Systematic Review/Meta-analysis

A systematic review and meta-analysis of the efficacy of medical treatments for the management of solitary rectal ulcer syndrome

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Abstract

Background/Aim: Solitary rectal ulcer syndrome (SRUS) is a benign, poorly understood disorder that is difficult to manage. Medical interventions such as sucralfate, sulfasalzine, human fibrin, and a high fibre diet are reported as the first line of treatment. The aim of this study is to perform a systematic review and meta-analysis of the efficacy of medical treatments for SRUS.

Materials and Methods: Databases including PubMed, Cochrane, and Embase were searched for randomised clinical trials (RCT) and observational studies that evaluated medical treatments for SRUS. Two authors independently performed selection of eligible studies based on eligiblity criteria. Data extraction from potentially eligible studies was carried out according to predefined data collection methods. Medical treatments, including sucralfate, sulfasalzine, human fibrin, a high fibre diet, and psyllium powder as a single or combination therapy were compared to placebo alone or combined with other treatments. The primary outcome was the proportion of patients with ulcer remission; this was presented as pooled prevalence (PP) with a 95% confidence interval (CI). The I^2 value and Q statistic test were used to test for heterogeneity. In the presence of heterogeneity, a random-effects model was applied.

Results: A total of 9 studies with 216 patients (males = 118, females = 98) diagnosed with SRUS were analysed in the final meta-analysis. The pooled effect estimate of treatment efficacy revealed that, of the patients receiving medical treatment, 57% had resolution of their ulcers (PP 0.57; 95% CI; 0.41 to 0.73). Statistically significant heterogeneity was observed (I^2 = 63%; $\tau 2$ = 0.64, P = <0.01). The scarcity of RCTs comparing medical treatments with other interventions was a major limitation.

Conclusions: The majority of patients receiving medical treatment for the management of SRUS experience resolution of their ulcers.

Keywords: Medical therapy, rectal ulcer, resolution

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INTRODUCTION

Solitary rectal ulcer syndrome (SRUS) is a benign but poorly understood disorder that affects all age groups. Characteristic symptoms include straining during defecation, rectal bleeding, tenesmus, mucoid secretion, anal pain, and a sense of incomplete evacuation.[1,2] The presentation varies, leading it to be referred to as "the

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three-lies disease" since the lesions may not be solitary, ulcerative, nor even restricted to the rectum.[3] SRUS affects approximately 1 in 100,000 individuals per year.[4] Affected individuals are usually young adults, although there are a few case series of children and elderly adults with SRUS.[5-9] There is a slight predominance in women with the disease primarily affecting males in the fourth decade and females in the fifth decade of life.[4]

The aetiology and pathophysiology of SRUS are not fully understood. The most commonly proposed aetiology of SRUS is chronic mucosal hypoperfusion, which may lead to ischaemic injury of the rectal mucosa.[6,10,11] This hypoperfusion can also lead to a paradoxical contraction of the pelvic floor muscles, subsequent mucosal prolapse and pressure necrosis of the rectal mucosa. Other contributing etiologies include rectal hypersensitivity, local trauma secondary to repeated self-digitation, and chronic and severe constipation.[12-14] SRUS shares a range of clinical symptoms and endoscopic signs with other gastrointestinal disorders, such as inflammatory bowel disease (IBD) and colon cancer, causing the diagnosis to be challenging.[15] As a result, the delay between symptom onset and diagnosis ranges between 6.4 months and 4.7 years in adults,[16,17] and up to 3.2 years (range: 1.2-5.5 years) in paediatric patients.[18] Diagnosis is based on characteristic clinical symptoms, and endoscopic findings. Defecography, anorectal manometry, and histological examination of biopsy materials can be obtained as additional diagnostic tools.[14] The medical management of SRUS includes dietary management, laxatives, and enemas,[10,19-21] as well as oral medications such as sucralfate and sulfasalazine. However, there are no treatment guidelines for SRUS and, as such, management is highly dependent on the experience of individual physicians, who typically base treatment decisions on symptom severity and associated signs, such as the presence or absence of rectal prolapse. Hence, clinicians and patients would benefit from an evidence-based guideline for management.

