Effectiveness of mesalazine to treat irritable bowel syndrome

A meta-analysis

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Abstract

Aim: Accumulating evidence has explored the effect of mesalazine on irritable bowel syndrome (IBS). However, these studies remain inconsistent. Thus, a meta-analysis was conducted to estimate the role of mesalazine on IBS.

Methods: PubMed, Medline, Embase, Web of Science, and the Cochrane Library Database were searched for all relevant randomized, controlled, blinded trials on mesalazine in patients with IBS between January 1980 and October 2018. All statistical analyses were performed using Revman 5.3 software. A fixed-effects model was adopted, 95% confidence intervals for SMD was calculated. Heterogeneity was evaluated by $\chi^2$ test and $I^2$ statistic.

Results: Five studies involving 387 participants were finally included in this meta-analysis. The results showed that the SMD for clinical efficacy on abdominal pain in IBS patients treated with mesalazine in comparison to placebo was 0.19 (95% CI = –0.01 to 0.39, $P = .66$), which was statistically non-significant but clinically important. For beneficial effect of abdominal bloating, the SMD was 0.05 (95% CI = –0.20 to 0.30, $P = .70$), which was statistically non-significant. In regard to clinical efficacy on defecation frequency per day, the results revealed that the SMD was 0.29 (95% CI = –0.14 to 0.73, $P = .18$), which was statistically non-significant but clinically important. As for beneficial effect of general well-being, we found that the SMD was 0.41 (95% CI = –0.75 to 1.58, $P = .49$), which was statistically non-significant. With respect to stool consistency, the SMD was 0.01 (95% CI = –0.31 to 0.33, $P = .96$), which was statistically non-significant. For the effect of defecation urgency severity in IBS patients treated with mesalazine in comparison to placebo, we detected a surprising result with an SMD of 0.54 (95% CI = 0.05–1.04, $P = .03$), which was statistically significant. There was no significant difference between mesalazine group and placebo group on total mucosal immune cell counts of the patients with IBS with an SMD of –1.64 (95% CI = –6.17 to 2.89, $P = .48$) and there was also no significant difference in adverse reactions between two groups with an SMD of 1.05 (95% CI = 0.76–1.46 $P = .77$).

Conclusion: Mesalazine is not superior to placebo in relieving clinical symptoms of abdominal pain, abdominal bloating, and general well-being of IBS and has no advantage of reducing defecation frequency per day and immune cell infiltration and improving stool consistency though without adverse reactions of mesalazine compared with placebo. For defecation urgency severity, placebo is even superior to mesalazine for IBS patients. Thus, mesalazine might be a cost burden to patients without providing good effectiveness. In view of the small sample size of the current study and the differences in every experimental designs, this study has high heterogeneity and requires subsequent verification.

Abbreviations: 5-ASA = 5-aminosalicylic acid, GI = gastrointestinal, HADS = Hospital Anxiety and Depression Scale, IBS = irritable bowel syndrome, IBS-D = irritable bowel syndrome diarrhea-predominant, IBS-M = irritable bowel syndrome mixed diarrhea and constipation pattern, IBS-C = irritable bowel syndrome constipation-predominant, IBS-QoL = irritable bowel syndrome quality of life questionnaire, IBS-U = irritable bowel syndrome undifferentiated, PHQ12-SS = Patient Health Questionnaire-12 Somatic Symptom Scale, PI-IBS = postinfectious irritable bowel syndrome, SF-36 = short-form 36 items health survey.

