Silver nitrate cauterization for aphthous stomatitis: a systematic review

SYSTEMATIC REVIEW

ORIGINAL ARTICLE BY

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ABSTRACT

OBJECTIVE

To identify the efficacy of silver nitrate cauterization in shortening healing time of aphthous stomatitis.

METHODS

Three independent reviewers systematically searched through electronic databases including the Cochrane Library, PubMed, Trip Database and Scopus. We also performed hand searching to find all relevant studies outside the databases. We assessed quality and risk of bias of the included studies using The Cochrane Collaboration's Tool for Assessing Risk of Bias. We extracted data from the included studies. The meta-analysis was performed where appropriate.

RESULTS

There were two randomized controlled trials identified, involving 150 patients with aphthous stomatitis. Rate of complete re-epithelialization on the seventh day after the procedure was interpreted that using silver nitrate cauterization was no statistically significant difference from using placebo stick. (relative risk, 1.24; 95% confidence interval, 0.55 to 2.80; P=0.60; I^2=87%)

CONCLUSION

Rate of complete re-epithelialization of aphthous stomatitis was not different between using silver nitrate cauterization and placebo on the seventh day after the procedure.

INTRODUCTION

Aphthous stomatitis is an oral disease characterized by painful oral ulcers that appear multiple small erythematous lesion with circumscribed margins.[1] Its prevalence rate can be as high as 80%.[2–9] Its treatments comprised the uses of steroids, analgesics, topical anesthetic agents, anti-inflammatory agents, antiseptics, tetracycline suspension, sucralfate, carbon dioxide laser and silver nitrate cauterization.[10–22]

Regarding silver nitrate cauterization, in 2005 a randomized controlled trial study (RCT) in 85 patients with aphthous stomatitis concluded that the healing time of those undergoing silver nitrate cauterization was not shorter than that of placebo group.[21] However, the latter study in 2014 in 65 patients with aphthous stomatitis stated that the healing time of silver nitrate cauterization group was shorter than that of placebo group.[22] Due to this controversy, we conducted a systematic review in order to summarized all available evidences to identify the efficacy of silver nitrate cauterization in treatment of aphthous stomatitis.

METHODS

SEARCH METHODS FOR IDENTIFYING OF STUDIES

Three independent reviewers systematically searched through electronic databases including the Cochrane Library, PubMed, Trip Database and Scopus using the term "aphthous stomatitis" or "aphthous ulcer" and "silver nitrate". We also applied Medical Subject Headings (MeSH) searching strategy in term of "Stomatitis, Aphthous"[Mesh] AND "Silver Nitrate"[Mesh] to identify studies in the Cochrane Library and PubMed. We used PICO search strategy to identify studies in Trip Database using P: "aphthous stomatitis" and I: "silver nitrate" with no specific C and O. No restriction of language was assigned and translation was sought when necessary. We also tracked for articles in references of each included study. Moreover, we performed hand searching to find other relevant studies outside the databases such as Google Scholar, ClinicalTrials.gov, Web of Science and WorldCat using the term "aphthous stomatitis" or "aphthous ulcer" and "silver nitrate". All searches were done on February 11, 2017.

