Mild Moxibustion for Irritable Bowel Syndrome with Diarrhea (IBS-D): A Randomized Controlled Trial

Zhaoqin Wang
Fudan University
Manwen Xu
Huashan Hospital Fudan University Department of Integrative Medicine
Zheng Shi
Shanghai Research Institute of Acupuncture and Meridian
Chunhui Bao
Shanghai Research Institute of Acupuncture and Meridian
Huirong Liu
Shanghai Research Institute of Acupuncture and Meridian
Cili Zhou
Shanghai Research Institute of Acupuncture and Meridian
Yilu Yan
Shanghai Research Institute of Acupuncture and Meridian
Chunye Wang
Shanghai Research Institute of Acupuncture and Meridian
Guona Li
Shanghai University of Traditional Chinese Medicine Yueyang Hospital of Integrated Traditional Chinese Medicine and Western Medicine
Wei Zhang
Fudan University School of Public Health
Anqi Gao
Shanghai Research Institute of Acupuncture and Meridian
Huangan Wu (wuhuangan@126.com)
Shanghai University of Traditional Chinese Medicine

Research

Keywords: IBS-D, Mild Moxibustion, Randomized Controlled Trial

Posted Date: June 11th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-586966/v1

Version of Record: A version of this preprint was published at Journal of Ethnopharmacology on January 1st, 2022. See the published version at https://doi.org/10.1016/j.jep.2022.115064.

Abstract

Objective

To evaluate the effects of mild moxibustion (MM) for the treatment of irritable bowel syndrome with diarrhea (IBS-D) through comparisons with those of placebo moxibustion.

Patients and Methods:

This was a single-site, randomized controlled trial was conducted at Shanghai Research Institute of Acupuncture and Meridian in China and enrolled 76 participants who met the Rome IV diagnostic criteria for IBS-D between May 2017 and December 2019. 76 participants were randomized to either mild moxibustion (MM) or placebo moxibustion group (PM) in a 1:1 ratio. 18 sessions of MM or PM were implemented over the course of 6 weeks (3 times per week). The primary outcome was adequate relief after 6 weeks of treatment.

Results

Of 76 patients with IBS-D who were randomized (38 in the MM group and 38 in the PM group) were included in the intention-to-treat (ITT) analysis set. After treatment at week 6, the response rate was significantly higher in the MM group than the PM group (81.58% vs. 36.84%,) with an estimated difference of 44.74 (95% CI, 23.46 to 66.02, $P < 0.001$). No participant reported severe adverse effects.

Conclusion

The findings suggest that mild moxibustion may be more effective than placebo moxibustion for the treatment of IBS-D, with effects lasting up to 12 weeks.

Trial Registration:

ChiCTR, ChiCTR2100046852. Registered 29 May 2021 - Retrospectively registered, URL: http://www.chictr.org.cn/showproj.aspx?proj=127000

Introduction

Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal disorder, characterized by several symptoms such as abdominal pain or disorder bowel function (e.g. diarrhea, bloating, or constipation)[1, 2] IBS has three predominant subtypes: IBS with diarrhea (IBS-D), IBS with constipation (IBS-C) and IBS with mixed (IBS-M)[3]. The prevalence of IBS is 10%-20%, and 40% of IBS patients with diarrhea condition

(IBS-D)[4, 5]. IBS has a negative impact on quality of life (QOL), causes a heavy cost burden, and increases the risk of mental diseases such as depression[6].

The management of IBS-D included drugs treatment and non-pharmacological management[7]. The non-pharmacological management includes exercise and psychological therapies, specialized diets, fibre supplementation, peppermint oil, other herbal products, and probiotics. Loperamide and Eluxadoline are the most used pharmacological therapy for IBS-D, but it is focuses on symptom management like diarrhea[7]. However, such medications only relief related symptoms rather than disease modification, and the recurrence rates are high[8]. Many patients are reluctant to continued use medication due to few symptom improvements[9] and adverse effects, such as cardiovascular disorders and ischemic colitis[10]. Therefore, there is urgent to search for the therapies that effectively treat and manage this condition[11].

More and more patients are forced to seek complementary and alternative therapies because of the adverse effects and side effects of drugs[12–14]. Acupuncture and moxibustion are the effective treatment for IBS[12, 14], and there are several meta-analyses suggested benefits of acupuncture and moxibustion in terms of symptom control and quality of life improvements in patients with IBS[13, 15]. In our previous studies, we compared the efficacy of electroacupuncture with mild moxibustion for treating IBS-C and IBS-D, respectively, and showed that electroacupuncture resulted in symptoms improvement, modulating on brain-gut function in patients with IBS-C[14] and IBS-D[16]. However, these trials focused on the effect of electroacupuncture VS mild moxibustion on IBS, not mild moxibustion VS placebo moxibustion. Therefore, a strictly conducted randomized controlled trial with high methodologic quality to confirm the effectiveness and safety of mild moxibustion for IBS-D was considered necessary.

