recurrent aphthous stomatitis (ORAS) collected, a double blind, stratified-randomized clinical case-control study was performed between March 2017 and October 2018, were selected for this study patients of the outpatient Dental Clinical of the of Dental Collage/University of Babylon and from Dental Clinical Centers in Babylon city, only 52 included to participate in this study (36 males and 16 females aged between 28 - 30) were completed study for 4 weeks recall, were randomly divided into two groups; GA: 28 patients used zinc oral dispersible tablet (20 males and 8 females) and GB:24 patients (16 males and 8 females) were randomized to used placebo oral dispersible tablet.

All patients being informed of all the details of this investigation and signed a consent form prior to their participation. Preoperative evaluation included a complete medical and dental history, in this study, collection patients met the entry criteria similar to those for the oral ulcer [15,16].

Included in the study, in caused symptoms of pain for 2 days, subjects were a biopsy find of an (ORAS) that revealed infectious. Among the exclusion criteria were:

1- Severe Bilateral peripheral neuropathy.
2- Zinc use within two week before appear of (ORAS).
3- Zinc therapy was held constant beginning four weeks before study entry.
4- Smoking person.
5- Subjects were recruited stringent precautions taken to prevent and detect pregnancy in women of childbearing potential included the following: Pregnancy testing and patient education and warning labels on medication packaging and procedures also existed for counseling and monitoring should a pregnancy occur.

### Treatment regimens

Study participants were randomly assigned in a double-blind fashion, all patient with biopsy-confirmed aphthous ulceration of the lesions area were randomly divided into two groups, group A (GA), assigned to receive zinc oral dispersible tablet, 20 mg/day (study medications were provided by LINCOLIN Pharmaceuticals LTD), and group B (GB) with oral placebo dispersible tablet, 20 mg/day. All doses had administered orally once daily after meal for 14 days. Study protocol specified that at a reduced dose, the adverse effects, should permanently discontinued by stop taking the drug.

### Criteria for response

The primary end point of the study was the complete remission or absence of the major ORAS.

Evaluation of patients and follow-up

After the screening and baseline evaluations, the patients were seen weekly clinically by aware of the patients' treatment status to assess potential toxic effects of the study medication. At baseline and at each visit, a quality-of-life questionnaire was administered to

assess pain by food eating ability, and monitor body weigh changes. Repeat oral diagnosis for present of major ORAS was performed after each weeks of study treatment to assess the healing of major (ORAS) by the clinical evaluations follow-up.

### Statistical analysis

The data is entered and analyzed with SPSS version 13.1.220 (Stata Corp LP, Texas, USA). In the first place the Shapiro-Wilk normality test is applied to test normality (where n < 30), the data was normal disruption with P-value 0.578.

The planned study was 52 patients, the study was analyzable the results in these patients are presented. All analyses were performed on an intention-to-treat basis. Two-by-two classifications of ulcer-related lesion end points were tested by use of stratified exact tests [17-21]. (Randomization was stratified according to whether a patient volunteered to be in a pharmacokinetic sub-study). The P values for end of complete ulcer healing are exploratory, not confirmatory.

## Results

### Study population

The patients with the exclusion criteria were not included in this analysis. From 60 patients only 52 patients included in the analysis were enrolled in the major ORAS between March 2017 and October 2018 and 8 patients were excluded from the analysis because they were randomized inadvertently and never received study treatment, all patients had same baseline characteristics of the two groups were similar as in table 1 and figure 1 [15,22,23].

| | Group | Mean | S.D | Std. Error | t-value | P-value | Sig |
|---|---|---|---|---|---|---|---|
| Group A | Before treatment | 60.738 | 5.820 | 1.180 | 51.77 | 0.000 | HS |
| | After treatment | 61.096 | 5.659 | 1.180 | 51.123 | | |
| Group B | Before treatment | 61.861 | 5.832 | 1.122 | 58.608 | 0.000 | HS |
| | After treatment | 61.325 | 5.437 | 1.046 | 55.112 | | |

