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ORIGINAL ARTICLE

Effect of Acupuncture in Patients With Irritable Bowel Syndrome: A Randomized Controlled Trial

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Abstract

Objective: To evaluate the effect and safety of acupuncture for the treatment of irritable bowel syndrome (IBS) through comparisons with those of polyethylene glycol (PEG) 4000 and pinaverium bromide.

Patients and Methods: This multicenter randomized controlled trial was conducted at 7 hospitals in China and enrolled participants who met the Rome III diagnostic criteria for IBS between May 3, 2015, and June 29, 2018. Participants were first stratified into constipation-predominant or diarrhea-predominant IBS group. Participants in each group were randomly assigned in a 2:1 ratio to receive acupuncture (18 sessions) or PEG 4000 (20 g/d, for IBS-C)/pinaverium bromide (150 mg/d, for IBS-D) over a 6-week period, followed by a 12-week follow-up. The primary outcome was change in total IBS-Symptom Severity Score from baseline to week 6.

Results: Of 531 patients with IBS who were randomized, 519 (344 in the acupuncture group and 175 in the PEG 4000/ pinaverium bromide group) were included in the full analysis set. From baseline to 6 weeks, the total IBS-Symptom Severity Score decreased by 123.51 (95% CI, 116.61 to 130.42) in the acupuncture group and 94.73 (95% CI, 85.03 to 104.43) in the PEG 4000/pinaverium bromide group. The between-group difference was 28.78 (95% CI, 16.84 to 40.72; $P<.001$). No participant experienced severe adverse effects.

Conclusion: Acupuncture may be more effective than PEG 4000 or pinaverium bromide for the treatment of IBS, with effects lasting up to 12 weeks.

Trial Registration: Chinese Clinical Trials Register, ChiCTR-IOR-15006259.

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Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder characterized by abdominal pain or discomfort that is associated with stool irregularities.[1] IBS is estimated to affect approximately 11.2% of the world's population, with a prevalence of 7.1% in North America[2] and 5.9% in South-East China.[3] This disorder has a marked negative impact on quality of life (QOL) and disease burden. Constipation-predominant IBS (IBS-C) and diarrhea-predominant IBS (IBS-D) are the 2 main subtypes of IBS and account for two-thirds of all affected individuals.[4]

Due to a lack of understanding of the pathophysiology of IBS, the treatment strategy focuses on symptom management rather than disease modification. The current management for IBS includes lifestyle modification, specialized diets, psychological treatment, and pharmacologic therapies.[5] Various drugs are used for pharmacologic treatment, including antispasmodics, low-dose antidepressants, laxatives, and

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antidiarrheals,[6] and drugs are prescribed with the aim of altering problematic bowel habits and/or alleviating abdominal pain. However, such medications provide only temporary relief from symptoms, and high relapse rates (~40% on treatment discontinuation after 3 months) have been observed.[7] A large proportion of patients (60.1%) reportedly discontinued medication because of dissatisfaction attributed to few symptom improvements.[8]

Moreover, the side effects, including headache, dizziness, dry mouth, and insomnia, cannot be neglected. In particular, severe adverse events (AEs) such as cardiovascular disorders and ischemic colitis may occur with long-term use.[9] In summary, unsatisfactory treatment responses and AEs associated with pharmacologic therapies have resulted in a higher demand for alternative therapies.[10]

Acupuncture is considered a beneficial alternative treatment for functional gastrointestinal disorders.[11] One meta-analysis suggested promising benefits of acupuncture in terms of symptom control and QOL improvements in patients with IBS. However, several randomized controlled trials had methodologic limitations affecting the quality of evidence, such as the absence of patient blinding, unrestricted randomized schemes, small sample size, and lack of allocation concealment.[12] In our pilot studies, we compared the efficacy of acupuncture with that of pinaverium bromide and lactulose in patients with IBS-D (n= 70) and IBS-C (n= 60), respectively, and found that acupuncture resulted in greater symptom improvements, fewer side effects, long-term effects, and lower relapse rates.[13,14] However, these studies were single-center studies with small patient samples. Therefore, a multicenter randomized controlled trial with high methodologic quality was considered necessary.

Accordingly, we designed the present multicenter randomized controlled trial to evaluate the effect and safety of acupuncture for the treatment of IBS.[15] Our hypothesis was that 6-week acupuncture treatment would be more effective than polyethylene glycol (PEG 4000)/pinaverium bromide in the alleviation of IBS symptoms.

PATIENTS AND METHODS

Study Design

This multicenter randomized controlled trial was conducted in 7 hospitals in China (ChiCTR-IOR-15006259). The trial was performed over a period of 20 weeks, including a 1-week wash-out period, 1-week baseline assessment period, 6-week treatment period, and 12-week posttreatment follow-up period. Ethical approval was obtained from the ethics committee of Jiangsu Province Hospital of Chinese Medicine, which was overseeing all 7 hospitals. Written informed consent was obtained from all participants. The study was conducted from May 3, 2015, through June 29, 2018.