Accordingly, we designed the present randomized controlled trial to evaluate the effect and safety of mild moxibustion for the treatment of IBS-D. Our hypothesis was that 6-week mild moxibustion would be more effective than placebo moxibustion in the alleviation of IBS symptoms.

Methods

Study design

This randomized controlled trial was conducted between May 2017 and December 2019 at Shanghai Research Institute of Acupuncture and Meridian in Shanghai, affiliated with Yueyang Hospital of Integrated Chinese and Western Medicine, China (ChiCTR2100046852). The trial was performed over a period of 14 weeks, including a 1-week wash-out period, 1-week baseline assessment period, 6-week treatment period, and 6-week posttreatment follow-up period. This study was approved by the ethics committee of Yueyang Hospital of Integrated Chinese and Western Medicine, affiliated with the Shanghai University of Traditional Chinese Medicine. All patients signed informed consent before participation. This study followed the Consolidated Standards of Reporting Trials (CONSORT)[17] and Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA)[18].

Participants

Participants were recruited from Shanghai Research Institute of Acupuncture and Meridian between May 2017 and December 2019 through hospital-based Wechat, print advertisements, and posters at the outpatient unit. Eligible participants were men or women between the ages of 18 and 65 years; met the Rome IV diagnostic criteria and Bristol Form for IBS-D[19]; had IBD at least 6 months; willing to participate and signed informed consent. Key exclusion criteria were IBS-C/IBS-M or unsubtyped IBS; organic intestinal tract diseases; prior surgery related to the intestinal; received medications treatment that may affect intestinal function. Patients who received moxibustion within 6 months before enrollment were also excluded.

Randomization and blinding

All eligible participants were randomly divided into MM group or PM group in a 1:1 allocation ratio. The randomization sequence was generated by an independent statistician using SAS software (version 9.4), with a block of 4. Only the therapists knew the group allocation. Participants and other relevant researchers (the outcome assessors, data managers, and statisticians) were blinded to the group allocation.

Interventions

The moxibustion strategies were developed by senior researchers of moxibustion and Gastroenterology experts, based on the textbook and our previous study conclusions[14, 16]. Two (1 male and 1 female) licensed therapists with 3 years of experience administering the mild moxibustion and moxibustion treatments. Both therapists had at least a 5-year master's education and were registered practitioners of traditional Chinese medicine. All therapists and research assistants received a 3-day training before study initiation. Both treatments consisted of 18 sessions, each for 30min, and were administered over 6 weeks (3 times per week). Moxa cones (3 cm in diameter, Nanyang Hanyi Moxa Co. Ltd. China) and infrared thermometer (Fluke 62, USA) were used.

Participants in the MM group received mild moxibustion at the bilateral acupoints of Tianshu (ST25) and Zusanli (ST36). A moxa stick was ignited and positioned with a supporting device so that the tip of the moxa stick is 3–5 cm above the acupoints. The temperature of the acupoint is monitored by an infrared thermometer. The temperature was maintained at 43 ± 1°C to make the participants feel warm without any burning pain. For the PMFH group, the same acupoints as the treatment group were used. The same type of moxa stick was ignited but kept 8–10 cm above the acupoints, and the temperature of the acupoints was maintained at 37 ± 1°C. Participants were not felt warm at these acupoints.

Outcomes measurements

The primary outcome the response rate after 6 weeks of treatment[20, 21]. The response rate was based on the global treatment effect questionnaire[21], which asked, "Did you have adequate relief of your IBS symptoms over the last week in comparison with the baseline period?" This was scored with a 7-point

Likert scale, ranging from “extremely improved compared with the baseline period,” “improved compared with the baseline period,” “slightly improved compared with the baseline period,” “not changed compared with the baseline period,” “slightly aggravated compared with the baseline period,” “aggravated compared with the baseline period,” or “extremely aggravated comparison with the baseline period.”

Secondary outcomes included response rates measured at follow up (12 weeks); change in total and each domain IBS Symptom Severity Score (IBS-SSS)[22] from baseline to week 6 and week 12; total IBS-Quality of Life (IBS-QOL)[23] questionnaire score, and subscale IBS-QOL scores from baseline to week 6.

Any adverse events (AE) likely to be related to the acupuncture treatment were recorded. All AE were reported on the case report form (CRF) by independent assessors.

Sample size

The pilot study aimed to explore symptomatic improvement in patients with IBS-D on mild moxibustion compared to moxibustion. Based on clinical experience and references[24], sample size was calculated with 80% power and two-tailed alpha level of 0.05. We assumed 80% of the mild moxibustion group achieved response at 6 weeks, compared with 35% of the control group. Considering a dropout rate of 20%, a total of 76 participants were recruited.

Statistical Analysis

An intention-to-treat (ITT) approach was used and all randomly assigned participants were analyzed, with a 2-sided significance level of less than 0.05. Continuous Variables were described as mean (SD) or median (p25, p75), and categorical variables were described as frequency and percentage. For baseline characteristics, continuous variables were examined by independent sample t-test or Wilcoxon rank-sum test, and categorical variables were compared by chi-square test, Fisher’s exact test, or CMH chi-square test as appropriate.

