Systematic Review

Effect of mesalazine on recurrence of diverticulitis in patients with symptomatic uncomplicated diverticular disease: a meta-analysis with trial sequential analysis of randomised controlled trials

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Abstract

Objectives: To investigate the effect of mesalazine on recurrence of diverticulitis in patients with symptomatic uncomplicated diverticular disease (SUDD).

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Methods: We performed a systematic review and conducted a search of electronic information sources to identify all randomised controlled trials (RCTs) investigating the effect of mesalazine on the recurrence of diverticulitis in patients with SUDD. We used the Cochrane tool to assess the quality of included studies. Random-effects models were applied to calculate pooled outcome data. Trial sequential analysis was performed to assess the possibility of type I or II errors and compute the information size required for conclusive meta-analysis.

Results: We identified six RCTs which enrolled a total of 1,918 patients. There was no difference in recurrence of diverticulitis between the mesalazine and placebo groups (OR 1.20, 95% CI 0.96-1.50, P=0.11). A low level of heterogeneity among the studies existed (I²=9%, P=0.36). When mesalazine dose was ≤2g/day, there was no difference in recurrence rate between the two groups (OR 1.10, 95% CI 0.79-1.54, P=0.58). When mesalazine dose was >2g/day, the risk of recurrence was higher in the mesalazine group (OR 1.28, 95% CI 1.02-1.62, P=0.04). The information size was calculated at 2461 patients. Trial sequential analysis showed that the meta-analysis was conclusive and the risk of type 2 error was minimal.

Conclusions: Mesalazine does not prevent recurrence of diverticulitis in patients with SUDD. Further studies are required to investigate the role of mesalazine as an adjunct to other medical agents in the prevention of diverticulitis in patients with SUDD.

What does this paper add to the existing literature?

Mesalazine alone does not prevent recurrence of diverticulitis compared to placebo in patients with symptomatic uncomplicated diverticular disease. Trial sequential analysis showed that the meta-analysis was conclusive and the risk of type 2 error was minimal.

Introduction

Diverticular disease is common and its incidence is increasing as the age of the population rises. [1-2]. Up to one-third of people aged 45 years and older and up to two-thirds of people older than aged 85 years may be affected [3]. Recurrent diverticulitis or d., diverticulitis associated with abscess, phlegmon, fistula, obstruction, bleeding, or perforation, may need surgery.

There is some agreement regarding the role of surgery in symptomatic diverticulitis, but less so for the place of medical treatment.. Historically, prophylactic surgery was recommended after 2 significant attacks of diverticulitis [1], however, recent guidelines have advocated a more conservative approach with fewer patients undergoing excisional surgery. There are significant numbers of patients who are
at potential risk of having repeated episodes of diverticulitis, raising the important clinical question as to whether any medical therapy can alter the natural history of the disease thereby avoiding the need for surgery.

In recent years there has been a trend toward a pharmacological approach to the prevention of diverticulitis particularly because there is limited evidence of benefit for segmental colectomy (i.e. sigmoidectomy). We are not aware of any disease-modifying pharmacologic measures which are currently approved in North America or Europe to prevent recurrent attacks of diverticulitis. However an increasing number of European studies have reported the efficacy of different regimens of mesalamine, antibiotics, and probiotics (alone or in combination) in diverticular disease. The evidence of benefit, however, remains inconclusive.

With the assumption that chronic inflammation in colonic diverticular disease is similar to the inflammation occurring in idiopathic inflammatory bowel disease, it has been suggested that the former patients may benefit from treatment with anti-inflammatory medication such as mesalazine. This was the rationale for this systematic review and meta-analysis. Our primary aim was to investigate the effect of mesalazine on the recurrence of diverticulitis in patients with uncomplicated symptomatic diverticular disease. A secondary objective was to perform trial sequential analysis to investigate whether further trial data are required to inform decision making, and compute the information size that would be required for the evidence to be considered conclusive.

Methods

This systematic review was performed according to an agreed predefined protocol. The review was conducted and presented according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement standards.