Participants

Participants were recruited from the outpatient centers of the 7 hospitals and surrounding communities. Participants were considered eligible if they fulfilled the Rome III diagnostic criteria and Bristol Form Scale for IBS-C and IBS-D,[16] were 18 to 70 years old, had IBS for 6 or more months, and had a baseline IBS-Symptom Severity Score (IBS-SSS) of 75 or higher. All participants voluntarily joined this trial. Major exclusion criteria were IBS with mixed bowel habits or unsubtyped IBS, organic intestinal diseases, and a history of abdominal and/or rectal surgery.

Randomization and Masking

First, all eligible participants were stratified into IBS-C and IBS-D subgroups. Next, participants within each stratum were randomly divided into acupuncture and PEG 4000/pinaverium bromide groups in a 2:1 allocation ratio. Patients with IBS-C received PEG 400 and patients with IBS-D received pinaverium bromide. The randomization sequences were generated by SAS, version 9.4 (SAS Institute Inc), with a dynamic block size. The outcome assessors, data manager, and statisticians were blinded to group allocation.

Interventions

Acupuncture Group. Hwato brand disposable sterile needles (size 0.30×40 mm) were used to stimulate the Baihui (GV20), Yintang (GV29), Taichong (LR3), Zusanli (ST36), Sanyinjiao (SP6), Tianshu (ST25), and Shangjuxu (ST37) acupoints in the supine position. After skin disinfection, the needles were slowly and vertically inserted 25 mm into SP6, ST36, and ST37; 25 to 40 mm into ST25; and 15 mm into LR3. Needles were horizontally inserted 15 mm into GV20 and GV29. Small equal manipulations involving twirling, lifting, and thrusting were implemented every 10 minutes to elicit deqi, a sensation of soreness, numbness, heaviness, and distention. The needles were retained for 30 minutes. Acupuncture treatment was performed once every other day, 3 times a week for 6 weeks (total 18 sessions); this was considered an ideal treatment regimen. Our pilot studies suggested that the same acupuncture treatment for patients with either IBS-C or IBS-D exhibited satisfying efficacy in terms of symptom control.[14,17] These results were consistent with the bidirectional regulation effect of acupuncture.

PEG 4000/Pinaverium Bromide Group. According to the American Gastroenterological Association guideline and World Gastroenterology Organisation Global guideline,[18,19] participants in the PEG 4000/pinaverium bromide group received pharmacologic treatment according to their IBS subtype for 6 weeks. Participants with IBS-C received 2 sachets of oral PEG 4000 powder (Forlax, 10-g powder; Beaufour Ipsen Pharma) daily. Participants with IBS-D received oral pinaverium bromide tablets (Dicetel, 50-mg tablet; Abbott Products SAS) thrice daily.

All participants were advised to follow their routine lifestyles and diets during the study period. In case of constipation for 3 or more consecutive days, 20 mL of glycerol or sorbitol anal enema was prescribed. In case of 5 or more defecation episodes per day, loperamide, 2 mg (Imodium, 2-mg capsule; Xian Janssen Pharmaceutical Ltd) was prescribed. All rescue medication use was documented in the case report form.

Measurements

Participants completed the self-reported IBS-SSS questionnaire[20] at baseline and weeks 1, 2, 4, 6, and 18. The IBS-SSS comprises 5 domains that are scored from 0 to 100 (total score, 0-500). These domains measure the severity of abdominal pain, number of days in pain every 10 days, severity of abdominal distention, satisfaction with bowel habits, and interference of IBS with life in general. A decrease of 50 points is adequate to reliably indicate clinical improvement.[20]

The IBS-Quality of Life (IBS-QOL) questionnaire[21,22] was also administered at baseline and weeks 6 and 18. The IBS-QOL comprises 34 IBS-specific items, with the following 8 subscales: dysphoria, interference with activity, body image, health worry, food avoidance, social reaction, sexual concerns, and relationships. Higher scores indicate better QOL. A meaningful clinical response is represented by an increase of at least 14 points.[23]

Outcomes and Follow-Up

The primary outcome was change in total IBS-SSS from baseline to week 6. Secondary outcomes included changes in total IBS-SSS from baseline to weeks 1, 2, 4, and 18; changes in IBS-SSS for each domain, total IBS-QOL scores, and subscale IBS-QOL scores from baseline to week 6; and proportion of participants using rescue medicine.

The AEs were appropriately assessed, managed, and categorized by the acupuncturists and related clinical specialists. All AEs were documented in the case report form, and severe AEs had to be reported to the principal investigator and medical ethics committees within 24 hours after occurrence.

Statistical Analyses

According to our previous pilot study, we anticipated a decrease of 115 and 105 points in total IBS-SSS for the acupuncture and control groups from baseline to week 6. Two-sided tests were performed. The

standard deviation was set at 37. Sample size was calculated with 80% power and 2-sided significance level of 5%. The required sample size was 322, with 161 participants in each group. The estimated dropout rate in our protocol was 20%; this was changed to 10% after considering the high treatment acceptance rates. Eventually, 354 and 177 participants were enrolled in the acupuncture and PEG 4000/pinaverium bromide groups, respectively.