The primary outcome of response rate at week 6 was assessed with the χ^2 test. The same approach was used for the response rate at week 12. The change from baseline in IBS-SSS and IBS-QoL were evaluated by covariance analysis. All statistical analyses were performed using SAS software (version 9.4), and *P* values less than 0.05 were considered significant.

Results

Figure 1 shows 97 IBS-D patients were screened. Of the 21 patients who were excluded, 5 declined to participate, and 16 did not meet the inclusion criteria. Of the 76 eligible patients enrolled and randomly assigned (38 mild moxibustion group and 38 placebo moxibustion group). 3 patients in the mild moxibustion group and 5 patients in the placebo moxibustion group dropped out. At the end of treatment, 35 participants in the mild moxibustion group and 33 participants in the placebo moxibustion group had completed treatment. The missing data were imputed by the LOCF method (Last observation carried

forward). Baseline sociodemographic and clinical characteristics were similar between the two groups. (Table 1)

Table 1
Baseline Characteristics of Participants, by Group

Characteristic	Mild moxibustion group (n = 38)	Placebo moxibustion Group (n = 38)	*P*
Mean age (SD), y	50.21(12.21)	44.26(15.10)	0.075
Sex, n (%)			0.428
Female	21 (55.26)	20 (52.63)	
Male	17 (44.74)	18 (47.37)	
Mean Height (SD), cm	167.3 (8.90)	166.74 (7.65)	0.774
Mean weight (SD), kg	61.85 (12.85)	61.67 (12.26)	0.593
Education, (IQR), y	15 (11, 16)	16 (12, 16)	0.347
Mean disease duration (IQR), m	6 (3, 10)	9 (4.5, 14)	0.337
IBS-SSS score (SD)	295.76 (82.27)	295.00 (89.59)	0.971
Severity of abdominal pain	56.36 (31.11)	58.95 (26.69)	0.705
No. of d in pain every 10 d	44.85 (27.63)	44.74 (26.79)	0.847
Severity of abdominal distension	41.21 (27.92)	41.05 (33.35)	0.935
Satisfaction with bowel habits	75.45 (20.01)	74.47 (19.55)	0.756
Interference of IBS with life in general	77.88 (21.03)	75.79 (21.76)	0.633
IBS-QOL score (SD)	92.85 (26.84)	93.95(32.85)	0.879
Dysphoria	24.03 (7.86)	24.11(8.35)	0.969
Interference with activity	22.48 (6.03)	22.63 (7.14)	0.926
Body image	8.48 (2.95)	9.11 (3.51)	0.527
Health worry	8.48 (3.05)	8.97 (2.90)	0.492
Food avoidance	9.91 (4.07)	9.82 (2.87)	0.664
Social reaction	8.91 (3.52)	10.32 (3.81)	0.140
Sexual concerns	4.58 (2.89)	4.16 (2.15)	0.887
Relationships	9.12 (3.13)	9.18 (2.99)	0.931
Expectation of moxibustion, n (%)			0.824
Complete believe	27 (71.05)	26 (68.42)	

Characteristic	Mild moxibustion group (n = 38)	Placebo moxibustion Group (n = 38)	*P*
Believe	5 (13.16)	7 (18.42)	
Little believe	6 (15.79)	5 (13.16)	

For the primary outcome, the intention-to-treat (ITT) analyses at the end of treatment (week 6) showed response rates were significantly higher in the mild moxibustion group than placebo moxibustion group (81.58% vs 36.84%,) with an estimated difference of 44.74 (95% CI, 23.46 to 66.02, $P < 0.001$). Similar results were observed for a follow-up visit (week 12), there were statistically significant differences in the response rates between the 2 groups 50.02 (95% CI, 24.38 to 71.68; $P < 0.001$). (Fig. 2 and Table 2).

Table 2
Response rate during the entire study

Variable	Mild moxibustion Group (n = 38)	Placebo moxibustion Group (n = 38)	Difference (95% CI)	*P*
Adequate relief, %				
Week 6	81.58	36.84	44.74 (23.46 to 66.02)	< 0.001
Week12	76.32	26.30	50.02 (24.38 to 71.68)	< 0.001

Table 3 shows the change of total and domain scores of IBS-SSS at weeks 6 and week 12. The mild moxibustion group reported lower scores than the placebo moxibustion group in total at week 6 during the final treatment report, and at week 12 during follow-up visit: 186.41 (95% CI, 152.85 to 219.98; $P < 0.001$) and 216.11 (95% CI, 183.82 to 248.39; $P < 0.001$). Moreover, there were statistically significant differences between the mild moxibustion group and placebo moxibustion group in the severity of abdominal pain, no. of day in pain every 10 days, the severity of abdominal distension, satisfaction with bowel habits, and interference of IBS with life in general domains.

