2021

Does Mesalamine Decrease Abdominal Pain in Adults With IBS?

Ruth Joanis
Philadelphia College of Osteopathic Medicine

Does Mesalamine Decrease Abdominal Pain in Adults With IBS?

Ruth Joanis, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies

Philadelphia College of Osteopathic Medicine

Philadelphia, Pennsylvania

December 18, 2020

Abstract

Objective: The objective of this EBM review is to determine whether or not the use of mesalamine decreases abdominal pain in adults with IBS.

Study Design: Review of 3 randomized control trials.

Data Sources: All articles were published in English between 2012 and 2016. Articles were obtained from peer-reviewed journals using PubMed.

Outcomes: The outcome measured was the level or presence of abdominal and was measured via binary scale, 10-point visual analogue scale rated by patients on a 0 to 10 scale with 0 being no pain and 10 being the maximum level of pain and via patient symptom diary questionnaire.

Results: *Barbara et al.* showed that mesalazine reduced abdominal pain and discomfort superior to placebo in patients with IBS, but this was not statistically significant, with a p-value of 0.404. *Tuteja et al.* showed that mesalamine was superior to placebo at reducing abdominal pain from baseline in patients with post-infective IBS, but this was not statistically significant, with a p-value of 0.83. *Lam et al.* showed that mesalazine did not decrease abdominal pain in patients with IBS-D superior to placebo, with a p-value of 0.83.

Conclusions: All three articles used mesalazine to treat abdominal pain and used placebo as the control group. Although two articles showed that mesalamine can decrease abdominal pain at a superior level to placebo, the results we not clinically significant. The third trial showed that mesalamine was not superior to placebo in decreasing abdominal pain. Further studies and perhaps larger studies are needed to determine if mesalamine can have a statistically significant impact on decreasing abdominal pain.

Keywords: IBS, mesalamine, abdominal pain, inflammation

INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal disorder characterized by abdominal pain with disorder in defecation and stool consistency in the absence of another cause for these symptoms.[1] It is the most common function bowel disorder and can be encountered in a variety of practice settings.[2] Physicians as well as physician assistants may encounter the disorder in the settings in which they work. It is diagnosed based on the Rome IV criteria which states that abdominal pain must be present at least once a day for at least three months and must include two or more of the following criteria: related to defecation, change in the appearance of the stool, or change in the frequency of the stool. There are two main types of IBS, IBS-D, which is diarrhea predominant and IBS-C, which is constipation predominant. Patients may also suffer from a combination of both which is categorized as mixed with alternating diarrhea and constipation. Symptoms of the disorder include bloating, diarrhea, constipation, excessive flatulence, and abdominal pain.[1] Abdominal pain and discomfort are hallmark symptoms of the disorder and are usually one of the symptoms that drive patients to seek medical attention.[2]

The disorder is associated with comorbid conditions including psychiatric conditions such as anxiety and depression, and visceral hypersensitivity.[3] There has also been shown to be a genetic link to the disorder, with patients who have a family history being predisposed to developing IBS at some point in their lifetime.[2] Despite these associations the pathophysiology if IBS is still poorly understood and mainly considered to be idiopathic.[4]

The symptoms patients with IBS experience can have an immense impact on their quality of life. An article in Expert Opin estimated that in 2015 the US lost $205 million in productivity due to IBS.[5] IBS has a marked impact on the healthcare system as well. The total cost of

healthcare visits in the US for IBS was estimated by Aran Ediciones to be $20,000,000 yearly in 2016 which includes the cost of laboratory and diagnostic studies needed to rule out other conditions.[6] IBS is the reason for greater than 3.5. million office visits each year in the US.[6]