Eligibility criteria

We included all randomised controlled trials (RCTs) comparing the effect of mesalazine versus placebo on recurrence of diverticulitis in patients with symptomatic diverticular disease. The study population comprised of all adult patients age >18 with endoscopic or radiological evidence of diverticular disease with at least one diverticulum in the left colon, patients with at least one previous documented episode of uncomplicated diverticulitis that resolved without colonic resection, patients with symptoms attributable to diverticular disease of the colon (upper or lower abdominal pain/discomfort, bloating, tenesmus, diarrhoea, abdominal tenderness, or nausea) and patients with no
evidence of acute diverticulitis at the time of recruitment. Any dose, titration, or duration of mesalazine was considered as intervention of interest, and placebo or no treatment was considered as comparator. We excluded patients with complicated diverticulitis (diverticulitis with associated abscess, fistula, obstruction or perforation), patients with previous colonic surgery, patients with active colorectal cancer or history of colorectal cancer, or patients with chronic inflammatory bowel disease.

**Outcome measure**

The recurrence of diverticulitis was considered as the outcome measure. The recurrence was defined as clinical and radiological evidence of acute diverticulitis at maximal follow up.

**Literature search strategy**

Two authors (AK, Shahin H) independently searched the following electronic databases: MEDLINE, EMBASE, CINAHL, and the Cochrane Central Register of Controlled Trials (CENTRAL). The last search was run on 25 November 2017. Thesaurus headings, search operators and limits in each of the above databases were adapted accordingly. The literature search strategy is outlined in Appendix I. In addition, World Health Organization International Clinical Trials Registry (http://apps.who.int/trialsearch/), ClinicalTrials.gov (http://clinicaltrials.gov/) and ISRCTN Register (http://www.isrctn.com/) were searched for details of ongoing and unpublished studies. The bibliographic lists of relevant articles and reviews were interrogated for further potentially eligible studies. No language restrictions were applied in our search strategies.

**Study selection**

The title and abstract of articles identified from the literature searches were assessed independently by two authors (AK, Shahin H). The full-texts of relevant reports were retrieved and those articles that met the eligibility criteria of our review were selected. Any discrepancies in study selection were resolved by discussion between the authors. An independent third author (Shahab H) was consulted in the event of disagreement.
Data collection

We created an electronic data extraction spreadsheet which was pilot-tested in randomly selected articles and was adjusted accordingly. Our data extraction spreadsheet included: study-related data (first author, year of publication, country of origin of the corresponding author, journal in which the study was published, study design, study size and clinical condition of the study participants), baseline demographic and clinical information of the study populations (age, gender, mesalazine dose, time from most recent episode of diverticulitis to recruitment of patients) and primary outcome data. Data collection was performed independently by two authors (AK, Shahin H) and disagreements were resolved by discussion. If no agreement could be reached a third author (Shahab H) was consulted.

Methodological quality and risk of bias assessment

Two authors independently assessed the methodological quality and risk of bias of the included articles using the Cochrane tool for assessing the risk of bias of randomized trials. The Cochrane tool assesses domains including selection bias, performance bias, detection bias, attrition bias, reporting bias and other sources of bias and, for each individual domain, classifies studies into low, unclear, and high risk of bias. Disagreements were resolved by discussion between the reviewers. If no agreement could be reached, a third author acted as an adjudicator. A risk of bias graph was constructed to present the results.