INCLUSION AND EXCLUSION CRITERIA

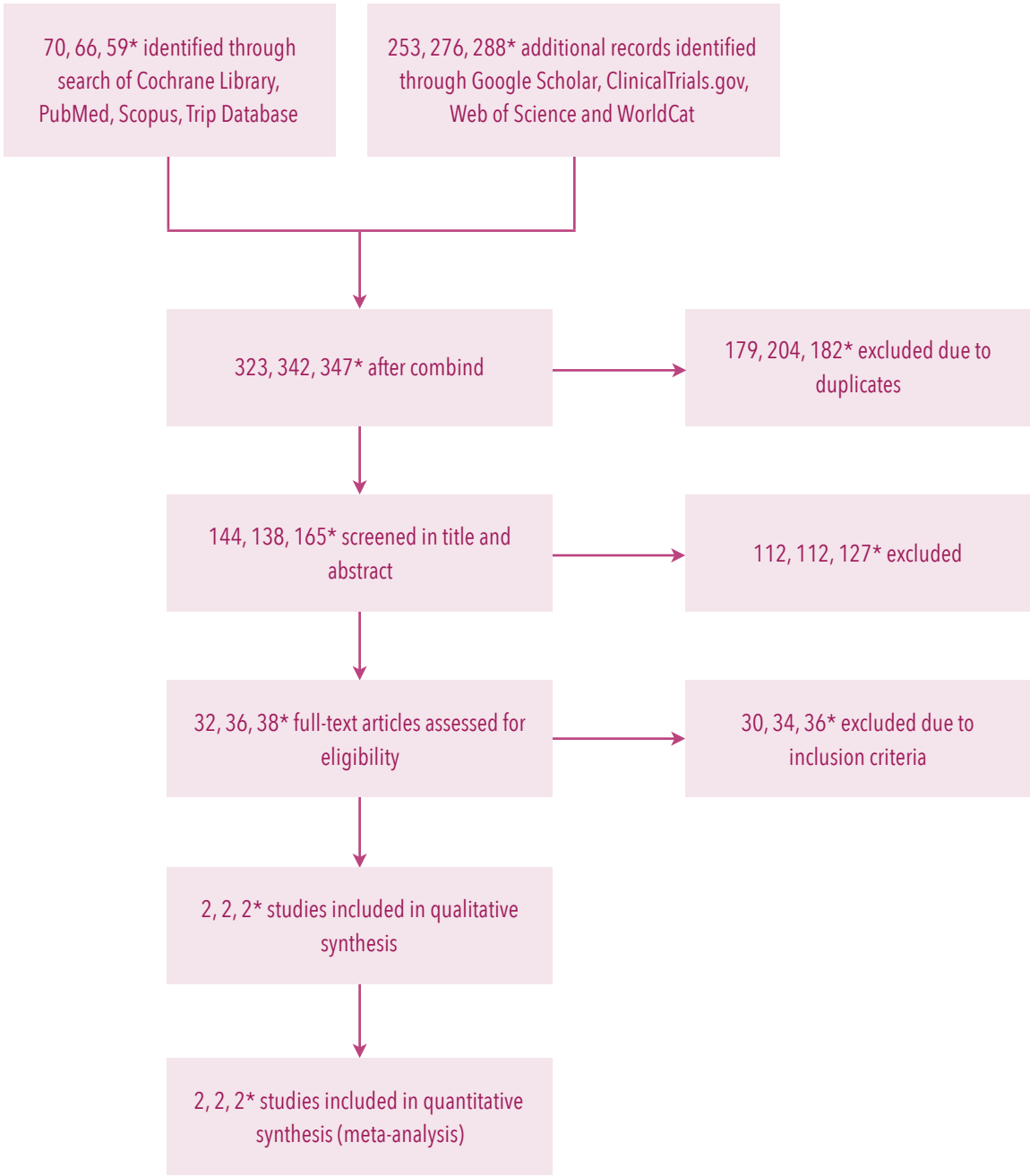
We included only RCTs that patients with aphthous stomatitis were treated with silver nitrate cauterization regardless any outcomes. To focus on the efficacy of silver nitrate cauterization in treating patients with aphthous stomatitis, studies were excluded if they met following this criteria; studies which compared combination therapy of silver nitrate cauterization and other agents.

ASSESSMENT OF REPORTING BIASES

We used The Cochrane Collaboration's tool for Assessing Risk of Bias to present the risk of bias as random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias by categorizing them as high risk, low risk, or unclear risk.[23]

DATA EXTRACTION

We extracted the data from the included studies regarding the first author, year of publication, a



*The three numbers refer to the quantity of results searched by the three reviewers; WL, NW and PJ, respectively.