Keywords: adverse reactions, clinical symptoms, immune cells, irritable bowel syndrome, mesalazine, meta-analysis

1. Introduction

Irritable bowel syndrome (IBS) is a common functional gastrointestinal (GI) disorder characterized by chronic or recurrent abdominal pain, abdominal bloating in association with altered bowel habits irrelevant to structural or biochemical abnormalities affecting 5–20% of the general population. Consisting of symptoms such as diarrhea-predominant (IBS-D), constipation-predominant (IBS-C) or a mixed diarrhea and constipation pattern (IBS-M), IBS is associated with a marked reduction of life quality in affected individuals and high health care costs. About two-thirds of IBS patients were discovered with psychological abnormalities, such as depression, anxiety, and multiple somatic symptoms. Until now, there is no single fully plausible organic cause for IBS, though some known factors including altered gut microbiome, gastroenteritis, stress bile, and...
short-chain fatty acids, may contribute to IBS, most theories ascribe it as a multifactorial disease. For the last few decades, doctors just prescribed corresponding drugs, such as antispasmodic agents, antidiarrheal agents, cathartic agents, GI motion-sensing regulators, probiotics, and antidepressants, to relieve some sort of clinical symptoms according to different types of IBS. Unfortunately, the therapeutic approach for IBS is unsatisfactory and limited to relieving the main symptoms in patients.

Mesalazine (5-aminosalicylic acid, 5-ASA) exerts a significant anti-inflammatory effect and has been shown to affect a variety of mediators and signalling pathways involved in leucocyte chemotaxis and function and epithelial defence. Previous studies have revealed that the intestinal mucosa of patients with IBS contains more immune cells, cytokines, immune mediators, which represents immune activation and mucosal impairment. So here comes the idea that mesalazine may be effective for IBS by playing an anti-inflammatory role. Several studies have showed that mesalazine was an effective and safe approach to reduce mast cell infiltration and can improve abdominal pain, diarrhea, bowel habits and general well-being in patients with IBS. But there are also researches indicated that mesalazine has no meaningful effects on decreasing the number of mast cells and improving symptoms of IBS patients.

Based on the existing knowledge in this field, we aim to conduct a meta-analysis of the pooled data from RCTs to assess the efficacy of mesalazine therapy in IBS.

2. Materials and methods

2.1. Search strategy

The PRISMA protocol was prospectively conducted. Ethical approval was unnecessary because it was a meta analysis analyzing existing articles and did not need handle individual patient data. Two investigators (Li S and Xiang SH) searched PubMed, Medline, Embase, Web of Science, and the Cochrane Library independently unrestricted by language for articles between January 1980 and October 2018. The search was limited to humans. The search terms were: “mesalazine,” “5-aminosalicylic acid,” “5ASA,” “IBS,” “Irritable bowel syndrome,” “Rome criteria,” “randomized controlled trials,” “placebo-controlled.” We also used the reference lists of each relevant articles to enlarge the search. When further information was needed for analysis, the corresponding authors of related papers were contacted. For the gray literature, the Electronic Online Service through the British Library (http://ethos.bl.uk), the New York Academy of Medicine Grey Literature Report (www.greylit.org), and the conference paper databases and academic dissertation databases in CNKI and CBM were searched.

2.2. Data extraction and methodological quality

Inclusion criteria included: randomized, controlled trials in humans published as full articles or meeting abstracts in peer-reviewed journals. Exclusion criteria included: studies limited to animals, pre-clinical studies, case reports or case series, observational studies without control groups, reviews, duplicate reports, controlled trials with other therapeutic approaches, insufficient data in article.

Studies that met the inclusion criteria were graded for quality using the Jadad scale, we assessed the quality of the studies by the randomization method, allocation concealment, blinding of outcome assessment, and follow-up. The quality scale ranges from 0 to 7 points with a low quality report of score ≤ 3 and a high quality report of score ≥ 4. All articles included in this meta-analysis had a total quality score of more than 4 and those with a score ≤ 3 were excluded.

Reviewers independently extracted data on record details of first and correspondent authors, year and country of publication, diagnostic criteria, total numbers of experimental and control group, time and treatment for each study. In the case of disagreement, the decision was made by discussion or in consultation with a third author (Zhu HT).