Data synthesis and statistical analyses

We calculated the odds ratio (OR) as the summary measure. The OR is the odds of an event in the mesalazine group compared to placebo group. An OR of less than one would favour the mesalazine group and an OR of more than one would favour the placebo group. Individual patient was used as the unit of analysis. Information about dropouts, withdrawals, and other missing data were recorded and, if not reported, we contacted the study authors where possible. We based our analysis on intention-to-treat data from the individual clinical studies. We used the Review Manager 5.3 software for data synthesis. Because of the anticipated clinical between-study heterogeneity, we used the random effects model for analysis and results were reported in a forest plot with 95% confidence intervals (CIs). Heterogeneity among the studies was assessed using the Cochran Q test ($\chi^2$). We quantified inconsistency by calculating $I^2$ and interpreted it using the following guide: 0% to 50% may represent low heterogeneity, 50% to 75% may represent moderate heterogeneity and 75% to 100% may represent high heterogeneity. We planned to construct funnel plots and evaluate their symmetry to visually assess publication bias for outcomes reported by at least 10 studies. In order to quantify the
bias captured by the funnel plot and to formally assess reporting bias, we planned to calculate the Egger’s regression intercept for outcomes reported by at least 10 studies using the Comprehensive Meta-Analysis (CMA) software (Biostat, Englewood, NJ).

Trial sequential analysis

Trial sequential analysis was performed using the trial sequential analysis software 0.9.5.5 Beta (Copenhagen Trial Unit, Copenhagen, Denmark).[10] In order to control the risk of type 1 error, we planned to adjust the thresholds for the Z-values using O’Brien-Fleming α-spending function; allowing the type I error risk to be restored to the desired maximum risk. Crossing the O’Brien-Fleming α-spending boundaries by a Z-curve would indicate statistical significance. Moreover, we penalised the Z values according to the strength of the available evidence and the number of repeated significance tests as defined by the law of the iterated logarithm. The risk of type 2 error was controlled using the β-spending function and futility boundaries. Crossing the futility boundaries by a Z-curve would indicate that the two interventions do not differ more than the anticipated intervention effect. We used random effects models for the analyses. We handled the zero event trials by constant continuity correction which involved adding a continuity correction factor (1) to the number of events and non-events in each intervention group. A two-sided CI with 95% confidence level was used to indicate statistical significance. We estimated the information size for the analyses based on achievement of 80% power and 20% relative risk reduction between mesalazine and placebo groups.

Sensitivity and sub-group analyses

In order to explore potential sources of heterogeneity and assess the robustness of our results, additional analyses were conducted. We repeated the primary analysis using the random effects and fixed effect model. In addition, we calculated the risk ratio (RR) and risk difference (RD) for recurrence of diverticulitis. We assessed the effect of each study on the overall effect size and heterogeneity by repeating the analysis after removing one study at a time. We also planned to perform separate analyses for RCTs with low risk of selection bias in terms of randomisation and allocation concealment to assess the change in direction of the effect size. Moreover, we performed subgroup analysis based on mesalazine dose used: 1) mesalazine ≤2g/day versus placebo, 2) mesalazine >2g/day versus placebo
Results

Results of the search

Searches of electronic databases identified 187 articles of which six randomised control trials[11-14], which enrolled a total of 1,918 patients, were selected for this review. Overall, 1,292 patients were included in the mesalazine group and 626 patients were included in the placebo group. Among those treated with mesalazine, 463 patients (36%) received ≤2g/day of mesalazine and 829 patients (64%) received >2g/day of mesalazine. The mean age of patients was 57 in both groups. Forty seven percent of patients in mesalazine group and 50% in the placebo group were male. The mean time from the most recent episode of diverticulitis to recruitment of patients in the studies was 95 days in the mesalazine group and 101 days in the placebo group. The follow up was variable ranging from 12 to 24 months. The literature search flow chart, baseline characteristics of the included studies and baseline characteristics of the included population are demonstrated in Figure 1, Table 1 and Table 2, respectively.

Methodological quality and risk of bias

The summary and results of methodological quality assessment of the 6 RCTs [11-14] are demonstrated graphically in Figure2.

Outcome synthesis

There was no significant difference in recurrence of diverticulitis between the mesalazine and placebo groups (OR 1.20, 95% CI 0.96-1.50, P=0.11). A low level of heterogeneity among the studies existed (I²=9%, P=0.36) (Figure 3).