Figure 1. Flow of Studies by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

Table 1. Description of included studies.

Studies	No. of patients in intervention/ controlled group	Interventions	Control	Outcomes
Alidaee et al, 2005	47/38	Silver nitrate cauterization (99.8% purity; Merck, Darmstadt, Germany)	Placebo stick (sugar stick)	Rate of complete re-epithelialization on the seventh day after the procedure (83% vs. 89% ;P=0.39).
Gül Soylu Özler, 2014	35/30	Silver nitrate cauterization	Placebo stick (empty stick)	Rate of complete re-epithelialization on the seventh day after the procedure (60% vs 32% ;P<0.01).

number of participants of intervention and controlled groups, duration of studies, and outcomes in terms of rate of complete re-epithelialization on the seventh day.

STATISTICAL ANALYSIS

The meta-analysis was done and reported as relative risk (RR) and 95% confidence interval (CI). We presented the meta-analysis as forest plot. We calculated I^2 to assess the heterogeneity of the included studies. We used the fixed-effect model if $I^2<50\%$ and the random-effect model if $I^2\geq50\%$. We used funnel plot for assessing publication bias. All statistical analyses were done using Review Manager 5.3 statistical software.

RESULTS

Initially, there were 298, 327 and 325 studies identified by each of the three reviewers (by WL, NW and PJ, respectively) as potentially relevant studies from the electronic databases and other sources (Figure 1). Of these, 144, 138 and 165 studies remained after duplicate removed and were screened for their titles and abstracts. Of these 2, 2, 2 studies fulfilled the predefined inclusion criteria and were screened in details. We finally assented to have two related studies to be included in the quantitative analysis.

CHARACTERISTICS OF THE INCLUDED STUDIES

We found two studies with 150 patients with aphthous stomatitis. All of them were RCT comparing the use of silver nitrate cauterization to placebo for treating patients with aphthous stomatitis; 82 patients in silver nitrate cauterization group and 68 patients in placebo group. For the two placebo-controlled studies, patients in the control group were prescribed with either sugar stick or empty stick (Table 1).

RISK OF BIAS OF THE INCLUDED STUDIES

We assessed the quality of the two included studies by Alidaee et al and Gül Soylu Özler using The Cochrane Collaboration's Tool for Assessing Risk of Bias. Their risk of bias summaries with graphs are summarized in Figure 2, respectively.

RANDOM SEQUENCE GENERATION

A former study did not reported the methods of random sequence, it was described as unclear risk of bias. A latter study reported the methods of