The medical literature on medical treatments for SRUS in adult[22,23] and paedatric[5] patients reports varying rates of treatment success in achieving the goal of ulcer resolution. To date, there are no randomised controlled trials that have examined the long-term effectiveness of treatments.

Thus we planned to perform a systematic review and meta-analysis of the medical literature to analyse the efficacy of medical treatment for SRUS.

MATERIALS AND METHODS

This manuscript adheres to the reporting guidelines of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) for Meta-Analyses (PRISMA-MA).[24,25]

Study eligibility criteria

We included randomised clinical trials (RCTs) and observational studies, including prospective and retrospective cohort studies, case-control studies, cross-sectional and case series that assessed the efficacy and safety of medical therapy in patients diagnosed with SRUS.

Participants

All adult and paediatric patients diagnosed with solitary rectal ulcer syndrome by endoscopy, biopsies, and histologic analysis were included. Interventions: we included studies that assessed the effect of medical treatments, including sucralfate, sulfasalzine, human fibrin, a high fibre diet, and psyllium powder as a single or combination therapy administered orally or locally.

Comparison

This included no treatment, placebo alone, or combined with other treatments including pharmacological and non-pharmacological interventions. We analysed different medical intervention groups separately.

Types of outcomes

We included studies that reported the proportion of patients who had ulcer resolution from baseline to the follow-up of the study. While our aim was to collect data on the proportion of patients with ulcer recurrence after completion of medication therapy, no studies provided data on post-therapy recurrence rates. Exclusion criteria: patients with only rectal prolapse, colon cancer, irritable bowel syndrome, or colonic ulceration were excluded. Studies which used only surgical techniques, biofeedback, or patient counselling were excluded. All case reports and case series that did not provide sufficient details on disease outcomes (resolution of ulcers, recurrence of ulcers), case series with less than three cases, and studies published in a language other than English were also excluded.

Search strategy and study selection

We completed a comprehensive and systematic search of the major scientific databases, including PubMed, Cochrane Library, and EMBASE for studies published from inception to 15 May 2018. We used mesh terms and keywords including solitary rectal ulcer syndrome (SRUS), rectal ulcer syndrome; and 5-aminosalicylic acid, sucralfate, corticosteroids, laxatives, biofeedback, biofeedback therapy, behavioural modification, sulfasalazine enemas, sulfasalazine, botulinum toxin, or salicylates (detailed search strategy provided in appendix). Additionally, we also utilised the reference section of the included studies

and related gastrointestinal and other journals. Two authors (YQ and MM) independently reviewed the medical literature for study eligibility. All articles were initially screened based on the title and abstract. If they met our inclusion criteria, the full text was retrieved and assessed. Any disagreements pertaining to inclusion were resolved through discussion. Studies including patients with SRUS who received forms of therapy not included in our search terms were excluded from the analysis.

Data extracted

After reading the full text of the included studies, the data was extracted onto a predesigned Excel spreadsheet. To minimise errors in data entry, both reviewers independently extracted and entered data into the spreadsheet. The data extracted from each study included: the year of publication, number of patients included in the study, treatments administered, and proportion of patients who achieved partial or complete response.

Risk of bias assessment

Two reviewers (YQ and MM) independently assessed the methodological quality of each study using the Joanna Briggs Institute Critical Appraisal checklist tool, which was developed for the critical appraisal of case series. The checklist consists of 10 questions with responses to each question categorised into yes, no, unclear, and not applicable. For each study, questions eliciting answers of "yes" were awarded a score of "1," whereas answers of "no" or "unclear" were awarded a score of "0." The summed quality score for each study was obtained by adding the total score of all the questions from the checklist tool. Studies scoring ≥7 were considered high quality, whereas studies scoring <7 were considered low quality.

Statistical analysis

The primary outcome measure was the proportion of patients with healed ulcers (decrease in diameter of the ulcer from baseline to follow-up) according to endoscopic evaluation. This was presented as a pooled prevalence (PP) with a 95% confidence interval (CI). Heterogeneity and inconsistency tests were used to assess the variation in outcomes between studies. The heterogeneity and inconsistency of the measurements were identified using Cochran's Q statistical test and I^2 statistic and considered significant if P value <0.10 and I^2 value >50%. If heterogeneity existed and was confirmed, a random-effects model was applied with inverse variance to pool the studies. Otherwise, a fixed-effects model was chosen.