All analyses were based on the intention-to-treat population, defined as all randomly assigned participants with baseline data. Missing data were imputed using the last-observation-carried-forward method. The primary outcome was assessed using analysis of covariance and adjusted for baseline total IBS-SSS. The same approach was used for changes in total IBS-SSS at weeks 1, 2, 4, and 18. For other numerical variables, between-group comparisons were assessed using *t* tests or Wilcoxon rank sum tests as appropriate. For categorical variables, χ^2 tests or Fisher exact tests were used.

In the post hoc analysis, responders were defined as participants with a decrease of 50 or more points in the total IBS-SSS at week 6. The responder rate was estimated using χ^2 tests.

We also conducted 2 post hoc subgroup analyses to assess the effects of IBS subtype on change in the total IBS-SSS at week 6 (Supplemental Figure, available online at http://www.mayoclinicproceedings.org).

Three sensitivity analyses were conducted to assess the robustness of the results. First, we conducted analyses based on per-protocol analyses, wherein participants completed the treatment protocol. Second, changes in total IBS-SSS from baseline to weeks 6 and 18 were analyzed by fitting a mixed-effect model. Third, changes in IBS-SSS and IBS-QOL total score from baseline were examined using multivariate regression analysis (Supplemental Tables 1-3, available online at http://www.mayoclinicproceedings.org).

All statistical analyses were performed using SAS, version 9.4 (SAS Institute Inc). A 2-sided $P<.05$ was considered statistically significant.

RESULTS

Participant Characteristics

789 participants were screened from 7 sites. After excluding 258 participants, 531 (mean age, 46.03±13.03 years; 51.22% [272 of 531] men; mean disease duration, 7.62±8.00 years) were enrolled. After randomization, 12 participants withdrew their consents (2 in the PEG 4000/pinaverium bromide group and 4 in the acupuncture group withdrew because the treatment was not consistent with their expectation, while the other 6 participants in the acupuncture group did not have the time for high-frequency acupuncture interventions). The remaining 519 participants (344 in the acupuncture group and 175 in the PEG 4000/pinaverium bromide group) with baseline data were included in the full analysis set, and 467 (89.98%) participants completed the study (Figure 1). Compliance rates were 91.28% (314 of 344) and 87.43% (153 of 175) in the acupuncture and PEG 4000/pinaverium bromide groups, respectively. Missing data at week 6 were imputed for 36 participants (19 in the acupuncture group and 17 in the PEG 4000/pinaverium bromide group). Baseline demographic and clinical characteristics, except for total IBS-SSS and severity of abdominal distention, were similar between groups (Table 1).

Efficacy Analyses

Mean total IBS-SSS and domain scores at baseline and weeks 1, 2, 4, 6, and 18 are shown in Figure 2 and Supplemental Table 4 (available online at http://www.mayoclinicproceedings.org). The decrease from baseline in total IBS-SSS at week 6 was greater in the acupuncture group (123.51) than in the PEG 4000/pinaverium bromide group (94.73), with a mean difference of 28.78 (95% CI, 16.84-40.72; $P<.001$; Table 2). Similar results were observed in sensitivity analyses (Supplemental Tables 1-3) and for all subgroups except the IBS-C group (Supplemental Figure).

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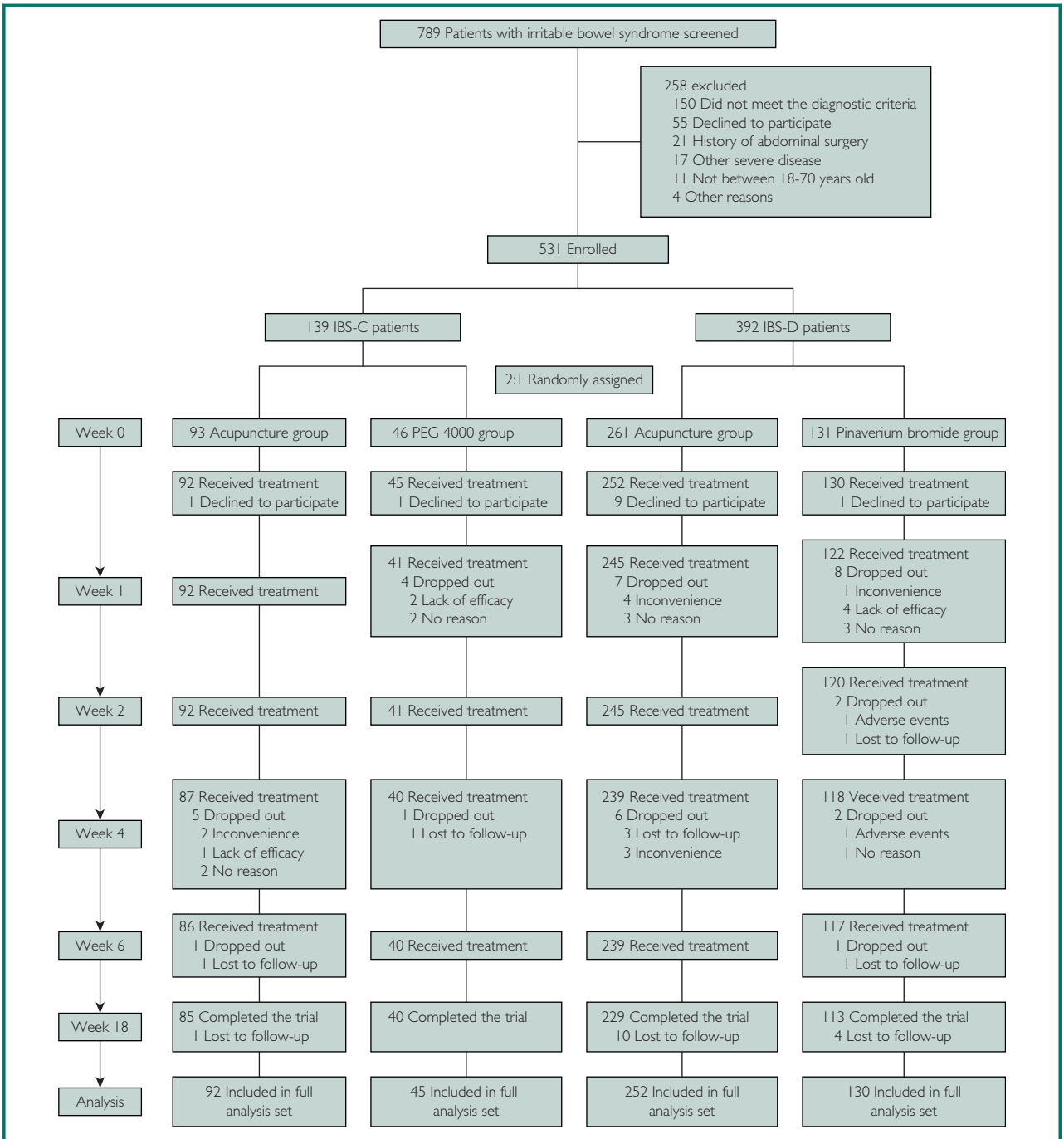

