Original Article

Systematic Review On Effectiveness Of Zinc Sulfate In Treatment Of Recurrent Aphthous Stomatitis

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Abstract

Background: Zinc sulfate is an inorganic compound used as a nutritional supplement, and it is known to aid in enhancing anti-inflammatory properties. Recurrent aphthous stomatitis is a commonest oral mucosal conditions characterized by painful recurring ulcers. Many current studies focus on establishing Zinc sulfate's potency against Recurrent aphthous stomatitis and its other uses in dentistry as it has anti-inflammatory activity with minimal adverse effects.

Aim: To determine the effectiveness of zinc sulfate in the treatment of recurrent aphthous stomatitis.

Materials and methods: A systematic review of clinical trials using zinc sulfate as an effective agent against Recurrent aphthous stomatitis. Various databases were searched and obtained a total of 112 articles, among which three studies were included. A systematic review was performed using PubMed, Scholar, Wiley, Cochrane and Science direct. From the total 112 articles that appeared from various sources, 109 articles were screened, and three studies were related to the research topic. This article was reported according to the systematic review guidelines.

Result: Three studies were included in the systematic review, of which all are clinical trials showed that Zinc sulfate had a crucial role in reducing inflammation and improving oral hygiene status. The P-value of the three articles selected are 0.001, 0.0001 and > 0.05.

Conclusion: With a comparative analysis between the existing related articles about the effectiveness of zinc sulfate in treating the recurrent aphthous stomatitis, the sequel of the effectiveness of zinc sulfate in the treatment of recurrent aphthous stomatitis have to be given.

Keywords: Zinc sulfate, Recurrent aphthous stomatitis, Mucoadhesive formulation.

INTRODUCTION

Recurrent aphthous stomatitis is one of the commonest lesions occurring in the oral cavity [(1)]. This condition is very common, affecting 20 percent of individuals of both sexes[(2)]. Generally, the symptoms may include burning, itching, or stinging, which may precede the appearance of any lesion by some hours, and the pain develops to the extent of the ulceration. It is worsened by physical contact, especially with certain foods which are acidic or abrasives [(3)]. The pain is worst in the days immediately following the initial formation of the ulcer and then recedes as healing progress [(4)].

This lesion is classified into three types which include, The minor which is the most common type of Recurrent aphthous stomatitis, occurring in about 80-85 percent of both sexes. The major type, which is one of the types of Recurrent aphthous stomatitis occurring in about 10 percent of both sexes. Major aphthous stomatitis usually affects non-keratinized mucosal surfaces, but less commonly, keratinized mucosa may also be involved, such as the dorsum of the tongue and the gingival [(5)]. Herpetiform aphthous ulcerations are also termed Stomatitis Herpetiformis [(6)].

They occur mostly in the non-keratinized mucosa of the oral cavity, such as buccal and labial mucosa, soft palate, ventrum of the tongue [(7)]. The prime etiology of this condition is immunodeficiency, although its exact etiology is not known. The causes may also include genetic abnormalities, endocrine and nutritional deficiencies. In addition to its deficiency of antioxidants is also a major cause [(8)]. Recurrent aphthous stomatitis appears to be non-contagious, non-infectious, not

sexually transmissible [9]. The risk factors in Recurrent aphthous stomatitis are considered either host-related or environmental [10].

As a result, these lesions can be treated with nutritional supplements, which mainly includes the element Zinc (Zn). In situations wherein Immunodeficiency is the cause of the condition, Immunosuppressive drugs are administered to the patients [11].

The major cause of oral mucosal ulcerations includes Zinc deficiency [12]. Zinc plays a major role in the process of wound healing and synthesizing collagen and hence maintains the integrity of the epithelium [13]. The increased level of Zinc (Zn) in serum reduces the possibilities of ulcerations in individuals. Zinc sulfate is proved to have anti-inflammatory action, which subsides the lesions [14]. Zinc sulfate compound is proved to have an effective ulcer healing capacity. Zinc sulfate has more rapid and sustained action in controlling Recurrent aphthous stomatitis. It makes the immune system more efficient and fights against various invading viruses. It is supplied and administered as various drug delivery systems such as Topical ointments, mucoadhesive patches etc. The systemic means of administration include Tablets, Lozenges and Gelatin capsules [15].
This review article enlightens the Effectiveness of Zinc sulfate for managing the condition of Recurrent Aphthous ulcers.