All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant, except where otherwise specified. All data analyses were performed using R 3.3.2 version by using package meta.

Subgroup analysis

Subgroup analyses were performed to assess the source of heterogeneity according to type of medication therapy.

Publication bias

Publication bias refers to the possibility of a systemic bias due to the over-reporting of positive results. This was assessed using funnel plot and the Beggs test. If publication bias was found, we applied the Trim and Fill method to compensate for the lack of studies on a particular side of the funnel.

RESULTS

Study characteristics of included studies

A total of 564 articles were identified from the initial search of databases. After removing the duplicates (n = 313), we reviewed the titles and abstracts (n = 251) to identify potentially relevant articles based on eligbility criteria. Out of these, 27 studies appeared relevant and were retrieved for a full text review. Of these, 9 were included in the final analysis [Table 1]. The remaining 18 studies were excluded due to irrelevant interventions (surgery = 12, biofeedback = 6) [Figure 1].

All included studies were conducted between 1990 and 2017. Three of the studies were from India,[5,23,26] two from Iran,[16,27] and one each from Poland, Turkey and the United States.[17,22,28] All were conducted in a hospital setting. All studies were case series except for one,[27] which was an RCT. In the included studies, patients were diagnosed via endoscopy or colonoscopy;[16,22] only four studies obtained histologic analysis of biopsy material[16,22,26,28] to confirm diagnosis.

Patient characteristics of included studies

Among the included studies, five included only adult subjects, three included only children,[5,16,28] and one study included both subgroups.[17] A total of 216 patients (males = 118, females = 98) diagnosed with SRUS were analysied in this meta-analysis. The sample size of individual studies ranged from five[23] to ninety nine patients.[27]

The average age of included patients was 27.12 (SD 18.76) years with an age range of 9 to 52 years.[16,28,29] Rectal bleeding, prolapse, ulcers and a sense of incomplete evacuation were the most common clinical signs and symptoms at the time of diagnosis. The percentage of patients with a sense of incomplete evacuation ranged from 35% to 76%.[27,28] The ulcer types were primarily

Table 1: Study characters of included studies

Author	Year	Setting	Study Design	Females	Males	Age group	Mean age (Years)	Ulcer Healing
Zergani FJ *et al.*	2017	Hospital	RCT	44	55	Adults	31.78	17
Torres C *et al.*	2007	Hospital	Case series	10	13	Adults	52	3
Duplaga KK *et al.*	2017	Multicentre	Case series	13	18	Paediatric	13	14
EdErle AB *et al.*	1992	Hospital	Case series	5	7	Adults	55	6
Zargar SA *et al.*	1991	Hospital	Case series	3	3	Adults	33	4
Kochhar R *et al.*	1990	Hospital	Case series	3	2	Adults	NA	4
Suresh N *et al.*	2010	Hospital	Case series	16	6	Paediatric	10	19
Dehghani SM *et al.*	2008	Hospital	Case series	3	9	Paediatric	9.2	7
Urgancı N *et al.*	2013	Hospital	Case series	1	5	Both	13	2

