Topical sucralfate ointment for postoperative pain reduction after hemorrhoidectomy: systematic review

SYSTEMATIC REVIEW

ORIGINAL ARTICLE BY

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ABSTRACT

OBJECTIVE

To assess the efficacy of topical sucralfate ointment for postoperative pain reduction after hemorrhoidectomy.

METHODS

Three independent reviewers systematically searched through electronic databases including Cochrane library, Pubmed, Trip Database and Scopus using the term "hemorrhoidectomy" or "post hemorrhoidectomy pain" together with "topical sucralfate ointment". Furthermore, we also sought for additional studies using a hand searching to identify all relevant randomized controlled trials (RCT) that comparing effect of topical sucralfate ointment and other topical treatments for postoperative pain reduction after hemorrhoidectomy. We included RCT with patients undergoing hemorrhoidectomy and using topical sucralfate ointment. We performed risk of bias assessment of the included RCTs, and we later performed the meta-analysis.

RESULTS

Two RCTs were included in the meta-analysis with 138 patients undergoing hemorrhoidectomy; topical sucralfate ointment (N=69) and placebo (N=69). Topical sucralfate ointment had similar effect for pain score reduction to that of placebo at day 7 after hemorrhoidectomy (mean difference (MD) -0.47; 95% confidence interval (CI), -2.01 to 1.07; I^2 =88%) and at day 14 after hemorrhoidectomy (MD -0.16; 95% CI, -1.98 to 1.67; I^2=92%). Furthermore, patients in sucralfate group requested less daily amount of diclofenac than in placebo group at day 7 after hemorrhoidectomy (MD -64.58; 95% CI, -110.61 to -18.56; I^2=92%), but not at day 14 after hemorrhoidectomy (MD -54.25; 95% CI, -113.51 to 5.01; I^2=96%).

CONCLUSION

In patients undergoing hemorrhoidectomy, comparing efficacy between using topical sucralfate ointment and placebo for postoperative pain reduction after hemorrhoidectomy at day 7 cannot be concluded as our review had low volume of studies and participants as well as high heterogeneity.

INTRODUCTION

Hemorrhoids are abnormal dilatation and distortion of the veins of the internal hemorrhoidal venous plexus in the anal canal.[1] It presents when patients have increased abdominal pressure such as straining and chronic constipation.[1] Approximately 40% of patients with hemorrhoids are asymptomatic.[2] Symptomatic hemorrhoids usually present with painless rectal bleeding at the end of defecation or may drip into the toilet, perianal itching and pain due to thrombosis.[2] However, the exact prevalence worldwide of symptomatic hemorrhoids is very difficult to establish as only symptomatic patients will seek for treatment.[3] Its treatments depend on its grading, for instance, hemorrhoidectomy is used in those with grade III or IV hemorrhoids.[4,5] The most common complication of hemorrhoidectomy is postoperative pain due to external wounds cut through a nerve that innervated perianal skin or might be due to bacterial wound infection.[6,7] Conventional analgesics for pain control e.g., nonsteroidal anti-inflammatory drugs (NSAIDs) are often used for short term due to their side effects.[8,9]

Sucralfate is a compound of sucrose sulfate and aluminum hydroxide typically used in oral form for treatment dyspepsia or peptic ulcer.[10,11] It is poorly absorbed in the gastrointestinal tract and it becomes gel-like substance when contacts with water.[10,11] Its action is to release prostaglandin from the gastric mucosa that plays a role in gastric mucosal protection and it also has an antibacterial effect.[12,13] There were prior trials stated that topical sucralfate can stimulate epithelialization and angiogenesis, and it is effective in various condition e.g., second and third-degree burn, perineal excoriation and prevented acute radiation dermatitis.[14-16] Two RCTs from Iran with 48 patients and from Egypt with 90 patients with hemorrhoidectomy showed that using topical sucralfate ointment reduced postoperative pain and usage of analgesia.[17,18] However, there is no evidence of its efficacy for postoperative pain reduction in a patient undergoing hemorrhoidectomy from a systematic review. Thus, we conducted a systematic review to compare the efficacy between topical sucralfate ointment and other topical treatments for postoperative pain reduction after hemorrhoidectomy.