MATERIALS AND METHODS

STUDY DESIGN:

A Systematic review of clinical trials used zinc sulfate as an effective agent against recurrent aphthous stomatitis.

SEARCH STRATEGY:

The following electronic databases were used to find published articles on the effects of zinc sulfate in the treatment of Recurrent Aphthous Stomatitis,
PubMed, Ovid Medline, Elsevier science direct, Wiley online library, Grey literature, Cochrane library, Prospero.
Each database was searched to obtain the articles using Mesh representations. The Mesh term used was Recurrent aphthous stomatitis/ Recurrent aphthous ulcer/Canker sore and Zinc sulfate.
After the search, 112 articles were obtained, among which three articles were finalized for further studies.

ELIGIBILITY CRITERIA

Inclusion criteria:

1) Studies published in English
2) Articles on the effectiveness of zinc sulfate in recurrent aphthous stomatitis
3) Clinical trial studies
4) Full-text articles
5) Publications over the year

Exclusion criteria:

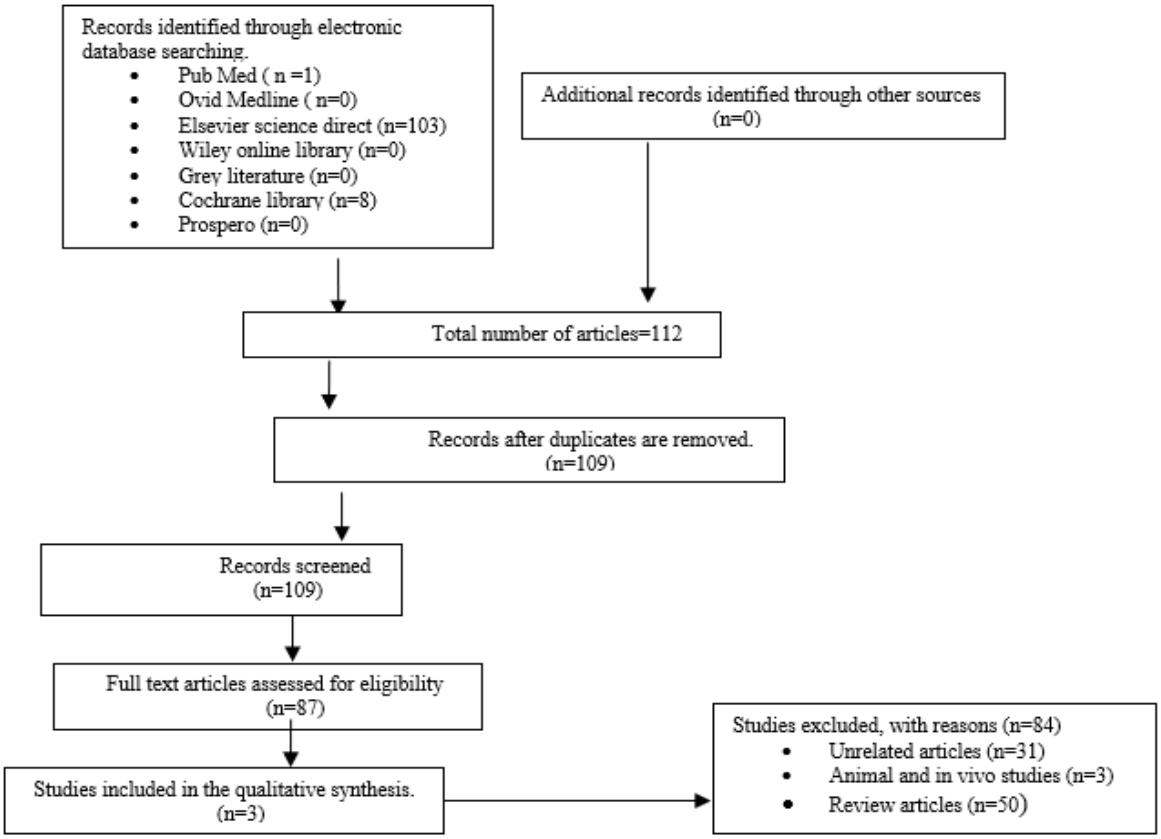
1) Articles published in other languages
2) Only abstracts available
3) Unrelated articles
4) Animal studies
5) In-vitro studies