IBS is traditionally treated with pharmacological and non-pharmacological treatment methods. Non-pharmacological treatments include psychotherapy, exercise, and diet modification which includes avoiding triggers e.g., FODMAP diet, increasing fiber intake, and addressing lactose intolerance.[4] Pharmacotherapy is targeted at symptomatic treatment. Antispasmodic agents such as dicyclomine and hyoscyamine are used to ease abdominal pain and decrease visceral hypersensitivity. Peppermint oil capsules are also used as an antispasmodic agent. Low dose tri-cyclic antidepressants and SSRIs are also used for treating abdominal pain as well as other symptoms.[4] For IBS-C lubiprostone and linaclotide are used to treat constipation by increasing serotonin levels, aiding in bowel movement regularity. Bulking agents such as psyllium and osmotic laxatives such as polyethylene glycol are used to attract water to the lumen of the colon aiding in stool passage. For IBS-D loperamide and diphenoxylate atropine are used as antidiarrheals. In rare cases antibiotics may also be used if the onset of IBS is after an acute case of gastroenteritis. These cases are deemed as post-infective IBS.[1]

Mesalamine also known as mesalazine is a topical salicylate that is used as a treatment for ulcerative colitis to decrease bowel inflammation. It has been previously found that patients with IBS can exhibit low levels of inflammation in bowel mucosa especially after acute cases of gastroenteritits.[2] According to a study published in the British Medical Journal up to 36.8% of subjects developed IBS following recovery from acute infectious gastroenteritis, suggesting the possibility that IBS has an inflammatory etiology.[2] Other factors can also contribute to this low-grade inflammation including stress, atopy, genetics, and various other factors.[2] Since it has

already been demonstrated that patients with IBS can have low levels of inflammation in GI mucosa including inflammatory markers and immune cells and a study has been previously demonstrated that mesalamine decreased inflammatory markers and immune cells in the bowel mucosa of patients with IBS intuitively using the anti-inflammatory mesalamine to treat the symptoms of the disorder may be the solution to treating the underlying cause of IBS instead of simply treating the disorder symptomatically.[2]

OBJECTIVE

The objective of this selective EBM review is to determine whether or not mesalamine decreases abdominal pain in patients with IBS when compared to placebo.

METHODS

The studies used in this review were found by searching PubMed using the keywords "irritable bowel syndrome" and "mesalamine". The studies selected for this review fit the clinical topic selected and the results measured were Patient-Oriented Evidence that Matters (POEMs). The studies selected consisted of randomized control human trials published after 2009. All other studies including non-human studies were excluded. Table 1 presents inclusion and exclusion criteria for each individual study. After review of criteria, 3 studies were selected for this review. All of the studies were written in English and were obtained from a peer-reviewed journals.

The population studied were adults, 18 years and older. The intervention used was mesalamine. The comparison group for each study was placebo. Each study used various doses of the drug. Barbara et al. used 800 mg of mesalazine three times daily for 12 weeks, Tuteja et al. used 1.6 g of mesalamine twice daily for 12 weeks, and lastly Lam et al. used 2 g of mesalazine daily for one week then twice daily for 11 weeks. The outcome measured from all

three studies was the subjective decrease in abdominal pain intensity. Pain intensity was measured using a binary scale in Barbara et al. and a scale of 0 to 10 for Lam et al. In the Tuteja et al. study, participants rated their abdominal pain as none, minimal, mild, moderate, or severe. Statistical significance of each study's results was reported as p-values.

OUTCOMES MEASURED

Outcome measured for all 3 studies was the participants' subjective decrease in abdominal pain. Outcomes from the different studies were measured via 10-point visual analogue scale labeled 0 to 10 with 0 being no pain and 10 being the maximum level of pain. One study also used patient symptom diary questionnaire where the participant was asked their level of pain and rated it as none, minimal, mild, moderate or severe.[1]

