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COCHRANE DIGEST

Mesalamine (5-ASA) for the prevention of recurrent diverticulitis (Review)

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Abridged Abstract [1]

Background Mesalamine, or 5-aminosalicylic acid (5-ASA) has been studied for the prevention of recurrent diverticulitis.

Objectives To evaluate the efficacy of mesalamine (5-ASA) for the prevention of recurrent diverticulitis.

Search methods We searched databases from 2010 to September 2017. In addition, we scanned reference lists from eligible publications, and we contacted corresponding authors to ask about additional trials.

Selection criteria We included randomized controlled clinical trials comparing the efficacy of 5-ASA versus placebo or another active drug for the prevention of recurrent diverticulitis.

Main results We included in this review seven studies with a total of 1805 participants.

We judged all seven studies to have unclear or high risk of bias. Investigators found no evidence of an effect when comparing 5-ASA versus control for the prevention of recurrent diverticulitis (31.3% vs 29.8%; RR 0.69, 95% confidence interval (CI) 0.43–1.09); very low quality of evidence).

Five of the seven studies provided data on adverse events of 5-ASA therapy. The most commonly reported side effects were gastrointestinal symptoms (epigastric pain, nausea, and diarrhea). No significant difference was seen between 5-ASA and control (67.8% vs 64.6%; RR 0.98, 95% CI 0.91–1.06; $P=0.63$; moderate quality of evidence), nor was significant heterogeneity observed ($I^2=0\%$; $P=0.50$).

Authors' conclusion The effects of 5-ASA on recurrence of diverticulitis are uncertain owing to the small number of heterogenous trials included in this review. Rates of recurrent diverticulitis were similar among participants using 5-ASA and control participants. Effective medical strategies for the prevention of recurrent diverticulitis are needed, and further randomized, double-blinded, placebo-controlled trials of rigorous design are warranted to specify the effects of 5-ASA (mesalamine) in the management of diverticulitis.

Commentary

Recurrence of acute diverticulitis is an important clinical problem, involving up to a quarter of patients after the first episode of diverticulitis. The therapeutic approach for the prevention of recurrent diverticulitis is actually based mainly on expert opinion rather than evidence-based data representing a daily challenge for the clinician.

The concept of using mesalamine [5-aminosalicylic acid (5-ASA)] for the prevention of recurrent diverticulitis is based on the detection of mild chronic inflammation in diverticular disease; this led to the hypothesis that mucosal inflammation could act as a trigger for acute diverticulitis and its recurrence.

This Cochrane review published 2 years ago aimed to evaluate the efficacy of 5-ASA for the prevention of recurrent diverticulitis (primary outcome) and the adverse effect of therapy (secondary outcome) [1].

In this review, research methods are the primary concern: first, the inclusion of trials using colonoscopy to diagnose diverticulitis is very questionable. In fact, in patients with diverticulitis, colonoscopy is burdened by a higher perforation rate and no data supporting the use of colonoscopy in this setting are available. In fact, no current European or US guidelines support this approach [2–4]. Second, it seems inappropriate to use rectal administration of 5-ASA for a condition that does not, by definition, affect the rectum, with the length of involvement of sigmoid that can be variable and unpredictable.

Carter et al. included 7 randomized controlled trials (RCTs) with a total of 1805 participants. Regarding the

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primary endpoint, 5-ASA was not superior to control intervention for the prevention of diverticulitis (RR 0.69; 95% CI 0.43–1.09) with a very low quality of evidence. Certainly, the most important point is the considerable heterogeneity of the included studies ($I^2 = 79\%$). There is heterogeneity regarding: control regimens (5-ASA + probiotics vs probiotics, 5-ASA + antibiotics vs antibiotics, 5-ASA vs placebo, 5-ASA vs no treatment, and 5-ASA + probiotics vs placebo), 5-ASA dosage, participants' age and gender, and number of prior episode of diverticulitis. Other critical methodological issues are the diagnostic method for the index and recurrent episode of diverticulitis (computed tomography (CT) scan/ultrasonography vs other methods), and risk of bias (unclear vs high risk of bias).

Although not considered by the authors, there are other points that should have been considered: (a) the time elapsed since the index episode, (b) the severity of the index episode (uncomplicated vs complicated diverticulitis), (c) the therapeutic regimen (daily vs cyclic) and duration of 5-ASA administration, and (d) length of follow-up.

In view of this heterogeneity, the most interesting results of this Cochrane review are those related to the subgroup analysis, that was undertaken only for control regimen, method of diagnosis and risk bias.

First, the subgroup analysis based on treatment comparators revealed significant treatment effect with 5-ASA + antibiotic vs antibiotic monotherapy (RR 0.19; 95% CI 0.06–0.63) and with 5-ASA vs no therapy (RR 0.32; 95% CI 0.18–0.57), but each of these comparisons was based only on one small, open-label trial with high or unclear risk of bias. On the other hand, no significant difference for 5-ASA + probiotics vs probiotics (RR 0.50, 95% CI 0.05–4.94), for 5-ASA vs placebo (RR 1.08, 95% CI 0.87–1.35) and for 5-ASA + probiotics vs placebo (RR 1.39, 95% CI 0.50–3.86) was found. Therefore, as underlined by the authors when evaluating the placebo-controlled double-blind trials, no efficacy of 5-ASA for recurrence prevention was found.