3. Results

3.1. Description of studies

The strategy of study selection is displayed in Fig. 1. Forty-one articles were identified by electronic searches, only five published from January 1980 and October 2018 met our inclusion criteria. Among them, two were conducted in Italy, the other three were conducted in USA, UK, and Iran, respectively. The five studies consisted of 387 patients, among them, 189 patients were distributed into the mesalazine group and the remaining 198 patients were assigned into the controlled group. Subtyping of IBS by predominant stool pattern modified according to Longstreth are IBS-D, IBS-C, IBS-M, and IBS-undifferentiated (IBS-U). There is also a saying that IBS-D may develop after inflammation due to bacterial gastroenteritis (postinfectious-IBS [PI-IBS]). Among the five included studies, two focused on IBS-D, one focused PI-IBS, and other two put emphasis on all IBS patients without classification. Rome II criteria was adopted in two studies and Rome III criteria was accepted in the other three researches. All articles included in this meta-analysis had a total quality score of 5 according to the Jadad scale, indicating that the five articles were all high quality studies. Information such as first and correspondent authors, year and country of publication, diagnostic criteria, total numbers of experimental and control group, time and treatment were reported in Table 1.

3.2. Efficacy of mesalazine in the treatment of IBS

The outcomes assessed and reported varied widely across the five studies. Some papers reported the number of days and number of subjects with improvement, while others reported change in numeric symptom scores since baseline. For the latter, beneficial effects of mesalazine on abdominal pain were reported in all studies, efficacy on abdominal bloating and adverse events treated with mesalazine compared to placebo were reported in...
four studies, effects on defecation frequency per day were reported only by three studies, change of immune cells and efficacy on general well-being, stool consistency and defecation urgency severity were reported by two studies, respectively. Besides, some studies showed various psychological points-scoring system like Hospital Anxiety and Depression Scale (HADS), Patient Health Questionnaire-12 Somatic Symptom Scale (PHQ12-SS), IBS-specific quality of life questionnaire (IBS-QoL) and the short-form 36 items health survey (SF-36). As for clinical efficacy on abdominal pain, when the meta-analysis model was fitted, the chi-square test for heterogeneity ($I^2 = 40\%$, $P = .18$), indicating a small degree of heterogeneity, so a fixed-effects model was used and the results showed that the SMD for the clinical efficacy on abdominal pain in IBS patients treated with mesalazine in comparison to placebo was 0.19 (95% CI = 0.01 to 0.39, $P = .18$), which were statistically non-significant but clinically important (Fig. 2a). For beneficial effect of abdominal bloating in IBS patients treated with mesalazine compared with placebo, the SMD was 0.05 (95% CI = −0.20 to 0.30, $P = .70$), which were statistically non-significant. There was a small degree of heterogeneity ($I^2 = 40\%$, $P = .11$) (Fig. 2b). In regard to defecation frequency per day, the results revealed that the SMD was 0.29 (95% CI = −0.14 to 0.73, $P = .18$), which were statistically non-significant but clinically important and there was a small degree of heterogeneity ($I^2 = 19\%$, $P = .29$) (Fig. 2c). As for general well-being, we found that the SMD in IBS patients treated with mesalazine in comparison to placebo was 0.41 (95% CI = −0.75 to 1.58, $P = .49$), which were statistically non-significant and there was obvious heterogeneity ($I^2 = 82\%$, $P = .02$) (Fig. 2d). With respect to the effect of stool consistency, the SMD was 0.01 (95% CI = −0.31 to 0.33, $P = .96$), which were statistically non-significant. There was no heterogeneity ($I^2 = 0\%$, $P = .88$) (Fig. 2e). All above indicated that mesalazine was not superior to placebo in relieving clinical symptoms. For defecation Urgency severity in IBS patients treated with mesalazine compared with placebo, the SMD was 0.54 (95% CI = 0.05–

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Table 1: Characteristics of randomized controlled trials of mesalazine vs placebo in IBS.