Trial sequential analysis

The information size was calculated at 2461 patients. The Z-curve did not cross the alpha-spending boundaries and the absolute number for penalised Z value remained smaller than 1.96 in both sides. The Z-curve crossed the futility boundaries before the information size is reached; therefore, the meta-analysis is conclusive and the risk of type 2 error is minimal (Figure 4).
Sensitivity analyses

The direction of the effect size for recurrence rate remained unchanged when RRs or RDs were calculated. Removing the study by Parente et al[11] changed the direction of the effect size in favour of the placebo group. Removing the other studies at a time did not change the direction of the effect size. The use of fixed-effect model changed the direction of effect size in favour of the placebo group. The separate analyses for studies with low or moderate risk of bias did not affect the direction of the effect sizes.

Subgroup analyses

**Mesalazine dose ≤2g/day versus placebo.** Five studies[11-14] enrolling 921 patients compared mesalazine dose of ≤2g/day with placebo. There was no difference in recurrence of diverticulitis between the two groups (OR 1.10, 95% CI 0.79-1.54, P=0.58). A low level of heterogeneity among the studies existed (I²=27%, P=0.24).

**Mesalazine dose > 2g/day versus placebo.** Four studies [12-13] enrolling 1367 patients compared mesalazine dose of >2g/day with placebo. The risk of recurrence of diverticulitis was higher in the mesalazine group (OR 1.28, 95% CI 1.02-1.62, P=0.04). A low level of heterogeneity among the studies existed (I²=0%, P=0.95).

Discussion

Diverticular disease of the colon is a common reason for a surgical admission with inevitable consequences to healthcare costs. [15] There are several symptoms which describe this subtype of the disease. These symptoms vary from abdominal pain to alteration of bowel habits, often resembling irritable bowel syndrome. It has been recently suggested that pain in the left lower quadrant is the most reliable indicator of symptomatic uncomplicated diverticular disease.. [16-17]

We performed a systematic review of literature and meta-analysis with trial sequential analysis to assess the effect of mesalazine versus placebo on recurrence of diverticulitis in patients with symptomatic diverticular disease. We included six RCTs [11-14] which enrolled a total of 1,918 patients. We found no difference in the incidence of recurrence of diverticulitis between the mesalazine and placebo groups. The between-study heterogeneity was low. Trial sequential analysis showed that meta-analysis was conclusive and the risk of type 2 error was minimal.

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There is controversial evidence regarding the efficacy and benefit of mesalazine in preventing recurrent symptoms of diverticulitis. In a systematic review, Picchio et al [18] reported that mesalazine was more effective in obtaining symptom relief and in preventing diverticulitis occurrence in comparison with placebo in symptomatic uncomplicated diverticular disease. The study by Picchio et al included patients with symptomatic uncomplicated diverticular disease with no previous episode of diverticulitis and investigated the occurrence of first episode of diverticulitis as outcome measure (the recurrence of diverticulitis was not an outcome measure). Although the level of evidence for symptom relief was acceptable in the study by Picchio et al [18], the level of evidence for occurrence of diverticulitis was not robust enough. In the current study, we included patients with symptomatic uncomplicated diverticular disease who had had a previous episode of resolved diverticulitis and investigated the recurrence of diverticulitis as an outcome measure.

Overall, in the current study the risk of diverticulitis recurrence was 32% in the placebo group and 38% in the mesalazine group. These were consistent among the individual studies. The high recurrence rate in the placebo group highlights the high risk of diverticulitis recurrence within the first two years from the initial episode of diverticulitis in patients with symptomatic diverticular disease. This is a clinically significant finding that warrants a need for further research to find an intervention that can effectively prevent the recurrence of diverticulitis in this cohort of patients. Use of mesalazine as adjunct to other medical agents in prevention of diverticulitis in patients with symptomatic uncomplicated diverticular disease could be a potential subject for further research.