METHODS

SEARCH STRATEGIES

Three independent reviewers systematically searched through electronic databases including Cochrane library, Pubmed, Trip Database, Scopus and other sources e.g., Google Scholar using the combined search terms of "hemorrhoidectomy" or "post hemorrhoidectomy pain" together with "topical sucralfate ointment". We also applied Medical Subject Headings (MeSH) searching using the terms of "hemorrhoidectomy"[MeSH] AND "sucralfate"[MeSH] to identify studies on Pubmed and Cochrane library and applied PICO searching using the terms of P: hemorrhoidectomy with I: topical sucralfate on Trip Database. Furthermore, we also sought for additional studies using hand searching to explore other unidentified studies on the databases to identify all relevant RCTs comparing the efficacy of topical sucralfate ointment and other topical treatments for

Table 1. Characteristics of two studies

Studies	Number of patients (intervention/ control)	Patients' age (years)	Intervention and control	Postoperative analgesic drug	Outcomes
Ala et al 2013	24/24	20-70	10% topical sucralfate ointment 1 g versus topical placebo 1 g	Pethidine for first 24 hours then diclofenac tablets for 14 days	Using topical sucralfate ointment reduced postoperative pain after hemorrhoidectomy more than that of placebo at day 7 and day 14 (P<0.01). Using topical sucralfate ointment reduced daily amount of diclofenac usage at day 7 and day 14 (P<0.001).
Albatanony et al 2016	45/45	21-60	10% topical sucralfate ointment 1 g versus topical placebo 1 g	Pethidine for first 24 hours then diclofenac tablets for 14 days	Using topical sucralfate ointment and placebo had similar efficacy in relation to postoperative pain reduction after hemorrhoidectomy at day 7 (P=0.35) but placebo reduced more at day 14 (P=0.02). Using topical sucralfate ointment reduced daily amount of diclofenac usage at day 7 and day 14 (P<0.001).

postoperative pain reduction after hemorrhoidectomy.

INCLUSION CRITERIA

We included only randomized controlled trial (RCT) with patients undergoing hemorrhoidectomy using topical sucralfate ointment compare with other topical treatments. The outcome of our interest was pain intensity. We excluded the studies that used other topical forms of sucralfate e.g., cream, gel.

QUALITY OF REPORTING AND RISK OF BIAS

We used Jadad score to assess the quality of the included RCTs comprising the evaluations of randomization, blinding methods and adequate description of withdrawals or dropouts. In addition, we used The Cochrane Collaboration's Tool for Assessing Risk of Bias to demonstrate the risk of bias in relation to random sequence generation, allocation concealment, blinding of participant and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias by classifying them to be three degrees which are low, high, and unclear risk of bias.

DATA EXTRACTION

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

Table 2. Jadad score

	Ala et al	Albatanony et al
Was the study described as randomized ?	1	1
Was the method used to generate the sequence of randomization described and was it appropriate?	1	0
Was the study described as double blind ?	1	1
Was the method of double blind described and was it appropriate ?	1	1
Was there a description of withdrawals and dropouts ?	1	1
Score	5	4

numbers of participants, patients' age, outcomes of visual analog scale (VAS) of pain score and daily amount of diclofenac usage in each study.

DATA ANALYSES

The primary and secondary outcomes from the two trials were meta-analyzed and interpreted using the mean difference (MD) and 95% confidence interval (CI) and were shown as a forest plot. Later we calculated I^2 to evaluate the heterogeneity among the studies. We used the fixed-effect model if $I^2<50\%$ and random-effect model if $I^2\geq50\%$. The publication bias was evaluated as funnel plots. All statistical analyses were done using Review Manager 5.3 statistical software.

RESULTS

STUDY CHARACTERISTICS

Initially, there were 30, 22 and 33 records identified by reviewer I, II and III, respectively, which 9, 7, and 11 of them were duplicated. There were 21, 15 and 22 remained after duplicate removed and excluded 19, 13, 20 from screening articles and abstracts. The remaining two trials were included in the meta-analysis by the consensus of the three reviewers (Figure 1). Both studies compared topical sucralfate ointment and placebo for post hemorrhoidectomy pain reduction. Their characteristics are shown in Table 1.

ASSESSING THE QUALITY AND RISK OF BIAS

The quality of the two studies, Ala et al and Albatanony et al, were assessed using Jadad score to assess the risk of bias.19 They were score 5 and 4, respectively (Table 2). The risk of bias using The Cochrane Collaboration's tool for assessing the risk of bias for both studies was summarized in Figure 2 and Figure 2 and descriptive results are shown below.