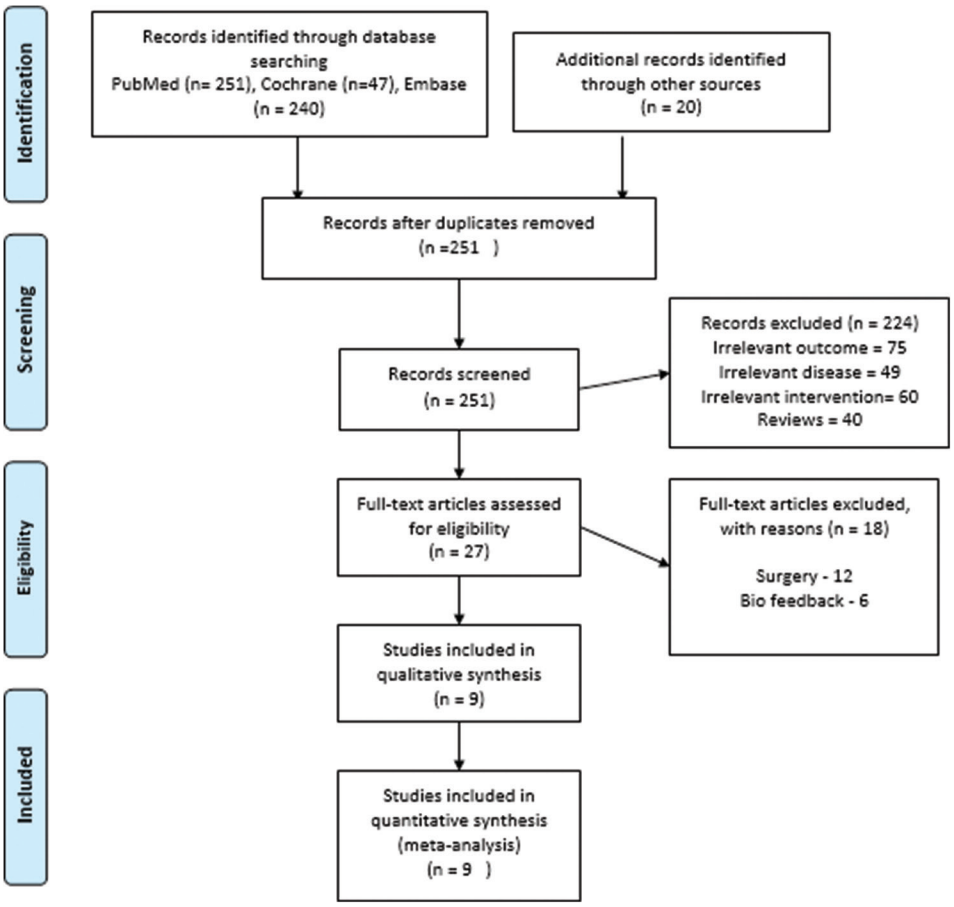

Figure 1: PRISMA chart depicting study selection

flat ulcers (79%) and polypoid ulcers (4.3% to 21%).[22,27] The time frame from symptom onset to diagnosis ranged from 6.4 months[16] to 4.7 years[17] and all studies included a follow-up colonoscopy. Four studies used combination therapy (behavioural therapy, sucralfate enemas, high fibre diet, and psyllium powder),[5,17,22,27] three studies used sucralfate,[23,26] and one study used human fibrin as the medical intervention.[29]

RISK OF BIAS ASSESSMENT

The overall mean score of included studies was 7.5± (2.5), which indicates that all included studies were found to be of high quality. However, among the included studies, two were low quality, and the remaining studies were of high quality [Table 2].

MAIN RESULTS

Ulcer healing

All studies reported the proportion of patients with resolved ulceration following medical therapy. The pooled effect estimate (PP 0.57; 95% CI of 0.41 to 0.73, 155 patients, 9 studies; I^2 = 63%, P = <0.01) from these studies revealed that of the patients receiving medical treatment, 57% had resolution of their ulcers [Figure 2].

Table 2: Quality assessment of included studies by JBI tool (Case series)

Study Questions	Torres C *et al.*	Dehghani SM *et al.*	Kochhar R *et al.*	Duplaga *et al.*	Urganci N *et al.*	Zargar SA *et al.*	Suresh N *et al.*	EdErle *et al.*
Were there clear criteria for inclusion in the case series?	Unclear	Unclear	No	Yes	No	Yes	Unclear	Unclear
Was the condition measured in a standard, reliable way for all participants included in the case series?	No	No	No	Unclear	Yes	Yes	Yes	Yes
Were valid methods used for identification of the condition for all participants included in the case series?	Yes	Yes	No	Unclear	Yes	Yes	Yes	Yes
Did the case series have consecutive inclusion of participants?	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Did the case series have complete inclusion of participants?	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Was there clear reporting of the demographics of the participants in the study?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was there clear reporting of clinical information of the participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the outcomes or follow up results of cases clearly reported?	Yes	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	Yes	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes
Was statistical analysis appropriate?	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Total score	8	8	3	7	6	10	9	9

Heterogeneity assessment

The 9 studies included in the meta-analysis demonstrated statistically significant heterogeneity ($I^2 = 63\%$; $\tau 2 = 0.6428$, $P = <0.01$). The random-effects model was chosen to pool the individual studies [Figure 2].