Table 3
Secondary outcomes (IBS-SSS)

Outcome	Mild moxibustion Group (n = 38)		Placebo moxibustion Group (n = 38)		Difference (95% CI)	*P*
	Mean	SD	Mean	SD		
IBS SSS Score						
Week 6	-218.79	100.58	-32.11	46.91	186.41(152.85 ~ 219.98)	< 0.001
Week 12	-243.03	96.74	-26.58	57.39	216.11(183.82 ~ 248.39)	< 0.001
Severity of abdominal pain						
Week 6	-42.12	28.04	-5.26	11.79	37.94(29.73 ~ 46.15)	< 0.001
Week 12	-48.18	30.66	-3.68	10.51	45.74(37.39 ~ 54.08)	< 0.001
No. of d in pain every 10 d						
Week 6	-34.24	25.74	-4.74	16.72	29.45(21.25 ~ 37.65)	< 0.001
Week 12	-38.79	26.19	-6.58	18.35	32.14(24.57 ~ 39.72)	< 0.001
Severity of abdominal distension						
Week 6	-30.91	30.04	-4.47	18.26	26.35(17.46 ~ 35.24)	< 0.001
Week 12	-34.24	30.21	-2.63	25.54	31.52(21.53 ~ 41.50)	< 0.001
Satisfaction with bowel habits						
Week 6	-52.73	29.40	-8.68	15.10	43.48(33.99 ~ 52.97)	< 0.001
Week 12	-58.48	28.30	-6.05	12.85	51.81(43.50 ~ 60.12)	< 0.001
Interference of IBS with life in general						
Week 6	-58.79	27.81	-8.95	10.85	49.10(39.96 ~ 58.24)	< 0.001
Week 12	-63.33	24.71	-7.63	11.95	54.74(46.99 ~ 62.48)	< 0.001

The results of IBS-QOL are reported in Table 4. After treatment, there were significantly greater in mild moxibustion group than placebo moxibustion group in IBS-QOL score and seven domains: dysphoria, interference with activity, body image, health worry, food avoidance, social reaction, and relationships. Of note, at week 6, there were no statistically significant differences between the mild moxibustion group and the placebo moxibustion group: -9.60(95% CI, -18.47 to -0.74; *P* = 0.169).

Table 4
Secondary outcomes (IBS-QOL)

Outcome	Mild moxibustion Group (n = 38)		Placebo moxibustion Group (n = 38)		Difference (95% CI)	*P*
	Mean	SD	Mean	SD		
IBS QOL Score						
Baseline	56.18	20.69	54.67	20.40	NA	0.759
Week 6	72.75	20.45	58.74	19.73	-12.84(-18.64~-7.03)	0.001
Dysphoria						
Baseline	49.91	24.56	49.67	26.08	NA	0.969
Week 6	72.73	22.18	55.43	23.03	-17.13(-23.46~-10.80)	0.002
Interference with activity						
Baseline	44.70	21.54	44.17	25.52	NA	0.926
Week 6	67.32	22.02	51.69	23.33	-15.23(-22.04~-8.42)	0.002
Body image						
Baseline	71.97	18.43	68.09	21.93	NA	0.527
Week 6	81.06	17.85	66.28	21.82	-12.28(-19.57~-4.98)	0.003
Health worry						
Baseline	54.29	25.44	50.22	24.16	NA	0.492
Week 6	73.23	21.73	59.65	23.61	-11.07(-19.18~-2.97)	0.010
Food avoidance						
Baseline	42.42	33.94	43.20	23.95	NA	0.664
Week 6	61.36	29.52	48.68	22.05	-13.08(-23.18~-2.97)	0.027
Social reaction						
Baseline	69.32	22.01	60.53	23.84	NA	0.140
Week 6	78.41	19.46	61.18	22.04	-11.44(-18.46~-4.43)	0.001
Sexual concerns						
Baseline	67.80	36.18	73.03	26.88	NA	0.887
Week 6	80.68	28.49	74.34	25.66	-9.60(-18.47~-0.74)	0.169
Relationships						

Outcome	Mild moxibustion Group (n = 38)		Placebo moxibustion Group (n = 38)		Difference (95% CI)	*P*
	Mean	SD	Mean	SD		
Baseline	48.99	26.08	48.46	24.88	NA	0.931
Week 6	67.17	24.99	52.63	23.01	-14.18(-22.06~-6.30)	0.008

Mild moxibustion related AEs occurred in 5.3% (2 of 38) of participants in the mild moxibustion group, 2 patients reported rodonalgia and itching. All mild moxibustion related adverse events were mild, and all participants continued to finish the trial.

Discussion

This pilot randomized, placebo-controlled trial showed that for patients with IBS-D, mild moxibustion had a 44.74–percentage point higher response rate at week 6 and a 50.02–percentage point higher at week 12 than placebo moxibustion group. This means mild moxibustion not only provided short-term relief but also long-term relief persisted up to 12 weeks after treatment. Patients in the mild moxibustion group also had improvements in IBS-SSS total score and each domain up to follow-up visit (12-week). Meanwhile, the quality of life had improved in the mild moxibustion group at week 6. In addition, there were no severe AEs during the entire study.