RANDOM SEQUENCE GENERATION

The former study was described as low risk of bias as it used a computer-generated table but the later

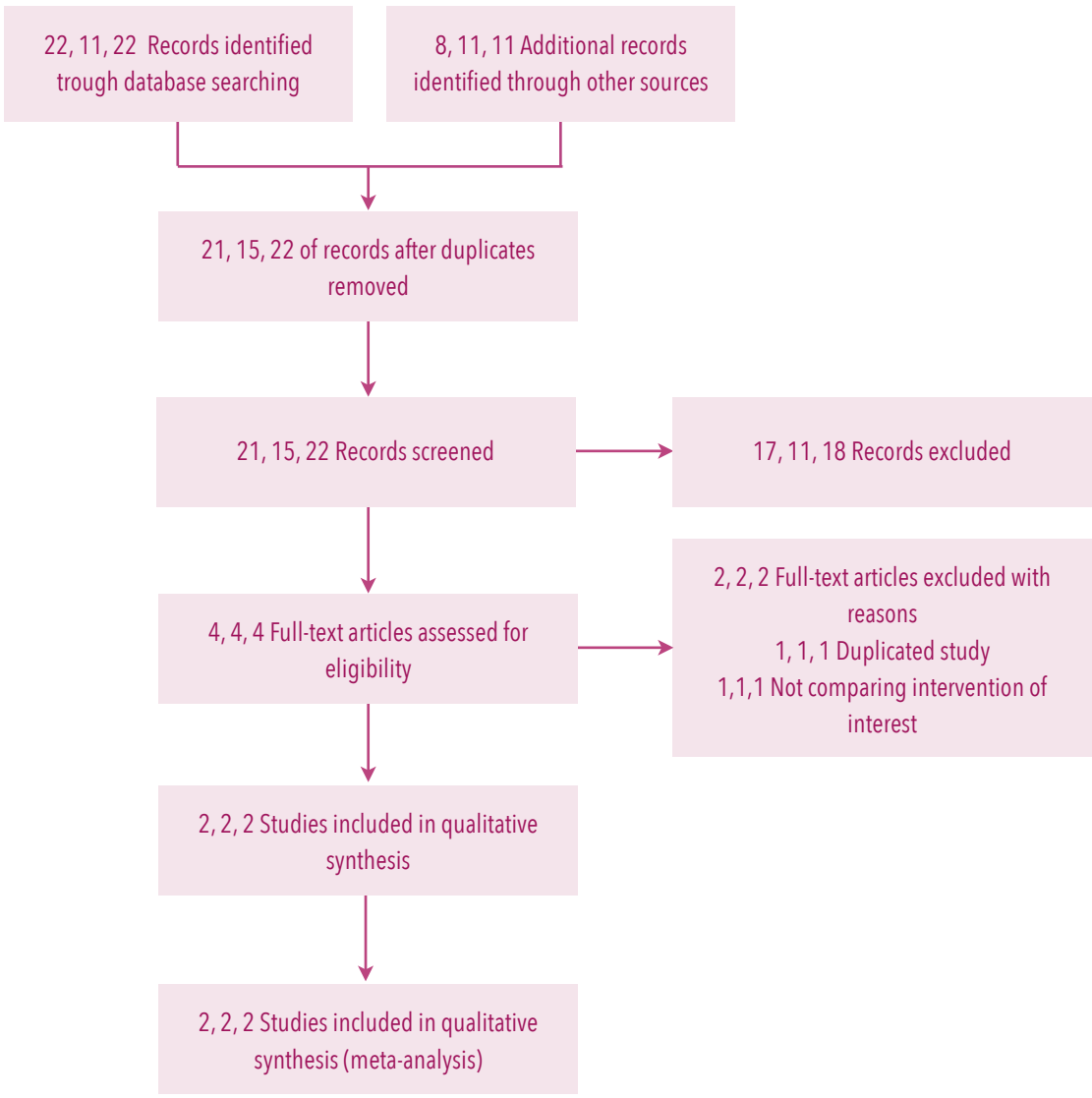

Figure 1. Study flow diagram

study was an unclear risk of bias as it lacked randomization methods description.