RESULTS

Barbara et al. (2016) performed a randomized control trial comparing the use of 800 mg of oral mesalazine to placebo. The population for this study were adults 18-65 with a diagnosis of any IBS subtype and was mostly made up of Caucasian females.[2] The participants were recruited from 21 Italian centers.[2] The full inclusion and exclusion criteria for this study can be found in Table 1. One-hundred and eighty patients were randomized and 88 were assigned to the mesalazine, while 92 were assigned to placebo.[2] The allocation of patients to each treatment group was concealed from those enrolling subjects and well as the subjects in the study.[2] Patients received mesalazine or placebo three times daily over the 12-week period based on their assigned treatment group. Patients visited the study center every 2 weeks during the treatment period and their abdominal pain was assessed by their answer to the question "did you have satisfactory relief of your abdominal discomfort or pain during the last week?".[2] Patients were considered

responders if they gave an affirmative answer to the question for more than 75% of the treatment period.[2]

Table 1. Demographics and Characteristics of Included Studies

Study	Type	#Pts	Age(yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Intervention
Tuteja[1] (2012)	RCT	20	18-75yrs	Age 18-75, male or female, history of new onset of IBS following acute gastroenteritis, presence of symptoms for more than 3 months, normal gross appearance of the colonic mucosa on endoscopy, negative tests	previous diagnosis of or history compatible with IBS prior to acute gastroenteritis, clinically significant cardiac, pulmonary, hepatic or renal disorder, chronic gastrointestinal (GI) disorder, allergy to aspirin or mesalamine, current pregnancy	3	Mesalamine 1.6 g bid for 12 weeks
Lam[7] (2016)	RCT	136	18-75yrs	Age 18-75, normal coloscopy with biopsy results, normal blood count, serum calcium and albumin, CRP, and negative celiac serology, no lactose intolerance, negative pregnancy test	Any positive screening tests, Prior history of major abdominal surgery, liver or kidney impairment, or chronic ingestion of any anti-inflammatory drugs or medications that can affect gut motility. Patients on unstable dose of SSRIs and TCAs for less than 3 months	115	2 g of mesalazine qd for 1 week then bid for 11 weeks
1	RCT	180	18-65yrs	18-65yrs, patients with Rome III criteria for diagnosis of IBS	Pregnant, breastfeeding, not using reliable contraception, NSAID use, corticosteroid use, mast cell stabilizers, the use of topic or systemic antibiotics in the last month, treatment with lactulose or with any compound that lowered the colonic pH and could prevent the release of the active moiety, major abdominal surgery, a history of inflammatory bowel disease or diverticular disease	57	Mesalazine 800mg tid for 12 weeks

According to the study 57 patients withdrew from the study prior to completion due to withdrawal of consent (14), adverse events (14), protocol violations (6), lost to follow-up (8), and other reasons (5).[2] Dropouts that were due to inefficacy were treated as non-responders, while all other reasons were considered responders and missing data was ignored. [2] Worst-case analysis and best-case analysis led to similar conclusions.[2] Due to this result the study concluded that the missing data had no effect on the end conclusion.[2] The study included 172 patients in the intention to treat analysis, 86 in each treatment group.[2] Twenty-eight patients in the mesalazine group were designated responders while 23 in the placebo group were designated responders.[2] The Number Needed to Treat (NNT) to achieve the treatment affect was 17. Although the results showed a greater number of responders in the mesalazine treatment group over placebo at 5.9%, the p-value was 0.404, which is not statistically significant, not less than or equal to 0.05.[2] Table 2 depicts the mean change from baseline of abdominal pain and discomfort for both treatment groups.

Table 2. Descriptive Statistics by Treatment Group for Abdominal Pain/Discomfort Intensity[2]

		Mesalazine (n=86)	Placebo (n=86)
Mean (SD)	Baseline (week 2)	4.59 (2.54)	4.50 (2.34)
Mean change versus baseline (SD)	End of treatment	-1.07 (2.54)	-1.21 (2.36)

Tuteja et al. performed a randomised control trial comparing the use mesalamine 1.6 g orally twice daily for 12 weeks to placebo in decreasing abdominal pain in patients with post-infective IBS.[1] Blinding was achieved for this study.[1] The population for this study were adults 18-75 years of age with diagnosed IBS after an acute case of gastroenteritis.[1] Fifteen of the

participants were returned missionaries or international travelers who developed IBS after acute gastroenteritis while abroad.[1] Further inclusion and exclusion criteria are listed in Table 1. Twenty patients were randomized and 10 were allocated to each treatment group, mesalamine and placebo.[1] Three patients withdrew from the study before completion.[1] Two from the mesalamine treatment group and one from placebo.[1] The results from these patients were excluded.[1] Level of pain was recorded for 7 days at baseline and then every 4 weeks.[1] The mean change from baseline is recorded in Table 3.