Second, other important differences are obtained in subgroup analysis considering the consistent (CT or ultrasonography) and non-consistent methods (clinical assessment, laboratory and colonoscopy) to diagnose diverticulitis. We have to remember that the gold standard for diagnosing acute diverticulitis is contrast-enhanced CT scan, while ultrasonography (that in this review is considered as a consistent method) can be considered as an accurate technique only if carried out by an expert investigator [3, 5]. Thus, colonoscopy and clinical findings are not accurate methods for diagnosis of diverticulitis and therefore, a diagnosis carried out with this approach raises serious doubts regarding its reliability. This point is further underlined by results of the subgroup analysis showing a significant effect of 5-ASA in the 3 trials using non-consistent methods to get diagnosis (RR 0.24, 95% CI 0.18–0.50).When consistent methods were considered, no significant treatment effect was found (RR 1.11, 95% CI 0.80–1.35). The only 3 trials employing CT scan for the diagnosis of primary diverticulitis and recurrence showed no significant treatment effect (RR 1.07, 95% CI 0.81–1.40).

Regarding the secondary endpoint, adverse effects, the authors analyzed only 5 trials (2 trials do not provide data) reporting that frequency of adverse effects is similar between 5-ASA and controls (RR 0.98, 95% CI 0.91–1.06), without heterogeneity among studies ($I^2 = 0$) and with moderate quality evidence.

Following the present review, 2 large phase-3, randomized placebo-controlled double-blind trials (SAG-37 and SAG-51) investigating the effect of mesalazine in the prevention of diverticulitis recurrence were published [6]. Kruis et al. randomized patients with prior diverticulitis (CT/ultrasonography-proven) to receive 3-g 5-ASA daily or placebo (SAG-37) or 1.5-g, 3-g mesalazine or placebo for 96 weeks (SAG-31), and found that mesalazine was not superior to placebo in preventing diverticulitis recurrence [6].

A more recent systematic review by Khan et al. aimed to investigate the effect of 5-ASA on the recurrence of diverticulitis in symptomatic uncomplicated diverticular disease (including also a trial by Kruis et al.) identified 6 RCTs, concluding that 5-ASA does not prevent the recurrence of diverticulitis [7]. The lack of efficacy of 5-ASA in preventing diverticulitis recurrence prompts the debate on the underlying pathophysiologic mechanisms in diverticulitis and the possible role played by mucosal v*s* luminal inflammation [8]. Instead of a mucosal contribution, a more plausible hypothesis is that inflammation related to luminal microenvironment leading to a bacterial dysbiosis might act as trigger for diverticulitis, so potentially explaining the lack of 5-ASA efficacy in this setting [9].

Even if no therapeutic regimen to prevent diverticulitis recurrence is currently available, a challenging issue is represented by the management of patients with persistent abdominal complaints after a diverticulitis attack. In this tricky clinical setting, clinicians should carefully assess the relationship between symptoms and colonic diverticula trying to differentiate abdominal complaints associated to *chronic diverticulitis* from irritable bowel syndrome (IBS), whose prevalence might increase after an episode of diverticulitis [10]. Currently, no standardized approach to differentiate these two clinical conditions is available. However, serum (i.e., white blood cells and C-reactive protein) and fecal inflammatory markers (i.e., calprotectin) might represent useful tools addressing the differential diagnosis between post-diverticular symptoms *IBS*-like or persistence/recurrence of diverticulitis. Another diagnostic step might be colonoscopy with inter-diverticular and rectal biopsies to exclude a rare condition as segmental colitis associated with diverticulosis (SCAD). SCAD is a defined pathological

entity characterized by chronic, sometimes relapsing, mucosal inflammation in the inter-diverticular mucosa (usually the sigmoid-descending colon) sparing the proximal colon and rectum and characterized by lower abdominal pain which responds to mesalamine, although the literature on this subject is composed only by case reports and reviews [3]. This suggested work-up might help clinician to avoid unnecessary surgery.

In the last years, the effect of 5-ASA has been evaluated also in patients with chronic intermittent abdominal symptoms associated with diverticula in absence of history of diverticulitis [11, 12]. Despite the encouraging evidence showed in two double-blind placebo-controlled studies, currently no strong data to routinely support its use are available.

Although there is no evidence to routinely support the use of 5-ASA in diverticular disease, 5-ASA is one of the most frequently prescribed drugs as recently reported in a Italian survey of pharmacologic treatment in patients with previous diverticulitis but also in symptomatic uncomplicated diverticular disease [13], highlighting the discrepancy between real-life clinical practice and an evidence-based approach.

Finally, this Cochrane review suggests that the effects of 5-ASA therapy on recurrence of diverticulitis are uncertain owing to the small number of heterogenous trials included. Further RCTs are needed to evaluate the best therapeutic approach in this setting.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent In this article no patient care was involved.

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