ALLOCATION CONCEALMENT

The former study was described as low risk of bias as it blinded data collector and used the identical appearance of containers. The later study also had a low risk of bias as it used closed envelope methods.

BLINDING OF PARTICIPANT AND PERSONAL

Both studies had a low risk of bias as they were double-blind trials with a description of blinding.

BLINDING OF OUTCOME ASSESSMENT

Both studies were described as unclear risk of bias as it did not address this information regarding this process in their studies.

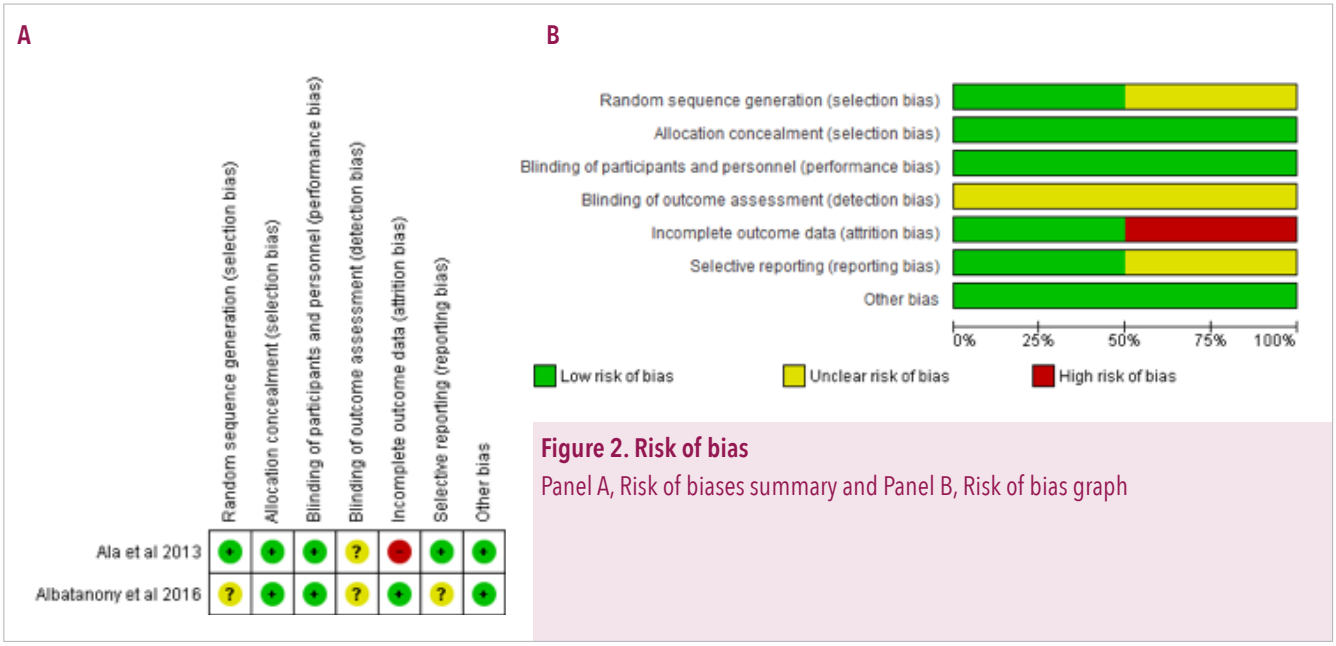

Figure 2. Risk of bias
Panel A, Risk of biases summary and Panel B, Risk of bias graph

INCOMPLETE OUTCOME DATA

The former study had a high risk of bias as it had dropouts. The latter study was a low risk of bias as it had no dropout.

SELECTIVE REPORTING

The former study was described as low risk of bias as all of the outcome data were reported while the later study had an unclear risk of bias as all of the pre-specified primary outcomes was not reported in the study.

OTHER POTENTIAL SOURCES OF BIAS

Both studies had a low risk of bias as they were free from any funding source.

THE PRIMARY OUTCOME

Using topical sucralfate ointment had similar efficacy for post hemorrhoidectomy pain reduction at day 7 after hemorrhoidectomy compared with that of using a placebo (MD -0.47; 95% CI, -2.01 to 1.07; I^2 =88%) (Figure 3).