FIGURE 1. Study flow chart shows the inclusion of patients with irritable bowel syndrome (IBS) treated by acupuncture or polyethylene glycol 4000/pinaverium bromide. IBS-C = constipation-predominant irritable bowel syndrome; IBS-D = diarrhea-predominant irritable bowel syndrome.

Decreases in total IBS-SSS at weeks 1, 2, 4, and 18 (vs baseline) were also greater in the acupuncture group than in the PEG 4000/pinaverium bromide group ($P<.05$ for all). Decreases in all domain scores at week 6 (vs baseline) were greater in the acupuncture group than in the PEG 4000/pinaverium bromide group ($P<.05$ for all). No

TABLE 1. Participant Baseline Characteristics[a]

Characteristics	Acupuncture Group (n=344)	PEG 4000/Pinaverium Bromide Group (n=175)
Age (y), mean ± SD	45.89±13.01	47.00±12.73
Sex, n (%)[b]		
Male	177 (51.75)	88 (50.29)
Female	165 (48.25)	87 (49.71)
Race, n (%)		
Han	338 (98.26)	173 (98.86)
Minorities	6 (1.74)	2 (1.14)
Weight (kg), mean ± SD	63.00±10.74	63.07±10.30
Marital status, n (%)		
Married	320 (93.02)	167 (95.43)
Unmarried	24 (6.98)	8 (4.57)
Education, n (%)[c]		
Primary education or less	41 (12.13)	15 (8.67)
Secondary education	137 (40.53)	78 (45.09)
Tertiary education	160 (47.34)	80 (46.24)
Coexisting illness, n (%)		
Digestive system disease	9 (2.62)	5 (2.86)
Diabetes	2 (0.58)	1 (0.57)
Hypertension	3 (0.87)	3 (1.71)
Other	18 (5.23)	13 (7.43)
Subtypes of IBS, n (%)		
IBS-C	92 (26.74)	45 (25.71)
IBS-D	252 (73.26)	130 (74.29)
Years with IBS, mean ± SD	7.89±8.17	7.26±7.72
Patients who used treatments for IBS, n (%)		
Chinese medicine	57 (16.57)	25 (14.29)
Pharmacologic medication	25 (7.27)	13 (7.43)
Acupuncture	2 (0.58)	2 (1.14)
Other	10 (2.91)	7 (4.00)
Total IBS-SSS, mean ± SD[d]	246.44±82.94	225.88±86.78
Severity of abdominal pain, mean ± SD	35.74±28.17	32.31±27.20
No. of days in pain every 10 d, mean ± SD	3.34±2.91	2.91±2.60
Severity of abdominal distension, mean ± SD[e]	39.15±28.67	31.11±29.61
Satisfaction with bowel habits, mean ± SD	71.73±18.77	68.11±21.53
Interference of IBS with life in general, mean ± SD	66.38±19.48	65.25±21.17
IBS-QOL scores, mean ± SD[f]	67.70±18.93	70.64±18.59

[a]IBS = irritable bowel syndrome; IBS-C = constipation-predominant irritable bowel syndrome; IBS-D = diarrhea-predominant irritable bowel syndrome; IBS-QOL = Irritable Bowel Syndrome—Quality of Life; IBS-SSS = Irritable Bowel Syndrome—Symptom Severity Score; PEG = polyethylene glycol; QOL = quality of life.