Subgroup analysis

Based on the availability of subgroup analysis, data was analysed to assess the sources of heterogeneity using parameters such as study design, age groups, and type of intervention.

Subgroup analysis based on age revealed that paediatric patients (PP 0.65; 95% CI of 0.41 to 0.83, 62 patients, four studies) had a higher proportion of ulcer resolution compared to adults (PP 0.57; 95% CI of 0.30 to 0.81, 82 patients, five studies), or a combination of adults and paediatric patients (PP 0.33; 95% CI of 0.08 to 0.73, six patients, one study) [Figure 3].

Subgroup analysis of the type of intervention revealed that patients receiving sucralfate (PP 0.65; 95% CI of 0.45 to 0.81,4 studies, 26 patients) had a higher proportion of ulcer resolution compared to those receiving combination therapy (PP 0.50; 95% CI of 0.20 to 0.79) or sulfasalzine (PP 0.47; 95% CI of 0.30 to 0.64, 30 patients, one study) [Figure 4].

Subgroup analysis of the study design revealed that patients enrolled in RCTs (PP 0.29; 95% CI of 0.19 to 0.42, 58 patients, one study) had a lower proportion of ulcer resolution than those enrolled in case series (PP 0.62; 95% CI of 0.47 to 0.76, 97 patients, eight studies) [Figure 5].

Medical treatment compared to control

Two of the included studies compared medical treatments with a control group. Meta-analysis of these studies revealed that medical treament was less effective than control at ulcer resolution OR 0.15 (95% CI of 0.07 to 0.34, 122 patients, two studies) [Figure 6].

Publication bias

The funnel plot assessment for publication bias showed that the studies distributed symmetrically around the

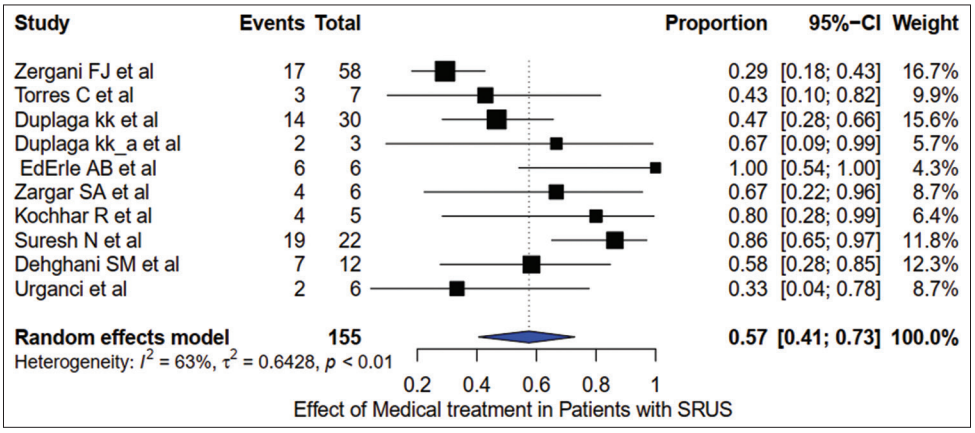

Figure 2: Forest plot showing proportion of SRUS patients who achieved ulcer resolution with medical therapy group with 95% CI. The horizontal line indicates 95% CI and the diamond indicates overall pooled estimate