| Reference (year) | Country | Diagnostic criteria used for IBS | N | Intervention | Experimental group | Control group | Duration of therapy | Jadad score |
|------------------|---------|---------------------------------|---|-------------|--------------------|---------------|--------------------|-------------|
| R. CORINALDESI[20] 2009 | Italy | Rome II | 10 | Experimental group | Mesalazine 800 mg tid | Placebo 800 mg tid | 8 weeks | 5 |
| ASHOK K. TUTEJA[24] 2012 | USA | Rome II | 9 | Experimental group | Mesalazine 1.6 g bid | Placebo 1.6 g bid | 12 weeks | 5 |
| Giovanni Barbara[25] 2014 | Italy | Rome III | 9 | Control group | Mesalazine 800 mg tid | Placebo 800 mg tid | 12 weeks | 5 |
| Mohammd Reza Ghadiri[21] 2017 | Iran | Rome III | 29 | Experimental group | Mesalazine 2.0 g qd | Placebo 2.0 g qd | 12 weeks | 5 |
| Mohammad Reza Ghadiri[21] 2017 | Iran | Rome III | 20 | Control group | Mesalazine 800 mg tid | Placebo 800 mg tid | 8 weeks | 5 |
1.04, \( P = .03 \), which were statistically significant and there was no heterogeneity (\( I^2 = 0\% \), \( P = .75 \)), suggesting that placebo is even superior to mesalazine for IBS patients in improving symptom of defecation urgency severity (Fig. 2f).

### 3.3. Efficacy of mesalazine in reduction of immune cells infiltration in IBS

Apart from the clinical efficacy of mesalazine on various symptoms, three trials also showed whether mesalazine can reduce immune cells and pro-inflammatory cytokine as compared with placebo.\(^{20-22}\) R. Corinaldesi et al found that mesalazine can significantly reduced the total mucosal immune cell counts compared with placebo (\( P = .0082 \)). It could significantly reduce mast cell counts (\( P = .0014 \)) but not T cells, B cells, or Macrophages. Pro-inflammatory cytokine IL-1b (\( P = .047 \)) and the mast cell mediators tryptase (\( P = .030 \)) and histamine (\( P = .016 \)) were also observed to be decreased significantly in mesalazine group as compared with to placebo. Ghadir et al and Ching Lam et al both showed that there was no significant difference on the total immune cells in patients with IBS-D following treatment of mesalazine compared with placebo. As Ching Lam et al did not provide numeric change in immune cells counts, we find that there was no significant difference between mesalazine and placebo on the total mucosal immune cell counts of the patients with IBS with an SMD of \( -1.64 (95\% \text{ CI} = -6.17 \text{ to } 2.89, P = .48) \) but with high heterogeneity (\( I^2 = 96\% \), \( P < .05 \)) (Fig. 3). Three articles showed some psychological
scores results, Ching Lam et al.\(^{[22]}\) assessed anxiety and depression using HADS and recorded multiple somatic symptoms using PHQ12-SS. Barbara et al.\(^{[25]}\) evaluated IBS-QoL and SF-36 and IBS-QoL was also recorded by Tuteja et al.\(^{[24]}\) but as effective data deficiency, we cannot do meta-analysis for them.

3.4. Adverse events

Most studies (4/5, 80\%) provided information about adverse events.\(^{[20,22,24,25]}\) One trial (20\%) did not report any safety data.\(^{[21]}\) We identified these 4 clinical trials which included 338 subjects. There were 169 subjects in the mesalazine group, in which 46 patients suffered from adverse events, and there were in the 169 subjects in the control group, in which 45 patients suffered from adverse events. When the meta-analysis model was fitted, the chi-square test for heterogeneity was 0\% (\(P = .45\)), indicating no heterogeneity, so a fixed-effects model was used and the results showed that the SMD for the adverse events in IBS patients treated with mesalazine in comparison to placebo was 1.05 (95\% CI=0.76–1.46, \(P = .77\)), which were statistically non-significant, suggesting there is no harm of mesalazine compared with placebo (Fig. 4).

3.5. Publication bias assessment

As negative results of some studies were not published in most condition, which lead to publication bias. The funnel plot indicated that there was no publication bias in our meta-analysis (Fig. 5).

