A Treatment Trial of Acupuncture in IBS Patients

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A TREATMENT TRIAL OF ACUPUNCTURE IN IBS PATIENTS

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Abstract

Objective—To compare the effects of true and sham acupuncture in relieving symptoms of IBS.

Methods—A total of 230 adult IBS patients (75% females, average age 38.4 yrs) were randomly assigned to 3 weeks of true or sham acupuncture (6 treatments) following a 3 week 'run-in' with sham acupuncture in an 'augmented' or 'limited' patient-practitioner interaction. A third arm of the study included a waitlist control group. The primary outcome was the IBS Global Improvement Scale (IBS-GIS) (range 1–7); secondary outcomes included IBS Symptom Severity Scale (IBS-SSS), Adequate Relief (IBS-AR) and IBS-Quality of life (IBS-QOL).

Results—Though there was no statistically significant difference between acupuncture and sham acupuncture on the IBS-GIS (41% vs. 32%, p=0.25), both groups improved significantly compared to the wait list control group (37% vs. 4%, p=0.001). Similarly, small differences that were not statistically significant favored acupuncture on the other three outcomes: IBS-AR (59% vs 57%, p=0.83), IBS-SSS (31% vs 21%, p=0.18) and IBS-QOL (17% vs 13%, p=0.56). Eliminating responders during the run-in period did not substantively change the results. Side effects were generally mild and only slightly greater in the acupuncture group.

Conclusion—This study did not find evidence to support the superiority of acupuncture compared to sham acupuncture in the treatment of IBS.

Keywords

acupuncture; IBS; randomized controlled trial

INTRODUCTION

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder characterized by chronic or recurrent abdominal pain or discomfort, usually in the lower abdomen, which is associated with disturbed bowel function and feelings of abdominal distention and bloating [1] that are often relieved by defecation. An estimated 10–15% of adults in North America suffer

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No Conflicts of Interest Exist

from IBS [2], and it is associated with a significant reduction in health related quality of life [3]. IBS is one of the most common reasons for work and school absenteeism [4]. Estimates of annual direct and indirect costs associated with IBS exceed 41 billion dollars in major industrial countries [5].

The pathophysiology of IBS includes alterations in intestinal motility, visceral hypersensitivity and abnormalities in the processing of visceral information. Until recently, most therapies for IBS have been directed at a specific intestinal symptom (e.g., diarrhea, constipation, or abdominal pain) and have not been effective for treating other symptoms associated with IBS. While more recent therapies have shown promise, treatment options for IBS remain limited. Therefore, it is not surprising that many patients with IBS have turned to complementary and alternative medicine (CAM) [6] such as acupuncture. In one survey, approximately one half of subjects with IBS reported using CAM [7].

Acupuncture, an ancient traditional Chinese medical practice, is becoming more widely accepted and used in Western society [8]. Traditional Chinese medicine is based on a theory of energy or life force ("qi") that runs through the body in channels called meridians. Qi is essential to health, and disruptions of this flow, which are believed to contribute to symptoms and diseases, can be corrected at identifiable anatomical locations ("acupoints") with acupuncture. In IBS, acupuncture is believed to alter visceral sensation and motility by stimulating the somatic nervous system and the vagus nerve [9–11].

A 2006 Cochrane Database article reviewed 6 randomized trials using acupuncture in IBS[12]. The studies were generally of poor quality, included relatively small numbers of patients, and differed significantly in acupuncture method utilized. Limitations notwithstanding, this review found inconclusive evidence as to whether acupuncture is superior to sham acupuncture in IBS. Subsequently, Schneider et al. [13] published the results of a well conducted study in which 43 IBS patients were randomized to acupuncture or sham acupuncture. There was no significant difference between the response rates in patients receiving acupuncture and sham acupuncture on a specific quality of life measurement for functional bowel digestive disorders (FBDDQL) [14] although patients in both groups improved significantly compared to baseline.

Our study comparing acupuncture to sham acupuncture was nested within a larger study examining the impact of the patient-practitioner interaction in IBS patients. In this larger study, which served as the run-in period for our study, participants were randomized to three weeks of: 1) waitlist, 2) sham acupuncture (twice a week) with a 'limited' patient-practitioner encounter, or 3) sham acupuncture (twice a week) with an 'augmented' patient-practitioner encounter (i.e, a warm, friendly, and supportive patient-practitioner interaction). The results of this three-week run-in are reported elsewhere [15]. After three weeks, participants receiving sham acupuncture were seamlessly and unknowingly re-randomized to continue for another three weeks on either acupuncture or sham acupuncture with the same 'limited' or 'augmented' patient-practitioner encounter that they had received during the run-in phase of the trial. This second three week period comprises the acupuncture study reported here.