THE SECONDARY OUTCOME

PAIN SCORE REDUCTION AT DAY 14 AFTER HEMORRHOIDECTOMY

There was no statistically significant difference for post hemorrhoidectomy pain reduction at day 14 between using topical sucralfate ointment and placebo (MD -0.16; 95% CI, -1.98 to 1.67; I^2 =92%) (Figure 4).

DAILY AMOUNT OF DICLOFENAC USAGE

Patients in sucralfate group requested less daily amount of diclofenac than in placebo group at day 7 after hemorrhoidectomy (MD -64.58; 95% CI, -110.61 to -18.56; I^2 =92%) but not at day 14 (MD -54.25; 95% CI, -113.51 to 5.01; I^2 =96%) (Figure 5).

AMOUNT OF PETHIDINE USAGE WITHIN FIRST 24 HOURS

For Ala et al., patients in sucralfate group requested similar amount of pethidine to that in placebo group at 0 to 6 hours after hemorrhoidectomy (MD

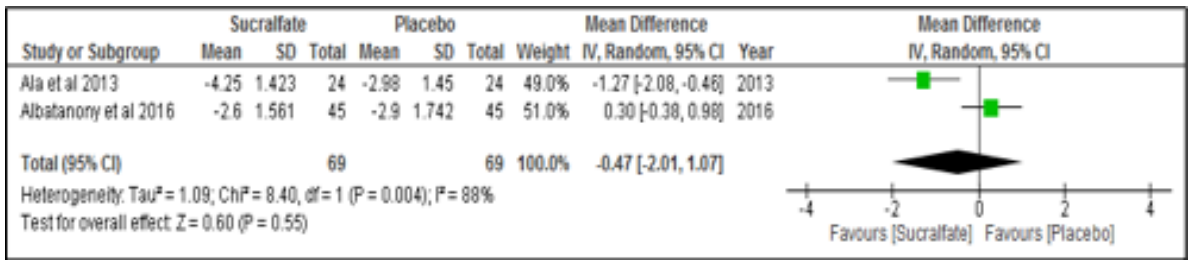

Figure 3. Forest plot: 10% topical sucralfate ointment versus placebo, outcome: Pain score reduction at day 7

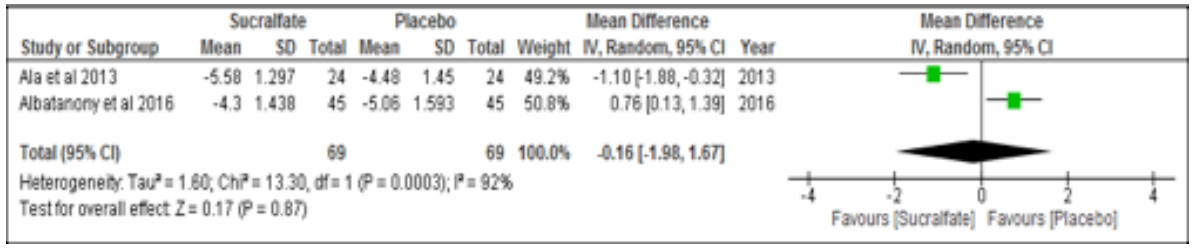

Figure 4. Forest plot: 10% topical sucralfate ointment versus placebo, outcome: Pain score reduction at day 14