SEARCH ENGINES

- Pub Med
- Ovid Medline
- Elsevier science direct
- Wiley online library
- Grey literature
- Cochrane library
- Prospero

After the search using the appropriate mesh terms, 112 articles were found from the online databases. After duplicates removal, 109 articles were screened, and 87 full-text articles were available. Inclusion-Exclusion criteria were applied, and the final three related articles were selected for further assessment. Figure 1 shows the flow diagram of several studies identified, screened, assessed for eligibility, excluded and included in the systematic review.

Figure 1: Flow chart denoting the number of studies identified, screened, assessed for eligibility, excluded and included in the systematic review



RESULT

TABLE 1: CHARACTERISTICS OF THE INTERVENTIONS IN THE INCLUDED STUDIES

SI. NO:	AUTHOR	YEAR	PATIENT SELECTION	DURATION	PREPARATION USED	INTERVENTIONS
1	Anahita Ghorbani et al	2020	46 patients with recurrent aphthous stomatitis	Seven days	• Zinc sulfate mucoadhesive tablet	Two groups of patients were given the zinc sulfate mucoaedhesive tablets.
2	Sharquie K et al	2008	45 patients with recurrent aphthous stomatitis	518 days	• Zinc sulfate • Dapsone • Glucose	Group A: zinc sulfate 150mg twice daily Group B: dapsone 50mg twice daily Group C: glucose 250mg as placebo
3	Recep ORBAK et al	2002	40 patients of age 13-51 of both sexes with recurrent aphthous stomatitis	699 days	Zinc sulfate 220 mg • Saccharose	Group I: individuals were administered zinc sulfate 220mg once per day before a meal for one month Group II: Individuals were administered placebo saccharose once per day before a meal for one month

Table 1: shows the characteristics of the intervention in the included studies. In all the above studies, the effectiveness of zinc sulfate against Recurrent Aphthous ulcers was reviewed and compared. Trials were conducted in patients with Recurrent Aphthous Stomatitis. Trial duration (One to One and half years) and preparation used varied in each study.

TABLE 2: OUTCOME DATA AS REPORTED IN INCLUDED STUDIES

SL NO.	AUTHOR	YEAR	OUTCOME	RESULT
1	Anahita Ghorbani et al	2020	The mucoadhesive formulation of zinc sulfate in patients with RAS dramatically accelerated inflammation and pain of the aphthous lesion compared to the placebo.	The outcome suggests that zinc sulfate reduces the pain, diameter of the wound, its surrounding inflammation and accelerates the recovery time of RAS (P = 0.001).
2	Sharquie K et al	2008	Both zinc sulfate and dapsone had significant therapeutic and prophylactic effects in controlling RAS; however,	The outcome suggests that zinc sulfate was more effective than dapsone in reducing the OCMI of the

			zinc sulfate had much more rapid and sustained action.	ulcers (P= 0.0001 for OCMI AND 0.001 for the diameter for ulcers).
3	Recep ORBAK et al	2002	The empirical use of systemic zinc sulfate supplementation in the treatment of RAS is recommended.	The outcome suggests that no side effect was seen with the use of systemic zinc sulfate. The serum zinc levels were also normalized with the treatment (P>0.05)

Table 2: shows the outcome and result of the effectiveness of zinc sulfate against Recurrent Aphthous Stomatitis in the above-mentioned studies. The outcome and results were positive in the above studies showing zinc sulfate can reduce the pain, wound diameter, its surrounding inflammation, and accelerates the recovery time of Recurrent Aphthous Stomatitis.