4. Discussion

In recent years, intestinal mucosal inflammation and immune factors in IBS patients are hot topics at home and abroad, many studies\(^{[10,29]}\) indicated that inflammatory response and immune abnormalities are associated with the pathogenesis of IBS. Some researches\(^{[15,30]}\) had shown an elevated number of immune cells especially mast cells and T lymphocytes, and release of
inflammatory mediators such as histamine, cytokines, and proteases in different segments of GI tract. It was showed that mesalazine can activate nuclear receptors, which downregulate inflammatory process and decrease inflammatory cytokines release.[31] In addition, mesalazine could significantly reduce the number of immune cells in the intestinal mucosa of patients with IBS, especially the number of mast cells.[20] There were also several initial studies showing that mesalazine can change intestinal flora of IBS patients[32] and improve the barrier function of the intestinal epithelium.[33]

This is the first published English article of meta-analysis of mesalazine in the treatment of IBS. Peng Li et al did a meta-analysis of this topic in Chinese and found clinical remission rate and abdominal pain score were significantly improved in the mesalazine group when compared with the control group and there was no significant difference in adverse reactions between the two groups.[14] But this article has some limitations. First, the medicine used in two groups were not uniform, for example, some articles used placebo in the control group, some chose standard therapy without mesalazine (patients with diarrhea received loperamide, patients with constipation received psyllium husks or lactulose syrup, patients with abdominal pain syndrome received mebeverine, some patients with severe meteorism received simethicone) and others chose symptomatic treatment (drugs such as pinaverium bromide combined with oryzanol, trimethubine sodium chloride dispersible tablets, flunarizine hydrochloride, bacillus subtilis enterococcus, loperamide combined with deanxit, hyoscyamine combined with cellulose, psyllium husks, lactulose syrup, mebeverine, and so on). For the experimental group, some articles used mesalazine and some used mesalazine combined with other drugs (trimethubine sodium chloride dispersible tablets, flunarizine hydrochloride, bacillus subtilis enterococcus, deanxit, hyoscyamine, cellulose). Secondly, the literatures included in this meta-analysis were dominated by Chinese literature, and the methodological evaluation suggests that the quality of Chinese literature is generally low (Jadad score < 2 in each of them). We think it is better to include rigorous, high quality research and exclude those of low quality, so the articles included in our study were all English papers of high quality with Jadad score more than 4. Besides, for the course of treatment, it was 28 days, or 1 month, or 40 days of all the Chinese articles, early study suggested benefit was most obvious after 8–12 weeks when choosing mesalazine to treat IBS, cause mesalazine was thought to be a disease-modifying treatment rather than symptomatic treatment.[21,23]

In this meta-analysis, though only five articles were included, they are all high quality articles with Jadad scale ≥ 5, and all of them have uniform medicine in the two groups with mesalazine in the experimental group and placebo in the control group. No significantly important adverse events were detected in the mesalazine compared with placebo (P = .77), and abdominal bloating (P = .70) as compared to placebo. We did not detect a beneficial effect of mesalazine on defecation frequency per day (P = .18), general well-being (P = .49) and stool consistency (P = .96) in IBS patients in comparison to placebo. In addition, mesalazine did not show significant reduction of immune cells (P = .48). However, we did observe a statistically significant tendency towards a decrease in defecation urgency in IBS patients (P = .03) who received placebo but not mesalazine. Probable explanations for the inefficacy of mesalazine in IBS patient compared to placebo may be short treatment duration, inadequate dosage and high placebo response seen some trials,[21,23] indicating that subjects usually felt better after participating in the clinical trials.

Some limitations of our study need to be acknowledged. First, only five studies were included which were of small sample size, the reasons may be that trials either were designed as a proof-of-concept study,[20,24] or has been limited by data deficiency from previous Randomized Controlled Trials (RCTs) evaluating the efficacy of mesalazine in IBS in sample size calculation and hence leading to small sample size,[25] or has difficulty in recruiting participants for psychosocial disturbances in patients and therefore underpowered to discover results change.[21] Secondly, subjects may be still heterogeneous though strict entry criteria were carried out, among the 5 studies included, 2 articles have enrolled IBS patients, other 2 trials have recruited IBS-D patients, and 13 participants with IBS-D from one of the articles fulfilled the definition of PI-IBS. Another one research has chosen post-infective IBS (PI-IBS) patients. Many studies indicate that PI-IBS is a subset of patients with IBS, occurs in 7–33% of patients following acute gastroenteritis and is usually diarrhea-predominant.[26–28] Considering the RCTs about assessing the benefical effect of mesalazine in IBS are few, we enrolled all those five studies. In fact, we did feel it would be better if the enrolled trials had separated PI-IBS from IBS and stratified by subsets of IBS, although it may be very difficult to recruit subjects and require more resources.