To the best of our knowledge, no prior RCT has evaluated the effect of different moxibustion on IBS-D. The findings of our previous trial that investigated the effects for IBS-D, showed the moxibustion is a promising therapy[25, 26]. And mild moxibustion could significantly improve some of the most intrusive symptoms of IBS patients[14]. Results of systematic reviews of the literature indicate that moxibustion may be a beneficial therapy in relieving IBS symptoms, but this conclusion was based on studies that were at high risk of bias in the included studies[13, 15, 27]. A great number of studies have shown that acupuncture or acupuncture combined with mild moxibustion has a certain effect on IBS-D[12, 28]. This trial is the first study focus on the different methods of moxibustion for IBS-D in short- and long-term improvement of response rates, IBS-SSS, and IBS-QOL.

Many studies have demonstrated the efficacy of moxibustion in treating IBS-D, but It still remains unclear how moxibustion alleviates IBS-D[29]. Our previous studies indicate that moxibustion could affect intestinal microbes[30, 31], visceral hypersensitivity[31, 32], the brain-gut axis[14, 16], gastrointestinal function[33]. Other studies showed the moxibustion or acupuncture have benefit effect for IBS-D by regulating the neuroendocrine system[34], the immune system[35], and other factors.

Our study also has several limitations. First, the blinded were not completely assessed. Compared with the placebo group, the mild moxibustion group was difficult to exclude the placebo effect due to the obvious warm feeling. In the future, the placebo moxibustion group should try to eliminate the influence of temperature, but at the same time ensure that it does not stimulate the acupoints. This will blind the

patients and minimize the placebo effect. Second, the time of visits was few. We only assessed the response rates at week 6 and week 12, it was impossible to accurately assessed when moxibustion works and the long-term effect during the follow-up period. Further research should set multiple visit time points and measure longer-term outcomes for different moxibustion. Third, we only assess the efficacy of mild moxibustion for IBS-D, the effect of mild moxibustion was satisfactory for IBS-D, not for IBS-C. Therefore, we could not determine the IBS-C that can benefit more from mild moxibustion. Finally, we only assessed the effect of mild moxibustion for IBS-D, in future studies we could use 3 or more methods of moxibustion to investigate the optimal method of moxibustion for IBS-D.

Conclusion

Mild moxibustion may be more effective than placebo moxibustion in alleviating the symptoms of IBS-D, with its effects lasting up to 12 weeks. It is feasible to conduct a large randomized controlled trial of different moxibustion for participants with IBS-D and the data of this trial could lead to an estimate of the sample size.

Abbreviations

IBS
Irritable Bowel Syndrome; **IBS-D**:Irritable Bowel Syndrome with Diarrhea; **IBS-C**:Irritable Bowel Syndrome with Constipation; **IBS-M**:Irritable Bowel Syndrome with Mixed; **QOL**:quality of life; **CONSORT**:Consolidated Standards of Reporting Trials; **STRICTA**:Standards for Reporting Interventions in Clinical Trials of Acupuncture; **IBS-SSS**:IBS Symptom Severity Score; **IBS-QOL**:IBS-Quality of Life; **AE**:adverse events; **CRF**:case report form; **ITT**:intention-to-treat; **LOCF**:Last observation carried forward.

Declarations

Acknowledgments

The authors thank Prof. Wei Zhang from Department of Biostatistics, School of Public Health, Fudan University for the statistical guidance. We would like to thank Prof. Lixing Lao from the Virginia University of Integrative Medicine in USA, for the improvement of methodology and language editorial support.

Authors' contributions

HW, ZS contributed to the study conception and design, AG, MX, CW, GL, and YY coordinated the clinical trial and the collection of samples and clinical data. WZ performed statistical analyses on clinical data. CB and HL supervised the study. ZW wrote the draft of the manuscript, and CZ revised carefully. All authors approved the final manuscript.

Funding

This work was supported by the National Basic Research Program of China (973 Program) (No. 2015CB554500), and the National Natural Science Foundation of China (No. 81873377). The funding body has no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

All participants provided written informed consent and the protocol was approved by the Ethics Committee of Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine (No. 2015-006).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Ford AC, Lacy BE, Talley NJ. Irritable Bowel Syndrome. N Engl J Med. 2017;376(26):2566–78.
2. Grayson M. Irritable bowel syndrome. Nature. 2016;533(7603):101.
3. Saha L. Irritable bowel syndrome: pathogenesis, diagnosis, treatment, and evidence-based medicine. World J Gastroenterol. 2014;20(22):6759–73.
4. Sultan S, Malhotra A. Irritable Bowel Syndrome. Ann Intern Med. 2017;166(11):Itc81–96.
5. Lovell RM, Ford AC. Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis. Clin Gastroenterol Hepatol. 2012;10(7):712 – 21.e4.
6. Black CJ, Ford AC. Global burden of irritable bowel syndrome: trends, predictions and risk factors. Nat Rev Gastroenterol Hepatol. 2020;17(8):473–86.
7. Pietrzak A, Skrzydło-Radomańska B, Mulak A, Lipiński M, Małecka-Panas E, Reguła J, et al. Guidelines on the management of irritable bowel syndrome: In memory of Professor Witold Bartnik. Prz Gastroenterol. 2018;13(4):259–88.
8. Cangemi DJ, Lacy BE. Management of irritable bowel syndrome with diarrhea: a review of nonpharmacological and pharmacological interventions. Therap Adv Gastroenterol. 2019;12:1756284819878950.