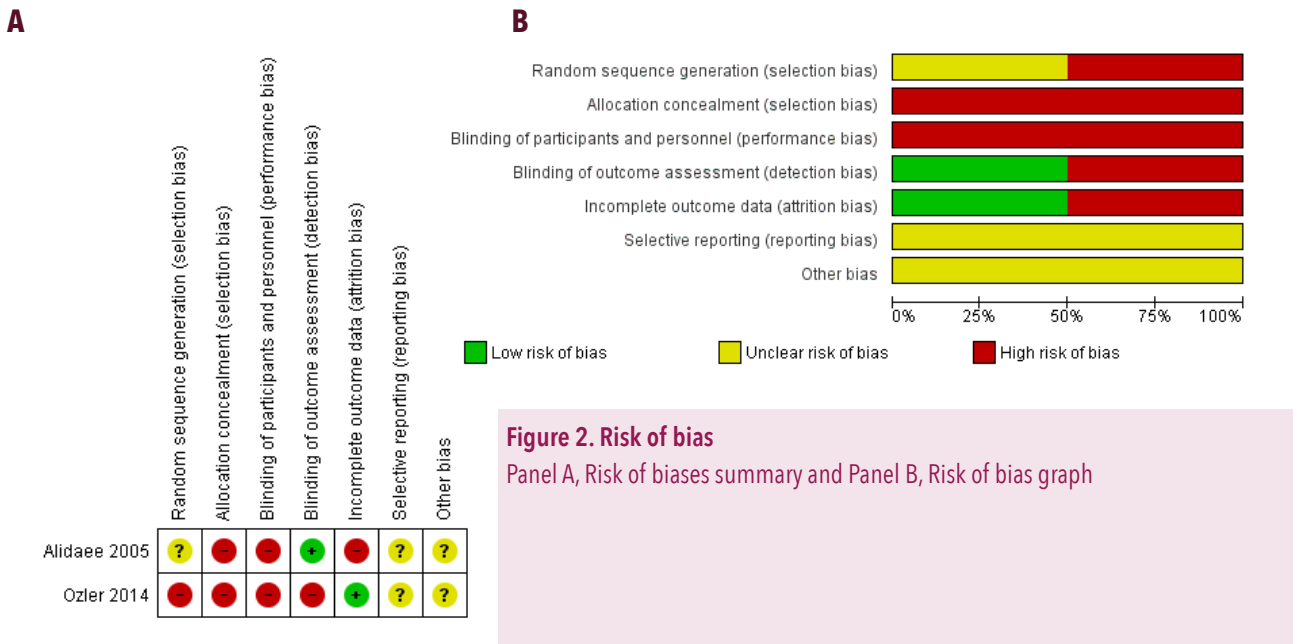


Figure 2. Risk of bias
Panel A, Risk of biases summary and Panel B, Risk of bias graph

random sequence by attendance to the ear nose throat clinic, it was described as high risk of bias.

ALLOCATION CONCEALMENT

A former study reported treatment allocation processed by sealed envelopes but the researcher was not blinded. It was described as high risk of bias. A latter study reported the methods of random sequence by attendance to the ear nose throat clinic with no allocation concealment. The study was described as high risk of bias.

BLINDING OF PARTICIPANT AND PERSONAL

Both studies were described as high risk of bias. A former study blinded only assessor and a latter study blinded only participant.

BLINDING OF OUTCOME ASSESSMENT

A former study evaluated the complete re-epithelialization using by another assessor. The study was described as low risk of bias. Evaluation of complete re-epithelialization of a latter study was described as a high risk of bias as assessor could know the intervention group.

INCOMPLEATE OUTCOME DATA

A former study was described as a high risk of bias as there were no description regarding missing patients on the seventh day of evaluation. A latter study had no missing patient, it was described as a low risk of bias.

SELECTIVE REPORTING

Both studies were rated as unclear risk of bias as they did not record adverse effects of the interventions.

OTHER POTENTIAL SOURCES OF BIAS

No other sources of bias were mentioned in both included studies. Thus, we described them as unclear risk of bias.

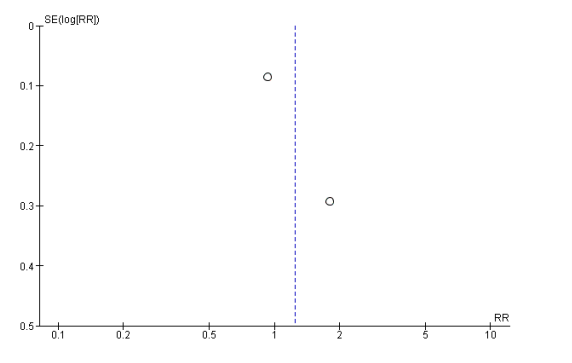


Figure 4. Publication
Funnel plot: Rate of complete re-epithelialization

RATE OF COMPLETE RE-EPITHELIALIZATION OF ULCERS ON THE 7th DAY AFTER THE PROCEDURE

There were two studies included with 150 patients with aphthous stomatitis. Comparing silver nitrate cauterization to placebo stick, rate of complete re-epithelialization on the seventh day after the procedure was not significantly different between the two interventions (RR, 1.24; 95% CI, 0.55 to 2.80; I^2=87%) (Figure 4).