The aims of this trial were threefold: 1) to determine if acupuncture provides greater relief of IBS symptoms than sham acupuncture or waitlist control, 2), to determine if eliminating patients who responded to sham acupuncture during the run-in period (i.e., patients who responded to sham acupuncture during the 3 weeks prior to randomization to acupuncture or sham acupuncture) widens the response rate differences between acupuncture and sham acupuncture, perhaps to the point of statistical significance, and 3) to determine if an 'augmented' patient-practitioner interaction enhances the difference in response rates between acupuncture and sham acupuncture.

METHODS

Study Design

In the larger trial 262 IBS-patients were randomized to a 3 week run-in of either: 1) waitlist (observation), 2) sham acupuncture (2 sessions per week) with a 'limited' patient-practitioner encounter, or 3) sham acupuncture (2 sessions per week) with an 'augmented' patient-practitioner encounter (i.e, a warm, friendly, and supportive patient-practitioner relationship). The larger study explored the effects of placebo and patient-practitioner relationship in IBS and is reported elsewhere [16].

For this study, at the end of week 3 patients who had received sham acupuncture were blindly re-randomized to either acupuncture or continuation of sham acupuncture. This randomization was stratified by the group assignment for the run-in period (augmented versus limited) and by the post run-in pain score (under 30 versus 30 or over on a 100-point visual analog scale). Patients continued with the same 'limited' or augmented' patient-practitioner interaction that they had received during the first 3 weeks of the study. Patients were unaware that only sham acupuncture had been administered during the run-in phase of this study and similarly were unaware of the existence of different patient-practitioner interactions. Patients who were initially in the waitlist control group continued on in this group. Figure 1 reviews the flow of patients through this study.

Treatment and study assessments were performed at the Beth Israel Deaconess Medical Center's General Clinical Research Center (GCRC). The Institutional Review Boards at the Beth Israel Deaconess Medical Center and Harvard Medical School approved the design and all participants provided informed consent.

Subjects—Participants were recruited from advertisements in media, fliers, and referrals from health professionals [17]. All subjects were at least 18 years old and met the Rome II criteria for IBS [18] . In addition, the diagnosis of IBS was confirmed by a board certified gastroenterologist experienced in functional bowel disorders (AJL) who also assessed for 'warning symptoms' (unexplained weight loss, family history of colon cancer or inflammatory bowel disease, and rectal bleeding) [19, 20]. Participants were allowed to continue their IBS medications (e.g., fiber, anti-spasmodics, loperamide) as long as they had been on stable doses for at least 30 days prior to entering the study and agreed not to change medications or dosages during the trial. Patients were also asked not to make significant changes to their diet during the study. Patients were excluded if they had previously received acupuncture, if they had abdominal surgery (excluding cholecystectomy, appendectomy, hysterectomy, hernia repair), or if they were on narcotics or other pain medications (except non-steroidal anti-inflammatory drugs).

Interventions

Acupuncture—For this study we used a manualized acupuncture protocol that combined a fixed number of always used acupuncture points and a menu of optional points that could be applied based on the participant's Chinese medicine diagnosis [21]. This method allows for reproducibility and also the flexibility that many acupuncturists claim is critical for their practice. Accordingly, we chose 6 main fixed acupoints and 11 optional points, which could be selected based on a traditional Chinese acupuncture diagnosis of the individual patient by the acupuncturist. This regimen was developed by a consensus team of eight senior acupuncturists, each with over 15 years of experience. The fixed points are very commonly used in IBS patients and included: Conception Vessel 10, Stomach 25, Liver 3, Spleen 4, Pericardium 6 and Stomach 37. The optional points were Stomach 36 and Conception Vessel 4 (for the Chinese diagnosis of deficiency), Large Intestine 4 Liver 14, (for stagnant qi or

energy), Stomach 40, Large Intestine 11 (for dampness), Stomach 27 (for cold), Conception Vessel 12 (for "retention of food"), Gall Bladder 34 (for "damp heat") and Spleen 10 and Spleen 6 (for "blood stasis"). The optional points were extensively discussed by the acupuncture team and were selected based by a shared understanding of Chinese medicine differential diagnosis. If the acupuncturist felt strongly that a fixed main point would be less desirable than an optimal point, they were allowed to replace a single fixed point with an optional point. The sensation of grasping the energy ("de qi") was obtained and the needles were left in place for twenty minutes [22]. Acupuncture treatment procedures were reviewed in regular team meetings.