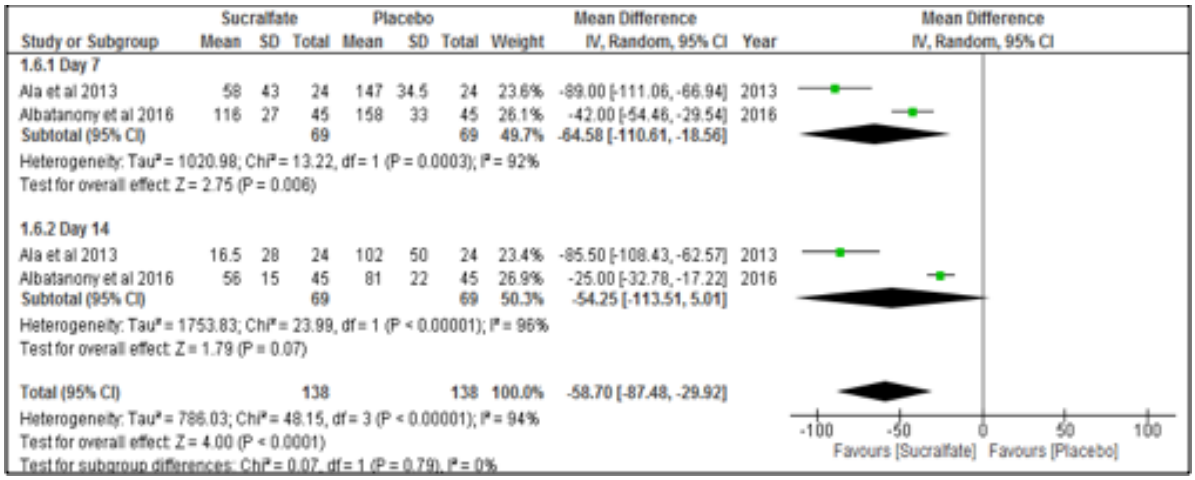

Figure 5. Forest plot: 10% topical sucralfate ointment versus placebo, outcome: Daily amount of diclofenac usage (mg).

-1.04; 95% CI, -14.76 to 12.68) and at 6 to 12 hours after hemorrhoidectomy (MD -4.17; 95% CI, -14.72 to 6.38). However, patients in the sucralfate group requested less amount of pethidine than those in the placebo group at 12 to 24 hours after hemorrhoidectomy (MD -9.37; 95% CI, -18.37 to -0.37). For Albatanony study, patients in sucralfate group requested less amount of pethidine within 24 hours after the operation than placebo group (MD -15.00; 95% CI, -26.45 to -3.55).