[b]Two participants in the acupuncture group had no history of gender.

[c]Six participants in the acupuncture group and 2 participants in the PEG 4000/pinaverium group had no history of education.

[d]IBS-SSS with the overall score of 0 to 500 is composed of 5 domains scored from 0 to 100 that measure the severity of pain, duration of pain, severity of abdominal distention, satisfaction with bowel habits, and interference of IBS with life in general. Higher scores indicate more severe symptoms. A statistical between-group difference with total IBS-SSS ($P<.01$).

[e]A statistical between-group difference with the score for the severity of abdominal distention ($P<.01$).

[f]The IBS-QOL measure is validated to assess impairment of QOL in IBS. The IBS-QOL measure consists of 34 IBS-specific items. A 5-point Likert response scale (1-5) was recorded in each item (not at all, slightly, moderately, quite a bit, and extremely or a great deal). The sum of the items is transformed into a score (100 = maximum QOL). Higher scores indicated better QOL.

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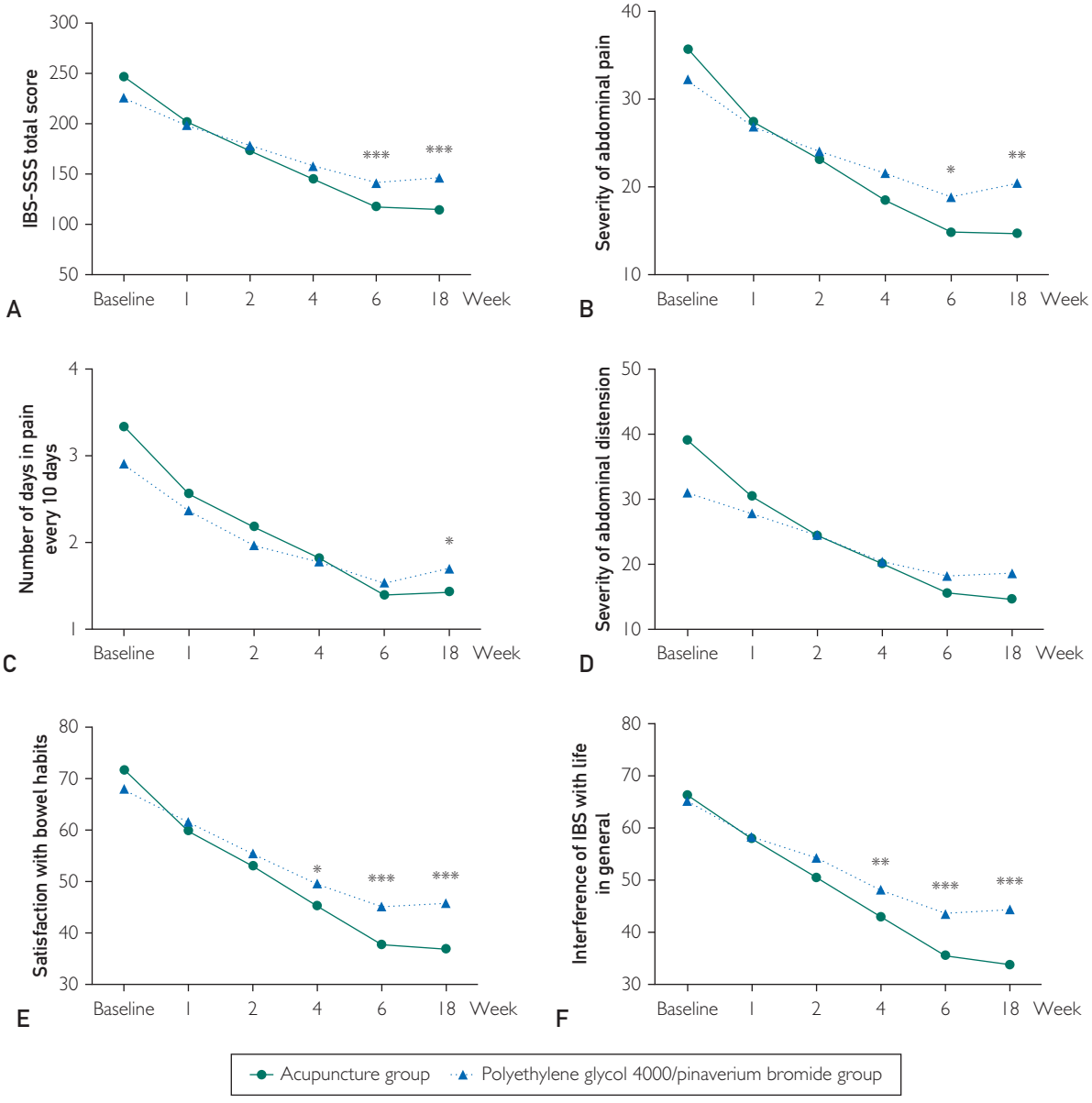