Colonic surgery, whether elective or emergency, is associated with significant morbidity and mortality, emphasising the need to seek alternative treatment strategies. There is increasing evidence that inflammation plays an important role in the pathogenesis of diverticular disease as evidenced by increased inflammatory infiltrate in the diseased colon as well as enhanced expression of proinflammatory cytokines [19]. Mesalazine, as an anti-inflammatory agent, is therefore an attractive proposition. Recent observations suggest that low-grade inflammation in patients with diverticular disease, and its impact on neuromuscular function in the colon may be partially responsible for symptomatic uncomplicated diverticular disease.[20] This may explain why mesalazine as an anti-inflammatory agent can result in symptom relief in patients with symptomatic uncomplicated diverticular disease.[18]

The dosage of mesalazine used to prevent recurrence is variable, ranging from 1.6g to up to 3g. Kruis et al.[21] found a trend towards significance in using mesalazine granules 3 g daily rather than placebo on controlling abdominal pain in symptomatic uncomplicated diverticular disease; Gaman et al.[22] found mesalazine granules 514.7 ± 30.5 mg daily better than placebo in preventing recurrence and flare up of diverticulitis. Our results showed neither less than 2g daily nor more than 2g daily mesalazine prevented recurrence of diverticulitis compared to placebo.
In this study, we used a systematic and explicit approach with consideration of consistency and generalisability of the results to provide a summary of the best available evidence and assess the risk of bias of relevant studies. The between-study heterogeneity was low for the single outcome and the included studies were homogenous in terms of baseline characteristics of the included patients. All of these will make our conclusions from the best available evidence reliable. However, the reported outcomes of our review should be viewed and interpreted in the context of inherent limitations. We identified only 6 randomised control trials and the required information size of 2461 patients was not reached. We only reported recurrence of diverticulitis as outcome and our study does not provide any evidence regarding the other outcome measures that can be significant. The allocation concealment was unclear in two of the included studies subjecting our results to potential selection bias.

Conclusions.

The best available evidence from randomised trials suggests that mesalazine alone does not prevent recurrence of diverticulitis compared to placebo in patients with symptomatic uncomplicated diverticular disease. Trial sequential analysis showed that the meta-analysis was conclusive and the risk of type 2 error was minimal. Further studies are required to investigate the role of mesalazine as adjunct to other medical agents in prevention of diverticulitis in patients with symptomatic uncomplicated diverticular disease.

Author contributions

Conception and design: Shahab H
Literature search and study selection: AK, Shahin H, Shahab H
Data collection: AK, Shahin H, Shahab H
Analysis and interpretation: AK, Shahin H, Shahab H
Writing the article: AK, Shahin H, Shahab H
Critical revision of the article: All authors
Final approval of the article: All authors
Statistical analysis: All authors

Conflict of interest

None declared.
Ethical approval

Not required.

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References


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<td>Clinical and radiological</td>
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<td>Germany</td>
<td>Alimentary pharmacology and therapeutics</td>
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<td>12 months</td>
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Table 2. Baseline characteristics of included population

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<td>333</td>
<td>63(38%) vs 74(44%)</td>
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<td>243</td>
<td>77(36%) vs 49(44%)</td>
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<td>232(53%) vs 76(52%)</td>
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<td>242(55%) vs 72(50%)</td>
<td>56(11) vs 56(11)</td>
<td>114(30) vs 125(26)</td>
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Figure 1. Study flow diagram
Figure 2. Risk of bias summary and graph showing authors’ judgements about each risk of bias item for randomised controlled trials.
Figure 3. Forest plots of the comparisons of diverticulitis recurrence. The solid squares denote the odds ratio (OR; the horizontal lines represent the 95% confidence intervals (CIs), and the diamond denotes the pooled OR.
**Figure 4.** Results of trial sequential analysis for diverticulitis recurrence. A) To the left, the red inward-sloping dashed lines make up the trial sequential monitoring boundaries. To the right, the outward sloping red dashed lines make up the futility region. The solid blue line is the cumulative Z curve. B) The solid green line presents penalised Z value.
## Appendix I

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† This search strategy was adopted for following databases: MEDLINE, EMBASE, CINAHL and the Cochrane Central Register of Controlled Trials (CENTRAL)