PUBLICATION BIAS

We generated the funnel plot of reported outcomes at rate of complete re-epithelialization on the seventh day comparing silver nitrate and placebo. However, the number of the studies using in the funnel plot were too few to assess for publication bias (Figure 5).

DISCUSSION

SUMMARY OF THE RESULTS

In our systematic review, two RCTs were identified with 150 patients with aphthous stomatitis and included in the analysis. We found no statistically significant difference in rate of complete re-epithelialization between using silver nitrate cauterization and placebo on the seventh day after the procedure. High heterogeneity was observed. In our review, the funnel plots of the outcomes were summarized. However, we did not analyze publication bias as the number of the included studies was too few.

STRENGTH AND LIMITATIONS OF THE REVIEW

Strength and limitations of the review

From our results, this is the first systematic review comparing silver nitrate to placebo in treating patients with aphthous stomatitis. Our study had several limitations. Firstly, our systematic review consisted of a small number of participants, since only two studies met our predefined inclusion and exclusion criteria. Secondly, one of them had high risk of bias because there was selection bias, performance bias, detection bias and reporting bias.22 This can lead to imprecise estimation of the pooled effect size. Thirdly, The included studies did not report adverse effects.21, 22 Finally, that study also did not describe type and concentration of silver nitrate cauterization which can directly affect the effect size and cause the heterogeneity. Due to the mentioned limitations, implementation of our findings should be done with cautions.

COMPARISON TO OTHER STUDIES

In our systematic review, there was no statistically significant difference in rate of complete re-epithelialization between silver nitrate cauterization and placebo on the seventh day after the procedure but there is no study to compare outcomes. This might be due to the fact that aphthous stomatitis is a self-limited disease.[20] Aside from this outcome, pain

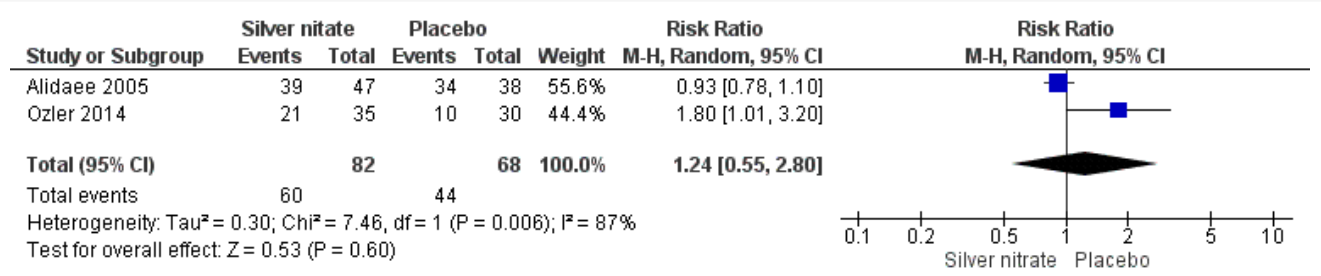


Figure 3. Rate of complete re-epithelialization on the seventh day after the procedure

reduction was also described in both of our included studies, however, we did not combine the effect size in term of pain reduction as they reported pain in different scales. However, both included studies suggested that silver nitrate cauterization was able to reduce pain.[21,22] Still, pain in patients with aphthous stomatitis can be ameliorated by topical steroid which found to have similar efficacy to silver nitrate cauterization in term of pain reduction.[10] Adverse effects were not recorded in both included RCTs but they were recorded where else. For instance, aphthous stomatitis diameter was enlarged from 5 mm to 3 cm in 6 days[24] in one case report and silver nitrate caused bisphosphonate-related osteonecrosis of the jaw in another case report.[25]

CONCLUSION AND IMPLICATION OF THE RESULTS

There was no statistically significant difference between using silver nitrate cauterization and placebo stick in rate of complete re-epithelialization on the seventh day after the procedure. For the further upcoming studies, we suggest a large number of participants in the study of RCT in order to evaluate the differences in

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