FIGURE 2. Analysis of the mean total Irritable Bowel Syndrome—Symptom Severity Score (IBS-SSS) and scores for its individual domains at baseline and weeks 1, 2, 4, 6, and 18 after treatment initiation for irritable bowel syndrome (IBS). A, Mean total IBS-SSS shows a decrease in both the acupuncture group and polyethylene glycol (PEG) 4000/pinaverium bromide groups. At week 18, the score for the PEG 4000/pinaverium bromide group shows a slight increase. At weeks 6 and 18, scores for the acupuncture group are significantly lower than those for the PEG 4000/pinaverium bromide group ($P<.001$ for all). B-F, Trends similar to those in (A) can be seen. (B), At weeks 6 and 18, abdominal pain is significantly milder in the acupuncture group than in the PEG 4000/pinaverium bromide group ($P=.04$, $P=.004$, respectively). (C), The frequency of abdominal pain is significantly lower in the acupuncture group than in the PEG 4000/pinaverium bromide group at week 18 ($P=.02$). (E), Participants in the acupuncture group are significantly more satisfied with their bowel habits at weeks 4, 6, and 18 than participants in the PEG 4000/pinaverium bromide group ($P=.02$, $P<.001$, $P<.001$, respectively). (F), At weeks 4, 6, and 18, interference of IBS with daily life is lesser in the acupuncture group than in the PEG 4000/pinaverium bromide group ($P=.005$, $P<.001$, $P<.001$, respectively). *$P<.05$; **$P<.01$; ***$P<.001$.

TABLE 2. Primary and Secondary Outcomes[a]

Variable	Acupuncture Group (n=344)	Polyethylene Glycol 4000/Pinaverium Bromide Group (n=175)	Difference (95% CI)	P[b]
Primary outcome				
Change in total IBS-SSS at wk 6, adjusted mean (95% CI)[c]	123.51 (116.61 to 130.42)	94.73 (85.03 to 104.43)	28.78 (16.84 to 40.72)	<.001
Secondary outcomes				
Change, total IBS-SSS, adjusted mean (95% CI)[d]				
Wk 1	42.48 (36.66 to 48.30)	31.97 (23.79 to 40.15)	10.51 (0.44 to 20.58)	.04
Wk 2	69.83 (63.91 to 75.76)	54.42 (46.10 to 62.74)	15.41 (5.17 to 25.65)	.003
Wk 4	97.12 (90.62 to 103.61)	76.45 (67.33 to 85.57)	20.67 (9.44 to 31.90)	<.001
Wk 18	127.21 (119.70 to 134.72)	88.60 (78.04 to 99.15)	38.61 (25.62 to 51.61)	<.001
Change, each domain score of IBS-SSS at wk 6, mean ± SD[e]				
Severity of abdominal pain	20.92±25.41	13.43±21.48	NA	.003
No. of d in pain every 10 d	1.95±2.51	1.37±2.03	NA	.003
Severity of abdominal distension	23.52±26.09	12.89±24.18	NA	<.001
Satisfaction with bowel habits	33.91±25.78	22.94±24.22	NA	<.001
Interference of IBS with life in general	30.81±25.71	21.68±24.45	NA	<.001
Change, IBS-QOL total score, mean (95% CI)				
Wk 6	13.35 (11.67 to 15.02)	8.95 (6.81 to 11.10)	4.39 (1.60 to 7.19)	.002
Wk 18	16.17 (14.27 to 18.06)	9.32 (6.99 to 11.65)	6.85 (3.85 to 9.85)	<.001
Change, each subscale score in IBS-QOL at wk 6, mean ± SD[f]				
Dysphoria	15.58±18.23	10.82±17.46	NA	<.001
Interference with activity	13.49±17.87	8.24±16.08	NA	<.001
Body image	13.15±18.57	7.89±17.19	NA	<.001
Health worry	18.19±21.79	11.90±21.00	NA	<.001
Food avoidance	14.51±20.93	10.38±17.94	NA	.03
Social reaction	12.75±18.84	8.29±14.41	NA	.007
Sexual concerns	6.69±17.80	6.07±16.62	NA	.56
Relationships	14.61±18.45	10.24±17.63	NA	.001
Patients using other measures for IBS, n (%)				
Wk 1-6				
Rescue medicine	23 (6.69)	12 (6.86)	−0.17 (−4.75 to 4.41)	0.94
Other	3 (0.87)	3 (1.71)	−0.84 (−3.00 to 1.32)	0.40
Wk 6-18				
Rescue medicine	36 (10.47)	29 (16.57)	−6.11 (−12.49 to 0.28)	0.047
Other	7 (2.03)	4 (2.29)	−0.25 (−2.92 to 2.42)	0.85

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TABLE 2. Continued

Variable	Acupuncture Group (n=344)	Polyethylene Glycol 4000/Pinaverium Bromide Group (n=175)	Difference (95% CI)	P[b]
Post hoc analysis				
Responder rate, n (%)[g]				
Wk 6	272 (79.07)	99 (56.57)	22.50 (13.99 to 31.01)	<.001
Wk 18	285 (82.85)	89 (50.86)	31.99 (23.58 to 40.40)	<.001