Table 3. Mean Change in Abdominal Pain from Baseline per Treatment Group after 12 Weeks of Therapy with 95% CI[1]

Treatment	p-value = 0.83
Mesalamine	1.5
Placebo	-1.1

The mean change from baseline was superior with use of mesalamine when compared to placebo.[1] However, these results were not statistically significant since the p-value was 0.83.[1]

Lam et al. performed a 12-week randomized control trial evaluating the decrease in abdominal pain in patients with IBS-D when treated with mesalamine 2 g twice daily compared to placebo.[7] Participants and those enrolling participants were blinded to allocation of treatment group.[7] The population for this study consisted of patients 18-75 with diagnosed IBS-D.[7] Other inclusion and exclusion criteria are listed in Table 1. One-hundred and thirty-six patients were randomized and 68 were assigned to each treatment group.[7] Twenty-one patients' results were not analyzed and were considered dropouts.[7] Reasons for dropouts included withdrawal of consent, loss to follow up, and adverse events.[7] This resulted in 57 patients in the mesalazine treatment group and 58 in the placebo control group.[7] Daily pain levels were recorded by patients

in a daily symptom diary.[7] At the end of treatment, weeks 11 and 12, the mean pain score was taken and can be seen in Table 4. The table shows that the end of trial difference between groups was -0.6 in favor of placebo, with a p-value of 0.83.[7] This showed that mesalazine was not superior to placebo at decreasing abdominal pain in patients with IBS-D.[7]

Table 4. Mean Abdominal Pain Score per Treatment Group at Weeks 11-12 (95% CI)[7]

Treatment group	P= 0.83
mesalazine	2.8
placebo	2.2

DISCUSSION

IBS is the most common functional bowel disorder encountered in provider practice, but the disorder pathophysiology is not clearly understood. Current treatment consists of treating whatever symptoms may arise without knowing the underlying cause to prevent symptoms from occurring. Inflammation is believed to play a role in the pathophysiology of IBS especially after cases of acute gastroenteritis.[1,2,7] Mesalazine is used in ulcerative colitis to decrease prostaglandins, which in turn decreases inflammation and symptoms associated with the disease.[1] Physicians, physician assistants and other practitioners already prescribe mesalazine for this purpose so its safety of use to an extent has already been established. The link between inflammation and IBS could be the key to treating the underlying cause of symptoms and decreasing them, namely abdominal pain.

Only two of the three studies discussed in this review showed a superior decrease in abdominal pain with use of mesalamine when compared to placebo. Even so, these results were not statistically significant. One limitation to these studies are the study populations. The study done by Tuteja et al. did not specify the ethnicity of its subjects, which could play a role in determining if mesalazine is more effective at decreasing abdominal pain in certain ethnicities

when compared to others.[1] The study also consisted of missionary travelers who's IBS started after an acute case of gastroenteritis which is not completely generalizable to the entire population of IBS patients.[1] Also it would be helpful for mean ages to be provided instead of simply the age range for the inclusion criteria and the median age. This would help to specify further what population has been target by the study. Another issue with the population is that is consisted of 11 men and 6 women, who were not evenly distributed across treatment groups.[1] The difference in the two treatment groups could affect the results of the study. The population for this study was also quite small with only 17 participants.[1] A larger study population would certainly be beneficial. Lastly the pharmacist was not blinded to the assigning of participants. This could certainly have affected the outcome of the study.[1]

The population for the study done by Lam et al. consisted predominantly of middle-aged females, but the allocation was evenly distributed among the two treatment groups.[7] Extended demographics for these participants would also have been helpful towards analyzing the treatment effect on that specific population. The study population for the study performed by Barbara et al. consists of a majority of middle-aged Caucasian females. Although this study is highly specific to that population, it is not generalizable to the population as a whole.