5. Conclusion

In summary, this meta-analysis suggests that mesalazine might be a cost burden to patients without providing good effectiveness for the treatment of IBS. Results should be interpreted prudently in view of some limitations of the enrolled studies. Future studies with long treatment duration and adequate dosage, especially larger studies are needed and more data like stratification by subsets of IBS are needed.

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Author contributions

Xu GQ designed the research and revised the manuscript; Xiang SH and Li S collected data; Ding L, Zhu HT and Yu JH analyzed and interpreted the data; Zhang FM wrote the manuscript, all the authors contributed to the design and interpretation of the study, read and approved the final version to be published. All the authors read and approved the final version to be published.

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References

[1] Longstreth GF, Thompson WG, Chey WD, et al. Functional bowel disorders. Gastroenterology 2006;130:1480–91.
[2] Boyce PM, Koloski NA, Talley NJ. Irritable bowel syndrome according to varying diagnostic criteria: are the new Rome II criteria unnecessarily restrictive for research and practice. Am J Gastroenterol 2000;95:3176–83.
[3] Hillila MT, Farkkila MA. Prevalence of irritable bowel syndrome according to different diagnostic criteria in a non-selected adult population. Aliment Pharmacol Ther 2004;20:339–45.
[4] Hungin APS, Whorwell PJ, Tack J, et al. The prevalence, patterns and impact of irritable bowel syndrome: An international survey of 40 000 subjects. Aliment Pharmacol Ther 2003;17:643–50.
[5] Chey WD, Kurlander J, Eswaran S. Irritable bowel syndrome: a clinical review. JAMA 2015;313:949–58.
[6] Spiller RC, Humes DJ, Campbell E, et al. The Patient Health Questionnaire 12 Somatic Symptom scale as a predictor of symptom severity and consulting behaviour in patients with irritable bowel syndrome and symptomatic diverticular disease. Aliment Pharmacol Ther 2010;32:811–20.
[7] Talley NJ, Zinsmeester AR, Van Dyke C, et al. Epidemiology of colonic symptoms and the irritable bowel syndrome. Gastroenterology 1994;107:927–34.
[8] Brandt LJ, Chey WD, Foxx-Orenstein AE, et al. American College of Gastroenterology Task Force on Irritable Bowel Syndrome. An evidence-based position statement on the management of irritable bowel syndrome. Am J Gastroenterol 2009;104(Suppl 1):S1–35.
[9] Saito YA, Locke GR, Talley NJ, et al. A comparison of the Rome and Manning criteria for case identification in epidemiological investigations of irritable bowel syndrome. Am J Gastroenterol 2000;95:2816–24.
[10] Ford AC, Moayyedi P, Lacy BE, et al. American College of Gastroenterology monograph on the management of irritable bowel syndrome and chronic idiopathic constipation. Am J Gastroenterol 2014;109(Suppl 1):S2–26.quiz S27.
[11] Agrawal A, Whorwell PJ. Irritable bowel syndrome: diagnosis and management. BMJ 2006;332:280–3.
[12] Klote U. The pharmacological profile and clinical use of mesalazine (5-aminosalicylic acid). Pharmacol Profile Clin 2012;62:53–8.
[13] Barbara G, De Giorgio R, Stanghellini V, et al. New pathophysiological mechanisms in irritable bowel syndrome. Aliment Pharmacol Ther 2004;20(Suppl 2):1–9.
[14] Barbara G, Stanghellini V, De Giorgio R, et al. Activated mast cells in proximity to colonic nerves correlate with abdominal pain in irritable bowel syndrome. Gastroenterology 2004;126:693–702.