TABLE 3: BIAS ANALYSIS OF INCLUDED STUDIES

Sl No.	AUTHOR AND YEAR	RANDOM SEQUENCE GENERATION	ALLOCATION CONCEALMENT	SELECTIVE REPORTING	INCOMPLETE OUTCOME DATA	BLINDING OF OUTCOME ASSESSMENT	BLINDING PARTICIPANTS AND PERSONALS
1	Anahita Ghorbani et al, 2020	+	_	_	_	+	+
2	Sharquie K et al., 2008	+	_	_	_	+	+
3	Recep ORBAK et al., 2002	+	_	_	_	+	+

Table 3: shows the bias analysis of all the included studies. It is categorized as high-risk bias "+", low-risk bias "_", and unclear "?". Categorization was done according to Cochrane risk of bias for randomized controlled trials.

DISCUSSION

In this study, after careful assessment, three clinical trials were selected for further evaluation and discussion.
In 2020, Anahita Ghorbani et al. conducted a clinical trial on using a mucoadhesive tablet of Zinc sulfate in 46 patients with Recurrent aphthous stomatitis for seven days. The outcome of this clinical trial is the mucoadhesive formulation of Zinc sulfate in patients with Recurrent aphthous dramatically accelerated the inflammation and pain of the aphthous lesion compared to the placebo.

In 2008, Sharquie K et al. conducted a double-blind placebo-controlled study on using Zinc sulfate, Dapsone and Glucose in 45 patients with Recurrent aphthous stomatitis for 518 days. The outcome of this study is both Zinc sulfate, and Dapsone had significant therapeutic and prophylactic effects in controlling Recurrent aphthous stomatitis, and Zinc sulfate had much more rapid and sustained action than Dapsone.

In 2002, Recep ORBAK et al. conducted a clinical trial on using Zinc sulfate and Saccharose in 40 patients of age 13-15 of both sexes with Recurrent aphthous stomatitis for 699 days. The outcome of this clinical trial is the empirical use of systemic Zinc sulfate supplementation in the treatment of recurrent aphthous stomatitis is recommended.

The frequency of ulceration and its severity varies from patient to patient. Recurrences usually occur at one- to four-month intervals, although some patients reported a history of ulcers being present for most of the time. However, the rate of zinc intake can be changed from one study to another. The oral zinc intake of a patient should consist of 220mg zinc sulfate (50mg of elemental zinc) one time daily for 28 days and the zinc administered orally at 168mg/day as zinc acetate (50mg of elemental zinc) should be one time daily for 2-3 weeks. This dosage is suitable according to the WHO recommendation. It is recommended that a multi-centre study be conducted in the future to gain more reliable results.

Hence the outcome obtained with the comparative studies suggests that Zinc sulfate can reduce the pain, the diameter of the wound, its surrounding inflammation, accelerates the recovery time, reducing the ulcers with no side effects on Recurrent aphthous stomatitis.

LIMITATION

No meta-analysis was performed during the clinical heterogeneity.

CONCLUSION

Zinc sulfate has anti-inflammatory activity against Recurrent aphthous stomatitis. This study demonstrates both clinically and statistically the effective action of zinc mucoadhesive tablets on reducing pain, as a topical drug delivery system on reducing pain, the diameter of the wound, and duration of the recovery period of Recurrent aphthous stomatitis compared with the placebo group. The serum zinc levels were also normalized with treatment. Thus with the comparative analysis between the obtained articles, the results are evident that Zinc sulfate has anti-inflammatory activity. It reduces the severity of pain of the ulcers, accelerates the healing time and can be used to treat recurrent aphthous stomatitis.

CONFLICT OF INTEREST: No conflict of interest

SOURCE OF FUNDING: Self

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