9. Mira JJ, Lacima G, Cortés Gil X. Perceptions of the public healthcare system from private-care patients with irritable bowel syndrome with constipation in Spain. Rev Esp Enferm Dig. 2018;110(10):612–20.
10. Nam Y, Min YS, Sohn UD. Recent advances in pharmacological research on the management of irritable bowel syndrome. Arch Pharm Res. 2018;41(10):955–66.
11. Pimentel M. Evidence-based management of irritable bowel syndrome with diarrhea. Am J Manag Care. 2018;24(3 Suppl):35-s46.
12. Pei L, Geng H, Guo J, Yang G, Wang L, Shen R, et al. Effect of Acupuncture in Patients With Irritable Bowel Syndrome: A Randomized Controlled Trial. Mayo Clin Proc. 2020;95(8):1671-83.
13. Billings W, Mathur K, Craven HJ, Xu H, Shin A. Potential Benefit With Complementary and Alternative Medicine in Irritable Bowel Syndrome: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol. 2020.
14. Zhao JM, Lu JH, Yin XJ, Wu LY, Bao CH, Chen XK, et al. Comparison of Electroacupuncture and Mild-Warm Moxibustion on Brain-Gut Function in Patients with Constipation-Predominant Irritable Bowel Syndrome: A Randomized Controlled Trial. Chin J Integr Med. 2018;24(5):328–35.
15. Tang B, Zhang J, Yang Z, Lu Y, Xu Q, Chen X, et al. Moxibustion for Diarrhea-Predominant Irritable Bowel Syndrome: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Evid Based Complement Alternat Med. 2016;2016:5105108.
16. Zhao JM, Lu JH, Yin XJ, Chen XK, Chen YH, Tang WJ, et al. Comparison of electroacupuncture and moxibustion on brain-gut function in patients with diarrhea-predominant irritable bowel syndrome: A randomized controlled trial. Chin J Integr Med. 2015;21(11):855–65.
17. Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. Int J Surg. 2012;10(1):28–55.
18. MacPherson H, Altman DG, Hammerschlag R, Youping L, Taixiang W, White A, et al. Revised STandards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA): extending the CONSORT statement. PLoS Med. 2010;7(6):e1000261.
19. Suzuki H. The Application of the Rome IV Criteria to Functional Esophagogastroduodenal Disorders in Asia. J Neurogastroenterol Motil. 2017;23(3):325–33.
20. Mangel AW, Hahn BA, Heath AT, Northcutt AR, Kong S, Dukes GE, et al. Adequate relief as an endpoint in clinical trials in irritable bowel syndrome. J Int Med Res. 1998;26(2):76–81.
21. Yang JW, Wang LQ, Zou X, Yan SY, Wang Y, Zhao JJ, et al. Effect of Acupuncture for Postprandial Distress Syndrome: A Randomized Clinical Trial. Ann Intern Med. 2020;172(12):777–85.
22. Francis CY, Morris J, Whorwell PJ. The irritable bowel severity scoring system: a simple method of monitoring irritable bowel syndrome and its progress. Aliment Pharmacol Ther. 1997;11(2):395–402.
23. Patrick DL, Drossman DA, Frederick IO, DiCesare J, Puder KL. Quality of life in persons with irritable bowel syndrome: development and validation of a new measure. Dig Dis Sci. 1998;43(2):400–11.