[15] Cencic N, Andrews CN, HolzhAUSEn M, et al. Role for protease activity in visceral pain in irritable bowel syndrome. J Clin Invest 2007;117:636–47.
[16] Barbara G, Wang B, Stanghellini V, et al. Mast cell-dependent excitation of visceral-nociceptive sensory neurons in irritable bowel syndrome. Gastroenterology 2007;132:26–37.
[17] Bahram S, Li Q, Vignali S, et al. Activation of human enteric neurons by supernatants of colonic biopsy specimens from patients with irritable bowel syndrome. Gastroenterology 2009;137:1425–34.
[18] Cremont C, Carini G, Wang B, et al. Intestinal serotonin release, sensory neuron activation, and abdominal pain in irritable bowel syndrome. Am J Gastroenterol 2011;106:1290–8.
[19] Dorofeev Andrey E, Kiziryan Elena A, Vasilenko Inna V, et al. Clinical, endoscopic and morphological efficacy of mesalazine in patients with irritable bowel syndrome. Clin Exp Gastroenterol 2011;4:141–53.
[20] Cornaldua R, Stanghellini V, Cremont C, et al. Effect of mesalazine on mucosal immune biomarkers in irritable bowel syndrome: a randomized controlled proof-of-concept study. Aliment Pharmacol Ther 2009;30:245–52.
[21] Ghadir MR, Poradineh M, Sotodeh M, et al. Mesalazine has no effect on mucosal immune biomarkers in patients with diarrhea-dominant irritable bowel syndrome referred to Shariati Hospital: a randomized double-blind, placebo-controlled trial. Middle East J Dig Dis 2017;9:20–5.
[22] 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;65:91–9.
[23] Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? Control Clin Trials 1996;17:1–2.
[24] Tuteja AK, Fang JC, Al-Suqi M, et al. Double-blind placebo-controlled study of mesalamine in post-infective irritable bowel syndrome—a pilot study. Scand J Gastroenterol 2012;47:1139–64.
[25] Barbara G, Cremont C, Annese V, et al. Randomised controlled trial of mesalamine in IBS. Gut 2016;65:82–90.
[26] Spiller RC. Postinfectious irritable bowel syndrome. Gastroenterology 2003;124:1662–71.
[27] Halvorson HA, Schlett CD, Riddle MS. Postinfectious irritable bowel syndrome—a meta-analysis. Am J Gastroenterol 2006;101:1894–9.
[28] Dunlop SP, Jenkins D, Spiller RC. Distinctive clinical, psychological, and histological features of postinfective irritable bowel syndrome. Am J Gastroenterol 2003;98:1378–83.
[29] Guilarte M, Santos J, de Torres I, et al. Diarrhoea-predominant IBS patients show mast cell activation and hyperplasia in the jejunum. Gut 2007;56:203–9.
[30] Park JH, Rhee PL, Kim HS, et al. Mucosal mast cell counts correlate with visceral hypersensitivity in patients with diarrhea predominant irritable bowel syndrome. J Gastroenterol Hepatol 2006;21:71–8.
[31] Rousseaux C, Lefebvre B, Dubuquoy L, et al. Intestinal anti-inflammatory effect of 5-aminosalicylic acid is dependent on peroxisome proliferator-activated receptor-gamma. J Exp Med 2005;201:1205–13.
[32] O’Malley L, McCarthy J, Kelly P, et al. Lactobacillus and bifidobacterium in irritable bowel syndrome: symptom responses and relationship to cytokine profiles. Gastroenterology 2003;128:541–51.
[33] Di Paolo MC, Merritt MN, Crotty B, et al. 5-Aminosalicylic acid inhibits the impaired epithelial barrier function induced by gamma interferon. Gut 1996;38:115–9.
[34] Li Peng, Shen Miao, Lou Guochun, et al. Meta analysis of mesalazine in the treatment of irritable bowel syndrome. Shi jie hua ren za zhi 2015;23:4911–8.
[35] Aron J. Response to mesalamine and balsalazide in patients with irritable bowel syndrome refractory to alosetron and tegaserod. Gastroenterology 2005;128:A329–30.