[a]IBS = irritable bowel syndrome; IBS-QOL= Irritable Bowel Syndrome−Quality of Life; IBS-SSS= Irritable Bowel Syndrome−Symptom Severity Score; NA= not applicable.
[b]All tests were 2 sided. $P<.05$ was considered significant.
[c]The primary outcome was analyzed with analysis of covariates and adjusted for baseline total IBS-SSS.
[d]Change from baseline on IBS-SSS total score at weeks 1, 2, 4, and 18 was analyzed with analysis of covariates and adjusted for baseline total IBS-SSS.
[e]Change of each domain in IBS-SSS was assessed using Wilcoxon rank sum test. Between-group differences were not provided.
[f]Change of each item in IBS-QOL was estimated using Wilcoxon rank sum test. Between-group differences were not provided.
[g]Patients with a reduction of 50 points or more on IBS-SSS total score were defined as responders.

significant between-group difference was noted in the rate of rescue medication use over weeks 1 to 6. However, this rate was significantly lower in the acupuncture group than in the PEG 4000/pinaverium group over weeks 6 to 18, with a difference of −6.11% (95% CI, −12.49% to 0.28%; $P=.047$).

The increase in IBS-QOL total score at week 6 was greater in the acupuncture group (13.35) than in the PEG 4000/pinaverium group (8.95), with a between-group difference of 4.39 (95% CI, 1.60-7.19; $P=.002$). A similar result was observed at week 18, with a between-group difference of 6.85 (95% CI, 3.85-9.85; $P<.001$). Six-week changes in all subscale scores ($P<.05$ for all) except the score for sexual concern ($P=.56$) were greater in the acupuncture group.

Post Hoc Analysis

The responder rate was significantly higher in the acupuncture group than in the PEG 4000/pinaverium bromide group, with between-group differences of 22.50% (95% CI, 13.99% to 31.01%; $P<.001$) and 31.99% (95% CI, 23.58% to 0.40%; $P<.001$) at weeks 6 and 18, respectively.

Safety Analyses

Acupuncture-related AEs occurred in 4.07% (14 of 344) of participants in the acupuncture group. Complications included subcutaneous hematoma and sharp pain. All acupuncture-related AEs were transient and required no specific treatment. No patient exhibited severe AEs (Table 3).

DISCUSSION

This multicenter trial found that acupuncture was more effective than PEG 4000/pinaverium bromide in alleviating IBS symptoms and improving QOL over a 6-week treatment period and 12-week follow-up period. There were no severe AEs.

The total IBS-SSS exhibited a mean decrease of 123.51 points from baseline to 6 weeks in the acupuncture group. This is consistent with findings from previous IBS studies, in which acupuncture resulted in a

TABLE 3. Adverse Events[a]

Adverse Event	Acupuncture Group (n=344)		Polyethylene Glycol 4000/Pinaverium Bromide Group (n=175)	
	Participants, n (%)	Events, n	Participants, n (%)	Events, n
Acupuncture-related adverse events				
Severe adverse events	0 (0.00)	0	0 (0.00)	0
Subcutaneous hematoma	12 (3.49)	15	0 (0.00)	0
Sharp pain	2 (0.58)	2	0 (0.00)	0
Acupuncture-unrelated adverse events				
Severe adverse events	0 (0.00)	0	0 (0.00)	0
Digestive system				
Constipation[b]	27 (7.85)	33	16 (9.14)	22
Diarrhea[c]	31 (9.01)	39	24 (13.71)	31
Dry mouth	1 (0.29)	1	3 (1.71)	4
Nausea	2 (0.58)	2	5 (2.86)	5
Vomiting	0 (0.00)	0	1 (0.57)	1
Respiratory system				
Upper respiratory tract infection	15 (4.36)	15	6 (3.43)	6
Nervous system				
Dizziness	1 (0.29)	1	4 (2.29)	4
Headache	1 (0.29)	1	0	0
Other				
Itchy skin	0	0	1 (0.57)	1

[a]Adverse events were analyzed in all participants who received treatment. Adverse events were counted by both type and frequency.
[b]Included new constipation caused by treatment or worse constipation.
[c]Included new diarrhea caused by treatment or worse diarrhea.

decrease of 78.4 to 215 points relative to baseline.[24,25] Another study demonstrated that acupuncture provided additional benefits over those of conventional primary care for IBS.[25] Meanwhile, our trial aimed to assess the effects of acupuncture through direct comparisons with PEG 4000/pinaverium bromide, which enabled us to demonstrate its clinical value in a better manner. In our study, 79.07% (272 of 344) of participants demonstrated a decrease of 50 or more points in total IBS-SSS, which is adequate to indicate clinical improvement.[20] In another study, the responder rate for acupuncture treatment with a total of 6 sessions over 3 weeks was 36%.[26] Our responder rate was likely higher because 18 acupuncture sessions over 6 weeks may have been sufficient to achieve maximum effects. Thus, our trial showed that acupuncture may have clinically meaningful benefits in IBS treatment.