Another issue that can be foreseen with all 3 studies is that they were outpatient trials where patients were not supervised for the entirety of the study.[1,2,7] The results were dependent on the patient's compliance with the study protocol, but there was no mention of a method ensuring patients adhered to the study protocol. The method of assessing the level of pain also had the potential to skew results as in Barbara et al.[2] It is more standardized to use a 10-point visual analog scale that does not sway patients to a specific response based on the words used to describe the level of pain.

An additional issue that arose in the Barbara et al. study is that there was a large number of dropouts in the study. Patients who did not complete the entire 12-week treatment were considered as having a major protocol violation.[2] Also the study states that all dropouts due to inefficacy were considered non-responders while all other dropouts were considered responders and the missing data was ignored.[2] This could have a significant impact in the outcome of the study. Lastly both Barbara et al and Lam et al allowed the used of medications traditionally used to treat IBS during the course of the study.[2,7] Discontinuing traditional treatments prior to and during the duration of the entire study may demonstrate the clarity of the effect of mesalamine of abdominal pain in patients with IBS.

CONCLUSIONS

Based on the three studies discussed in this review mesalamine does not decrease abdominal pain in adults with IBS superior to placebo. Two of the studies show showed a superior decrease in abdominal with use of mesalamine when compared to placebo, while one demonstrated that mesalamine was not superior to placebo, but the results were not statistically significant and did not give the confidence that these results were not simply due to chance.[1,2,7] Issues arose in these studies including the protocols used, the adherence of patients to these protocols, and other variables that were present that could skew the outcomes of the studies. Larger studies are needed to assess the effect that mesalamine therapy has in reducing abdominal pain in patients with IBS. It would also be important to limit the number of confounding variables to determine the true treatment effect of mesalamine on abdominal pain. Lastly it would be beneficial for patients to participate in an inpatient study where they could be observed and outside variables would be limited.

References

1. Tuteja, A. K., Fang, J. C., Al-Suqi, M., Stoddard, G. J., & Hale, D. C. Double-blind placebo-controlled study of mesalamine in post-infective irritable bowel syndrome – a pilot study. *Scand. J. Gastorenterol,*2012;47(10), 1159-1164. doi:10.3109/00365521.2012.694903
2. Barbara G, Cremon C, Annese V, et al. Randomized controlled trial of mesalazine in IBS. *Gut*. 2016;65(1):82–90. doi:10.1136/gutjnl-2014-308188
3. Enck P, Aziz Q, Barbara G, et al. Irritable bowel syndrome. *Nat Rev Dis Primers*. 2016;2:16014. Published 2016 Mar 24. doi:10.1038/nrdp.2016.14
4. Saha L. Irritable bowel syndrome: pathogenesis, diagnosis, treatment, and evidence-based medicine. *World J Gastroenterol*. 2014;20(22):6759-6773. doi:10.3748/wjg.v20.i22.6759
5. Deiana S, Gabbani T, Bagnoli S, Annese V. Emerging drug for diarrhea predominant irritable bowel syndrome. *Expert Opin. on Emerging Drugs*. 2015; 20(2):247-261. doi: 10.1517/14728214.2015.1013935
6. Mearin F, Ciriza C, Mínguez M, et al. Clinical Practice Guideline: Irritable bowel syndrome with constipation and functional constipation in the adult. *Rev Esp Enferm Dig*. 2016;108(6):332-363. doi:10.17235/reed.2016.4389/2016
7. Lam C, Tan W, Leighton M, et al. A mechanistic multicentre, parallel group, randomised placebo-controlled trial of mesalazine for the treatment of IBS with diarrhoea (IBS-D). *Gut*. 2016;65(1):91–99. doi:10.1136/gutjnl-2015-309122