24. Kaptchuk TJ, Kelley JM, Conboy LA, Davis RB, Kerr CE, Jacobson EE, et al. Components of placebo effect: randomised controlled trial in patients with irritable bowel syndrome. Bmj. 2008;336(7651):999–1003.
25. Yang L, Lu Y, Ding G, Zhang H, Ma X, Bao C, et al. Effect of warming moxibustion Tianshu (ST 25, bilateral) and Qihai (CV 6) for the treatment of diarrhea-dominant irritable bowel syndrome: a patient-blinded pilot trial with orthogonal design. J Tradit Chin Med. 2017;37(4):538–45.
26. Zhao JM, Wu LY, Liu HR, Hu HY, Wang JY, Huang RJ, et al. Factorial study of moxibustion in treatment of diarrhea-predominant irritable bowel syndrome. World J Gastroenterol. 2014;20(37):13563–72.
27. Park JW, Lee BH, Lee H. Moxibustion in the management of irritable bowel syndrome: systematic review and meta-analysis. BMC Complement Altern Med. 2013;13:247.
28. Shi Y, Chen YH, Yin XJ, Wang AQ, Chen XK, Lu JH, et al. Electroacupuncture versus Moxibustion for Irritable Bowel Syndrome: A Randomized, Parallel-Controlled Trial. Evid Based Complement Alternat Med. 2015;2015:361786.
29. Ma XP, Hong J, An CP, Zhang D, Huang Y, Wu HG, et al. Acupuncture-moxibustion in treating irritable bowel syndrome: how does it work? World J Gastroenterol. 2014;20(20):6044–54.
30. Wang X, Qi Q, Wang Y, Wu H, Jin X, Yao H, et al. Gut microbiota was modulated by moxibustion stimulation in rats with irritable bowel syndrome. Chin Med. 2018;13:63.
31. Bao CH, Wang CY, Li GN, Yan YL, Wang D, Jin XM, et al. Effect of mild moxibustion on intestinal microbiota and NLRP6 inflammasome signaling in rats with post-inflammatory irritable bowel syndrome. World J Gastroenterol. 2019;25(32):4696–714.
32. Zhao JM, Chen L, Zhou CL, Shi Y, Li YW, Shang HX, et al. Comparison of Electroacupuncture and Moxibustion for Relieving Visceral Hypersensitivity in Rats with Constipation-Predominant Irritable Bowel Syndrome. Evid Based Complement Alternat Med. 2016;2016:9410505.
33. Qi Q, Wu H, Jin X, Jin D, Wang Y, Wang C, et al. Effect of moxibustion on the expression of GDNF and its receptor GFRα3 in the colon and spinal cord of rats with irritable bowel syndrome. Acupunct Med. 2019;37(4):244–51.
34. Ma K, Liu Y, Shao W, Sun J, Li J, Fang X, et al. Brain Functional Interaction of Acupuncture Effects in Diarrhea-Dominant Irritable Bowel Syndrome. Front Neurosci. 2020;14:608688.
35. Lin X, Liu X, Xu J, Cheng KK, Cao J, Liu T, et al. Metabolomics analysis of herb-partitioned moxibustion treatment on rats with diarrhea-predominant irritable bowel syndrome. Chin Med. 2019;14:18.