The American Gastroenterological Association guideline suggests that PEG laxatives may be useful for constipation relief in IBS-C, with few reported side effects and low cost.[18] Pinaverium bromide is recommended as the first-line therapy for short-term relief from IBS-D symptoms.[19] Accordingly, we selected PEG 4000 and pinaverium bromide as the control medicines. Until now, no previous studies have used IBS-SSS to assess the effects of PEG 4000/pinaverium bromide for IBS treatment. We found that PEG 4000/pinaverium bromide decreased the total IBS-SSS by 94.73 points from baseline to week 6. However, the total IBS-SSS and responder rate at week 6 were lower and higher in the acupuncture group than in the PEG 4000/pinaverium bromide group, respectively. This result was comparable with those of 3 previous trials.[17,27,28] Notably, the results favored acupuncture over pinaverium for

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IBS-D treatment, whereas the efficacies of acupuncture and PEG 4000 for IBS-C were comparable. A statistically significant between-group difference in favor of acupuncture was observed for 4 domains of IBS-SSS. We found that acupuncture could lower the severity of abdominal pain and distention. Moreover, participants in the acupuncture group were more satisfied with their bowel habits and found that IBS had less interference with daily life after a 6-week treatment period.

The IBS-QOL is a validated tool for assessing IBS-associated QOL impairments. Baseline and posttreatment changes in IBS-QOL total score at week 6 in the PEG 4000/pinaverium bromide group were 70.64 and 8.95, respectively, similar to the findings in a previous cohort study (76.4 and 7.7-10.4, respectively).[29] However, the increase in IBS-QOL total score was greater in our acupuncture group at weeks 6 and 18 (vs baseline). An increase of 14 points represents a meaningful clinical response.[23] At week 18, the mean increase in the IBS-QOL total score was 16.17, which is indicative of clinically meaningful effects of acupuncture in terms of QOL improvements.

At the end of the 12-week follow-up period, changes in total IBS-SSS and IBS-QOL total score in the acupuncture group were greater than those in the PEG 4000/pinaverium bromide group. This suggests that acupuncture may have a satisfying long-term effect, which is critical for the prevention of IBS recurrence. Similarly, 2 previous trials assessing the long-term effects of acupuncture for IBS suggested that its benefits could persist for 12 months.[25,30] Although the potential mechanism of these long-term effects has not been well investigated, we speculate that the effects might be associated with regulation of the brain-gut axis. An animal study of IBS reported that receptor $P2X_3$ in the peripheral and central nervous systems was downregulated after the electroacupuncture treatment.[31] Meanwhile, our previous study showed that acupuncture could restore the brain-gut axis to a balanced level through neurotransmitter regulation.[32] Further studies need to investigate the mechanism underlying the long-term effects of acupuncture.

The strengths of our study are as follows. First, our study expanded on previous trials that compared acupuncture and pharmacologic therapies[12] by using a larger sample size of 531 participants. Second, it was a multicenter trial with 7 sites following a standard protocol. Participants were recruited from hospitals and surrounding communities, which increases the generalizability of our findings. Third, although we did not include a wait-list group, the 12-week follow-up period in the medication group could be seen as intrinsic nature of IBS. The long-term effect of acupuncture could be assessed by ruling out the possibility of remission by the disease itself. Therefore, we directly demonstrated the clinical value of acupuncture for IBS treatment.

This study also has limitations. First, sham acupuncture was not used to eliminate the placebo effect. However, our results could not be explained simply by the placebo effect. Our responder rate of acupuncture (79.07%; 272 of 344) was much higher than a previously reported rate of sham acupuncture (31.2%).[33] Furthermore, the same benefits in the acupuncture group lasted more than 12 weeks after treatment discontinuation, which could not be easily explained by the mere placebo effect, which recedes with time in patients with IBS.[34]

Second, we did not assess patient expectations. It seems that acupuncture may elicit expectation effects. However, Chinese patients do not have high expectations for acupuncture. One study found that 87% of Australian patients and 40% to 45% Chinese patients were willing to receive acupuncture to reduce postoperative nausea and vomiting.[35,36] In addition, a study showed that only 29.18% of patients with IBS believed that acupuncture could improve their symptoms.[25]

Third, our patients were not blinded, which could have led to performance bias.

Nevertheless, the outcome assessors were blinded to the group allocation, reducing the possibility of bias.

Fourth, we primarily assessed the overall efficacy of acupuncture for IBS, although exploratory subgroup analysis of IBS-C and IBS-D found that the effect of acupuncture was satisfactory for IBS-D, but not for IBS-C. The sample size for IBS-C was insufficient; therefore, we could not determine the subtype that can benefit more from acupuncture treatment.

CONCLUSION

Acupuncture may be more effective than PEG 4000/pinaverium bromide in alleviating the symptoms of IBS, with its effects lasting up to 12 weeks. Further studies that assess patient expectations, placebo effect, and different IBS subtypes are necessary to further clarify our findings.

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **AE** = adverse event; **IBS** = irritable bowel syndrome; **IBS-C** = constipation-predominant irritable bowel syndrome; **IBS-D** = diarrhea-predominant irritable bowel syndrome; **IBS-SSS** = IBS—Symptom Severity Score; **IBS-QOL** = IBS-Quality of Life; **PEG** = polyethylene glycol; **QOL** = quality of life

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