Sham Acupuncture—In this study we used Streitberger needles [23], a validated sham acupuncture device. This device has been shown to be indistinguishable from an actual acupuncture device; the 'needle' does not pierce the skin but creates the illusion of doing so as it retracts into a hollow handle. Streitberger and true acupuncture needles were applied for an identical period of time. To avoid acupuncture pressure effect, sham needles were placed over predetermined 'non-acupuncture' points in the relative vicinity of the genuine points. Our team's precise method of using the sham needles is extensively described elsewhere [24].

During the placebo run-in phase, acupuncturists were instructed to select at least five and a maximum of eleven 'non-acupuncture' points as if they were actually performing a genuine points. They were also encouraged to slightly switch or adjust their point selection within the parameters of the study protocol from treatment to treatment (which is what would usually happen regular practice). These maneuvers were done in order that patients who were randomized to genuine acupuncture would experience identical procedures in terms of number of needles and the attention of the acupuncturists when switched from placebo to genuine treatment. Of course, patients were entirely blind to the run-in phase of the trial and were unaware of any change from sham to genuine treatment in the protocol.

Practitioners—Four licensed acupuncturists, each with over 2,000 hours of professional training and over four years of post-graduate experience, performed the acupuncture in this study. The method used for their training and supervision is described elsewhere [25]. Before the study began, all acupuncturists agreed that the therapeutic intervention they were to perform was an effective form of acupuncture.

Patient-Practitioner Interaction—Patients continued to receive the same patient-practitioner interaction (i.e., 'limited' or 'augmented' relationship) as they had received in the initial three-week run-in. The details of the two scripted patient-practitioner interactions are reported elsewhere [16]. The random assignment of interactions across treatment arms allowed for a secondary comparison of acupuncture versus sham acupuncture, each with two different styles of patient-practitioner interaction without compromising the outcome of our primary study objective.

Outcome Measures

Primary Outcome—The a priori primary endpoint of the study was the Global Improvement Scale (IBS-GIS) that asked participants: "Compared to the way you felt before you entered the study, have your IBS symptoms over the past 7 days been: 1) "Substantially Worse", 2)"Moderately Worse, 3)"Slightly Worse", 4)"No Change", 5)"Slightly Improved", 6)"Moderately Improved" or 7) "Substantially Improved" [26, 27]. A responder was defined as a patient who answered either "moderately improved" or "substantially improved" to the foregoing question.

Secondary Outcomes—Secondary outcomes measured in this study were IBS Adequate Relief (IBS-AR) [28, 29], IBS Symptom Severity Scale (IBS-SSS) [30], and IBS Quality of Life Scale (IBS-QOL) [31, 32].

IBS Adequate Relief: IBS-AR is a dichotomous single item that asks participants "Over the past week have you had adequate relief of your IBS symptoms?" This type of outcome has been used extensively to assess efficacy in IBS clinical trials [33, 34] and has been shown to correlate with improvement in individual IBS symptoms [28]. A responder was defined as a patient who answered this question affirmatively.

IBS Symptom Severity Scale: The IBS-SSS contains five questions that are rated on a 100-point visual analogue scale (VAS): the severity of abdominal pain, the frequency of abdominal pain, the severity of abdominal distention, dissatisfaction with bowel habits, and interference with quality of life [30]. All five components contribute to the score equally yielding a theoretical range of 0–500, with a higher score indicating a worse condition. Previous studies have established that scores below 175 represent mild IBS symptoms, 175–300 represents moderate severity, and scores above 300 represent severe IBS [30]. A decrease of 50 points on the IBS-SSS has been shown to correlate with improvement in clinical symptoms. We, therefore, defined patients with a decrease of 50 points or more on the IBS-SSS as responders in this study.

IBS-Quality of Life: The IBS-QOL is a 34-item measure assessing the degree to which IBS interferes with patient's quality of life. Each item is rated on a 5-point Likert scale and all items are summed. The total score is then converted linearly to a 100 point scale, with higher scores indicating improved quality of life [35].. In accordance with a study by Drossman et al., we defined responders as patients whose IBS-QOL scores improved by 10 points or more from baseline [36].

STATISTICAL ANALYSIS

For the primary endpoint, our sample size afforded 80% power to detect a percentage point difference in responder rates. Chi square tests of independence were used to determine whether significant differences existed between groups in the proportion of responders. In addition, where possible (i.e., for continuous measures), we also used parametric statistics (t-tests and ANOVA) because of the potential for improved power. All analyses were intent-to-treat, using the last observation carried forward (LOCF) method. For clarity, we report here only non-parametric analyses for dichotomous outcomes (i.e., responder vs. non-responder). Except where noted in the text, parametric tests yielded similar results. All tests were two-tailed with alpha set at .05.