Figures

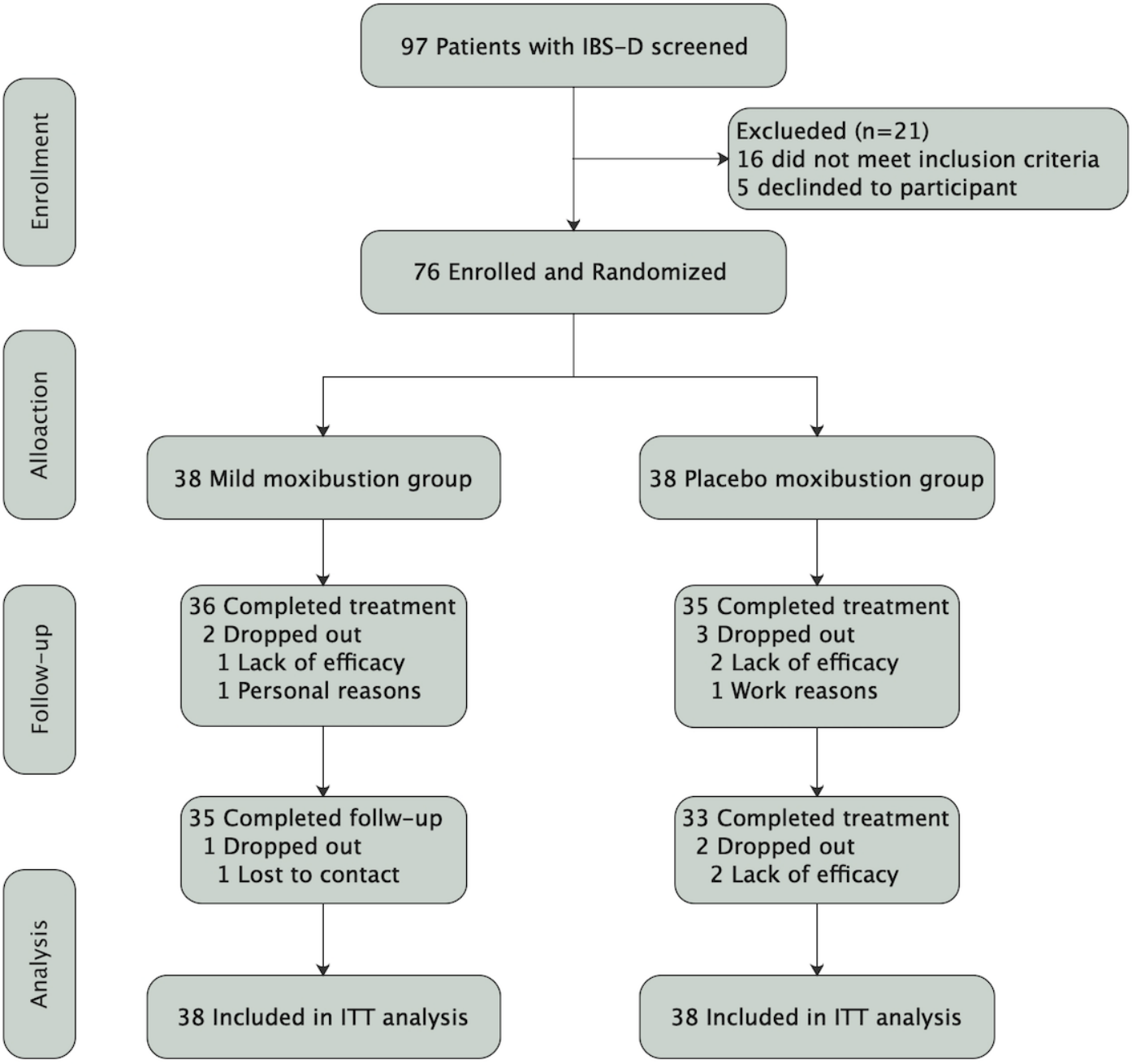

Figure 1

Study flow diagram.

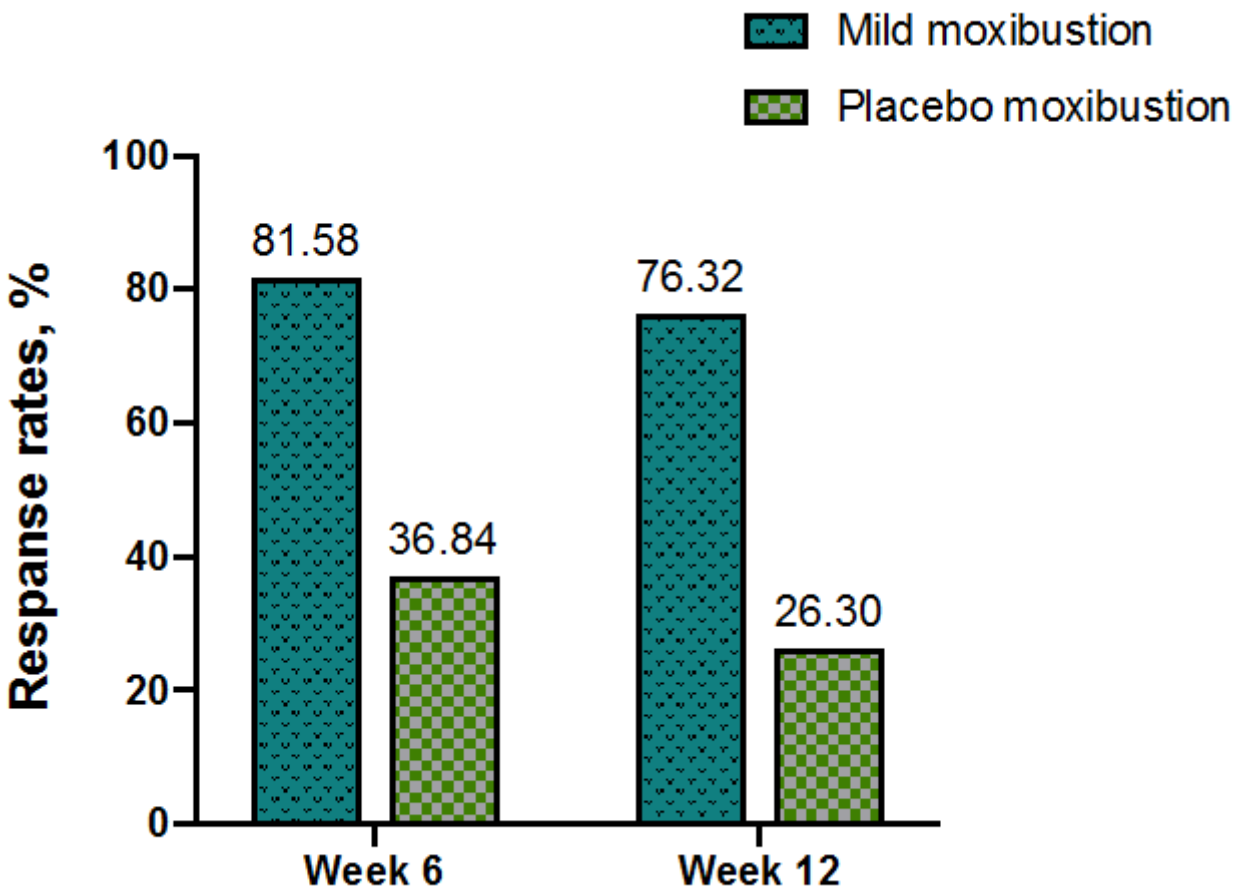

Figure 2

Response rates during the study.