***Table 1:*** *Data of the group A, and group B.*

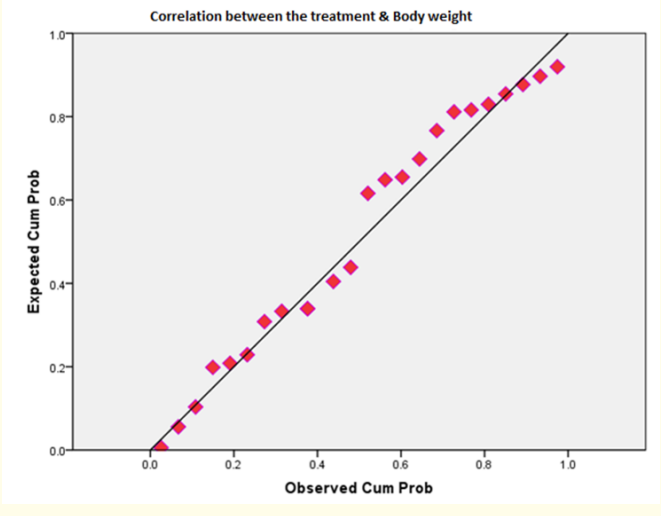


***Figure 1:*** *Correlation between drug and body Wight.*

## Discussion

In most cases, the aim of (ORAS) treatment is believed to reduce the pain, disease duration, and frequency of relapses [18]. This double-blind, randomized, placebo-controlled study shows that zinc oral dispersible tablet is effective in healing aphthous ulceration. The major ulcers healed completely by 5 days in 22 patients (78.6%) of group A, this agree with study of Sharquie., *et al* [25].

Compared with 8 patients were healing aphthous ulceration (33.3%) of group B healed completely by 13 days. These results are consistent with those we reported previously regarding the effectiveness of zinc oral dispersible tablet in treating patients who have aphthous ulceration of the mouth. Quality-of life measures indicated that the pain and impaired eating ability caused by aphthae were improved markedly in group A (Table 1).

### Clinical data

The figure 2 showed (ORAS) in oral mucosa, as a single or multiple recurring ulcer, painful with erythematous halo [1,26]. The data were tested in this study showed the effect of the drug on the weight (Table 1). The group A: had high significant impact P -value (0.000), also there was a strong correlation between treatment and weight (r = 0.98). In addition, the weight increase rate by (0.35%), the reduced disease duration or reducing pain, which lead to simplified the food eating are the most important goals in dentistry [27] and complete ulcer healing increase rate by (0.66%).

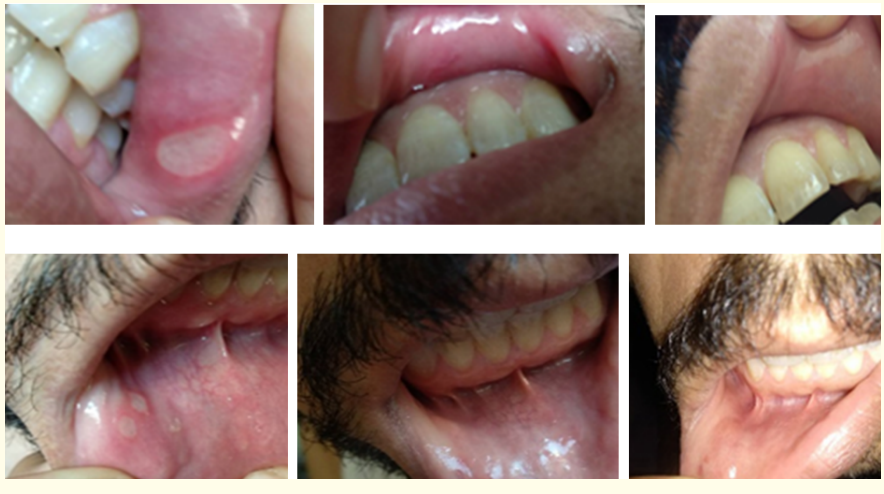

***Figure 2:*** *Clinical ulcer healing.*

The group B: the result showed a high significant impact where the p-value is (0.000), also there is a strong correlation between treatment and weight (r = 0.984), that mean there were significant effect in weight loss, in addition results showed the weight decrease rate by (0.537% kg), also the results showed that there was a very high impact effect in the weight and the complete ulcer healing increase rate by (0.21%). As showed in figure 1.

### Safety data

Two researchers investigated the topic and abstract in terms of the inclusion criteria. From the total of 60 patients only eight of patients had been out of this study. Either due to the zinc oral dispersible tablet group discontinued the study medication because of a treatment associated rash, or other three days after study entry, or discontinued study medication or had a dose reduction during the first two days of this study and be stopped, and the patients were never received study treatment and they be out of our study.

## Conclusion

With the condition of this study, showed that zinc oral dispersible tablet proved to be effective in healing aphthous ulceration of the infected patients. Repeat biopsies should be performed on ulcers not responding to zinc oral dispersible tablet treatment to exclude cytomegalovirus infection that may not have been diagnosed by the initial biopsy. The drug shortens the duration of the aphthae outbreaks, as well as the number, size and frequency of the lesions.

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