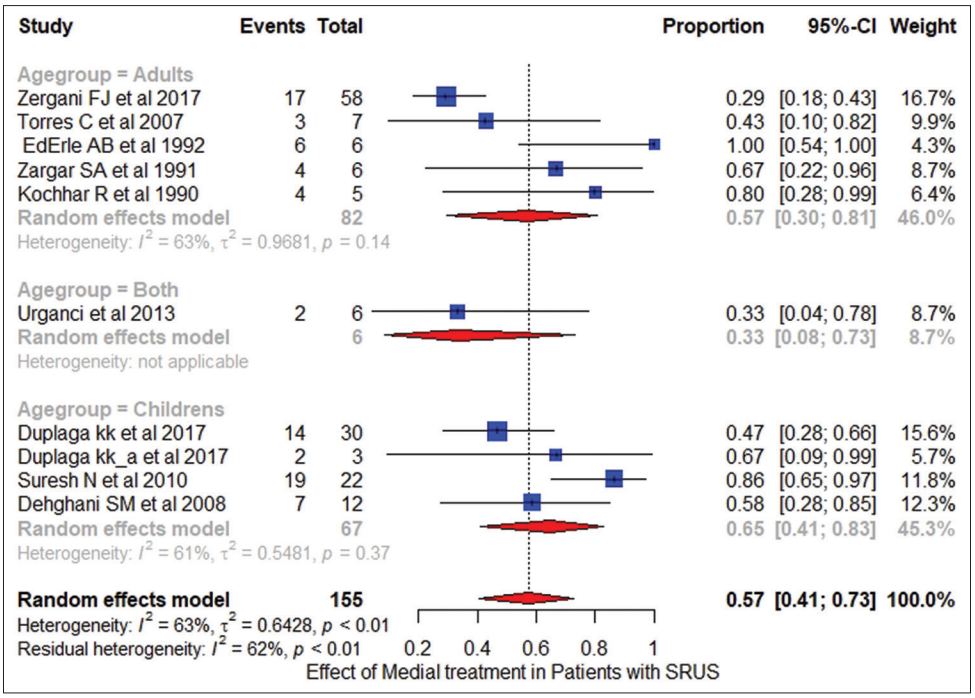

Figure 3: Forest plot showing the proportion of SRUS patients by subgroup analysis of age group who achieved ulcer resolution with 95% CI. TAhe horizontal line indicates 95% CI and the diamond indicates overall pooled estimate