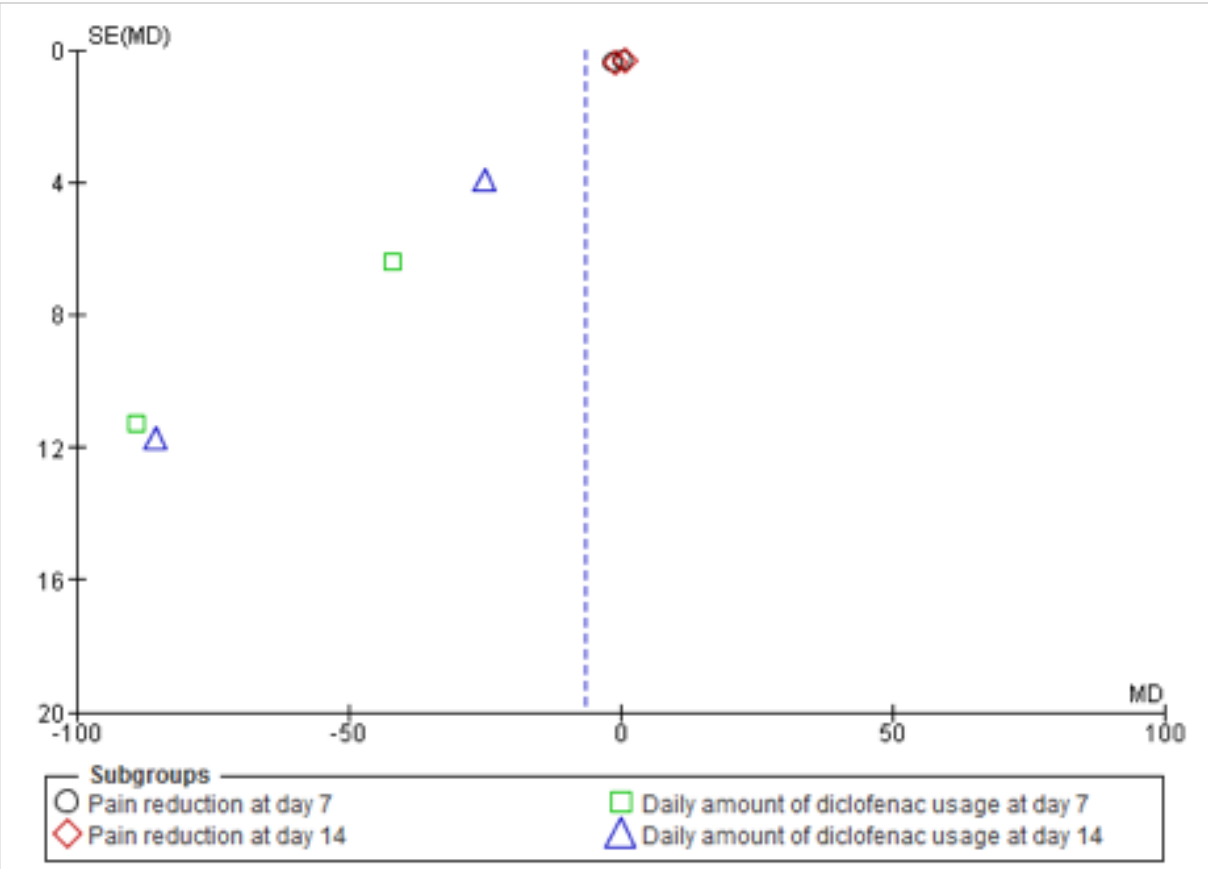

Figure 6. Funnel plot

PUBLICATION BIAS

In our review, the funnel plots of the outcomes were summarized (Figure 6). However, we did not assess publication bias because of too few numbers of the included studies.

DISCUSSION

SUMMARY OF EVIDENCE

In our systematic review, two RCTs were included with 138 patients undergoing hemorrhoidectomy in the analysis, we found that using topical sucralfate ointment had similar efficacy to that of placebo for post hemorrhoidectomy pain reduction at day 7 and day 14. Patients in topical sucralfate ointment group requested a less daily amount of diclofenac than that in the placebo group at day 7. All trials had a low risk of bias but this conclusion was based on high heterogeneity and small numbers of patients. The studies did not describe the adverse effect.

STRENGTH AND LIMITATIONS OF THE REVIEW

Our review is the first systematic review comparing the efficacy of using topical sucralfate ointment and placebo for postoperative hemorrhoidectomy pain reduction. We systematically searched from databases and other sources for published and

unpublished trials. We applied a comprehensive search with no language restrictions. We tended to identify all relevant trials. We conducted this review with the Cochrane handbook and meta-analyses checklist. Our search was comprehensive, our included studies had a low risk of bias.

Our systematic review has several limitations. The first limitation was the small numbers of participants as we found only two RCTs that met our inclusion and exclusion criteria. The second limitation is that an equal amount of topical form of the interventions for each patient was not easily ascertained, this might be a source of high heterogeneity in our review. The third limitation is the included trials did not report adverse effects, implementation of the findings should be careful.

COMPARISON WITH OTHER STUDIES

The use of sucralfate has been started since the animal trial.[16,20] It has been shown that it increased epidermal growth factor (EGF), basic fibroblast growth factor (bFGF) concentration, angiogenesis and granulation tissue in subcutaneous of rats.[16,20] Its use was later applied to those with second-degree burn patients showed that using sucralfate cream increased rate of epithelialization.16 It did not show any allergy or systemic toxicity and soothing on local application.[15] However, the participants in that study were very few.

In our review, we found that using topical sucralfate ointment had a similar effect to that of placebo for pain reduction after hemorrhoidectomy. Our findings contradicted with the previous trials, for instance, the previous two trials by Gupta et al using topical sucralfate in both forms of ointment and cream in those undergoing hemorrhoidectomy and fistulotomy. They stated that using the drug reduced pain after hemorrhoidectomy and fistulotomy more than that of placebo.[21,22] Nonetheless, their outcome measures might not be reliable as it did not have baseline pain. With the gel-like property of sucralfate when contacts with water, it has been used locally as in a study by Miura et al showed that using topical sucralfate reduced post adenotonsillectomy pain more than that of placebo.[23] Again, this trial also did not have baseline pain measure for efficacy evaluation. From all latest available literature, topical sucralfate does not seem to have enough reliable evidence to support the efficacy for postoperative pain reduction.

CONCLUSION AND PRACTICAL IMPLICATION

In patients undergoing hemorrhoidectomy, comparing the efficacy between using topical sucralfate ointment and placebo for postoperative pain reduction after hemorrhoidectomy at day 7 cannot be concluded as our review had a low volume of studies and participants as well as high heterogeneity. For the further study, we suggest an RCT with larger numbers of participants for better estimation of the effect with the proper evaluation of adverse effects evaluating the efficacy for pain reduction after hemorrhoidectomy between topical sucralfate ointment and placebo.

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