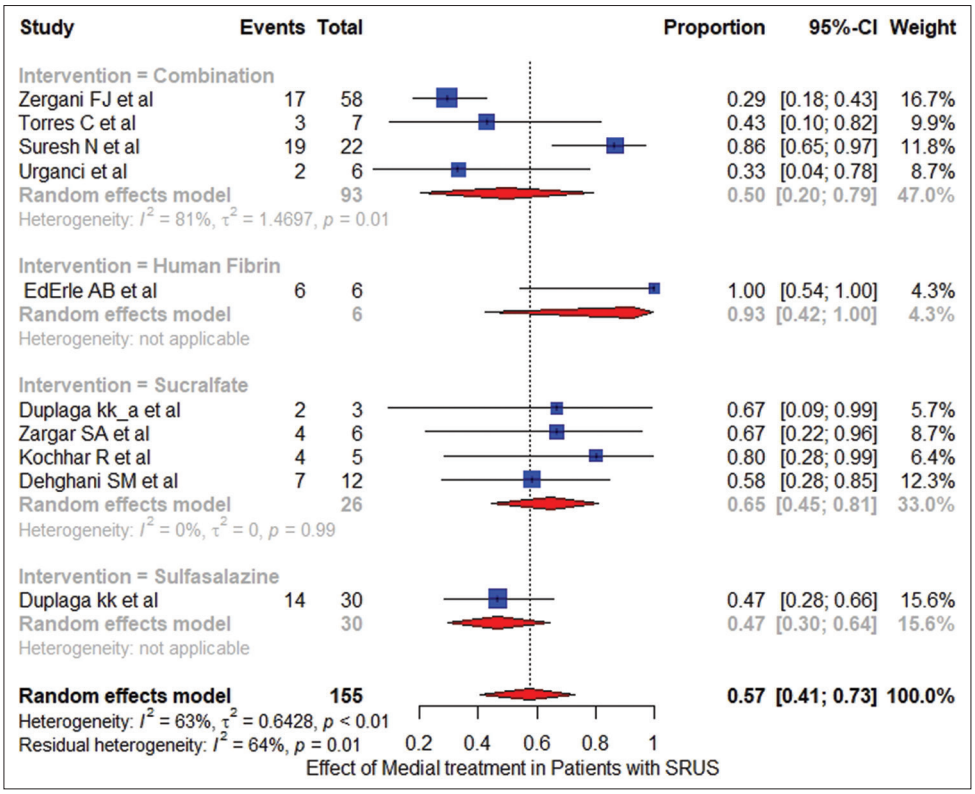

Figure 4: Forest plot showing the proportion of SRUS patients by subgroup analysis of intervention type who achieved ulcer resolution with 95% CI. The horizontal line indicates 95% CI and the diamond indicates overall pooled estimate

combined effect size [Figure 7]. Egger's Linear Regression Test (t = 2.5833, df = 8) showed a statistically insignificant *P* value (*P* = 0.03245), leading to failure to reject the null hypothesis of symmetry in the funnel plot.

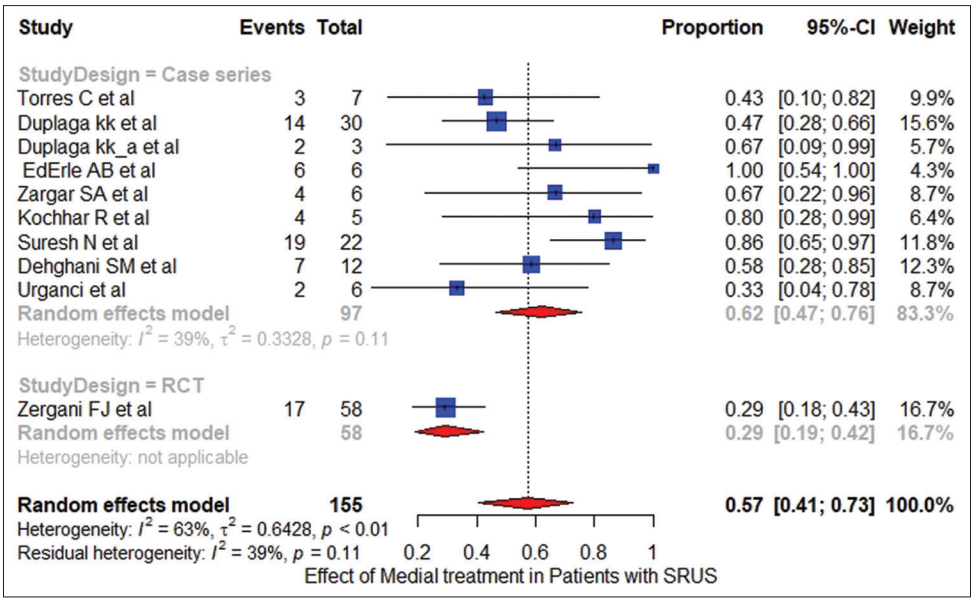

Figure 5: Forest plot showing the proportion of SRUS patients by subgroup analysis of study who achieved ulcer resolution with 95% CI. The horizontal line indicates 95% CI and the diamond indicates overall pooled estimate

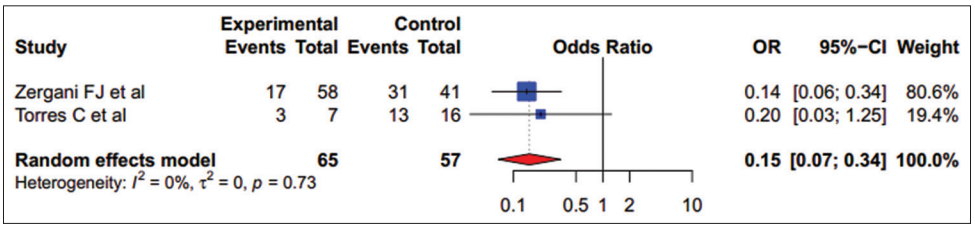

Figure 6: Forest plot showing the effect of medical treatment compared to control group in SRUS with 95% CI. The horizontal line indicates 95% CI and the diamond indicates overall pooled estimate

DISCUSSION

The management of SRUS is challenging due to its unclear pathogenesis, varied presentation, and lack of evidence-based treatment guidelines. Sulfasalazine, sucralfate, and mesalamine are the most commonly prescribed medical therapies for SRUS. However, the effectiveness of these medical treatments ranges from 28-80%,[5,27] indicating a need for clear treatment guidelines. To the best of our knowledge, this is the first meta-analysis to pool the effectiveness of medical treatments in patients with SRUS.

The present meta-analysis revealed that, among patients receiving medical treatment for SRUS, an average of 57% (range 41-74%) had resolution of their ulcers. Further subgroup analysis revealed that patients receiving sucralfate (PP 0.65; 95% CI of 0.45 to 0.81) were more likely to experience ulcer resolution compared to patients receiving combination treatments (PP 0.50; 95% CI of 0.20 to 0.79) or sulfasalazine therapy (PP 0.47; 95% CI of 0.30 to 0.64). The aluminium complex salts of sucralfate act to coat the rectal ulcer, which forms a barrier against irritants and allows the ulcer to resolve.[26] The combination therapies include behavioural therapy and a high fibre diet. Behavioural therapy aims to correct pelvic floor dysfunction and can precede surgery.[19] Our results suggest that sucralfate is superior to other medical therapies with regard to achieving ulcer resolution, but this observation is based on data primarily from case series and observational studies. Data from randomised controlled studies is needed to further validate this finding.

A high degree of heterogeneity (I^2 = 60%, P < 0.05) was observed in the effect estimates. This may be due to the varied age groups within the SRUS population, the use of different study designs and small numbers of patients. Subgroup analysis based on age group showed that children (PP 0.65; 95% CI of 0.41 to 0.83) had a higher proportion of ulcer resolution compared to adults (PP 0.51; 95% CI of 0.30 to 0.81). This might be due to the fact that in the studies that included children, patients were prescribed sucralfate in addition to other drugs, such as mesalamine, and sulfasalazine, which could have resulted in a synergistic effect on disease outcome.[30]

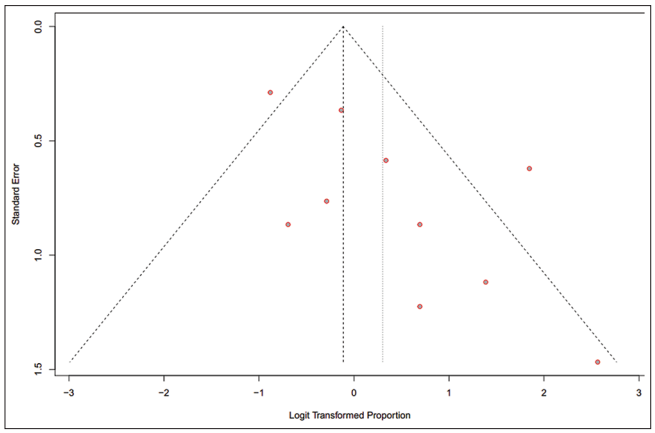

Figure 7: Evaluation of publication bias using a funnel plot. The plot measures study size (standard error) on the y-axis in relation to the effect size on the x-axis, with each study represented on the plot as a circle

LIMITATIONS

The scarcity of randomised clinical trials comparing medical treatments with other interventions was a major limitation. Second, studies included in this meta-analysis did not report information on the main predictors of the outcomes, such as severity of SRUS, presence of rectal prolapse, type of rectal prolapse (external prolapse or internal prolapse), type and severity of ulcers or time between baseline evacuation and follow-up endoscopy. As a result, sources for heterogeneity could not be explored. Another limitation is the lack of validated outcomes for SRUS which clearly limits the ability to measure the effectiveness of medical treatments.

CONCLUSIONS

Based on the available data from the included studies, our meta-analysis suggests that the majority of patients receiving medical treatments for the management of SRUS experience resolution of their ulcers. However, further randomised clinical trials and cohort studies of medical treatment in paediatric and adult populations are required to increase the validity and applicability of our results.

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Conflicts of interest
There are no conflicts of interest.

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