RESULTS

Patient Characteristics

Between December 2003 and February 2006, we screened 350 prospective participants and enrolled 262 into the study. Of the 262 potential patients, 32 patients (5 in the 'augmented' arm; 17 in the 'limited' arm; and 10 in the waitlist arm) discontinued the trial during the first three weeks (i.e., prior to randomization between acupuncture and sham acupuncture). Thus, 230 patients entered into the study reported here. Table 1 displays these patient characteristics by treatment group.

Acupuncture vs Sham Acupuncture

On the IBS-GIS 41% of patients who received acupuncture were responders (i.e., 'moderate' or 'substantial' improvement in their IBS symptoms during the preceding week), while 32% of patients who received sham acupuncture were responders (p=0.25). Although more of the acupuncture recipients were responders than sham acupuncture recipients, the difference was not statistically significant (p=0.25) (Figure 2). Similar non-statistically significant differences were seen in the responder rates for IBS-AR, IBS-QOL and IBS-SSS (Figure 2).

We had hoped that removing patients who responded to sham acupuncture during the 3 week run-in phase of the trial would diminish the response rate to sham acupuncture during the second 3 week phase of the trial and, therefore, widen the gap between acupuncture responders and sham acupuncture responders. However, contrary to our expectations, the gap between acupuncture responders and sham acupuncture responders narrowed for our primary outcome measure the IBS-GIS (24% vs. 25%, p=0. 96). Similarly, removing responders for the each of the secondary endpoints at the end of the run-in phase also did not yield statistically significant differences between acupuncture and sham acupuncture in the IBS-AR (33% vs 24%, p=.42), IBS-SSS (36% vs 21%, p=0.20) and IBS-QOL (18% vs. 11% p =0.53).

Acupuncture and Sham Acupuncture vs. Waitlist Control

Patients receiving acupuncture or sham acupuncture were more likely to be responders on the IBS-GIS than patients in the waitlist control group (37% vs. 4%, p<.001) (Figure 2). Likewise, patients receiving acupuncture or sham acupuncture versus those on the waitlist control were significantly more likely to be responders on the IBS-AR (58% vs. 35%, p<.001) and IBS-SSS (26% vs. 14%, p=.04). There was a numerical but not a significant difference for IBS-QOL (15% vs. 12%, p=.49) between those receiving acupuncture or sham acupuncture versus waitlist control.

Effect of Patient-Practitioner Interaction on Response Rates

For the IBS-GIS in both a limited and an augmented patient-practitioner interaction, acupuncture showed a slight, non statistically significant superiority to sham acupuncture (Table 2). Since the difference in response rates between augmented acupuncture and augmented sham acupuncture and between limited acupuncture and limited sham acupuncture is similar, the interaction in which acupuncture is delivered does not appear to affect its superiority over sham acupuncture. Similar results were seen for the secondary endpoints with the exception of the IBS-QOL in the 'limited' acupuncture arm.

Adverse Events

Three adverse events were reported during the acupuncture vs sham acupuncture phase of the study: 1) painful foot cramp following treatment (sham acupuncture), 2) nausea/hip pain (true acupuncture), and 3) rib pain after a fall (sham acupuncture). All of the events were considered to be unrelated to the study procedure.

Discussion

Our study is the largest RCT with acupuncture to be performed in IBS. Our results demonstrated that acupuncture and sham acupuncture are not significantly different in improving the symptoms of IBS, although both treatments are significantly better than no treatment (i.e., waitlist). Eliminating responders in the run-in phase of the study in which patients received only sham acupuncture had no substantive effect on the outcome. Finally, the context of the patient-practitioner interaction (i.e., a warm friendly and supportive relationship ('augmented')

or a neutral ('limited') relationship) also did not modify the difference in responder rates between acupuncture and sham acupuncture.

Our findings are consistent with the majority of trials of acupuncture in IBS included in the recent Cochrane Database Review [12] and the subsequent study by Schneider and colleagues [13] from Germany. Like our trial, the German study found a numerically small superiority of improvement in patients receiving acupuncture compared to patients receiving sham acupuncture. The German study included 43 patients and estimated that if acupuncture had efficacy beyond placebo the number of patients needed to adequately power such a study to be 566; we found the number of patients needed to adequately power such a study to be approximately 970. Importantly, in contrast to the study by Schneider and colleagues [13], which did not have a waitlist control (or standard of care) arm, our study found response rates in patients receiving acupuncture and sham acupuncture to be superior to that of patients in a waitlist control. This demonstrates unequivocally that symptom improvement was not the result of natural history or regression to the mean. Our findings are consistent with the results of recent large German acupuncture trials for other illnesses, such as chronic low back pain [37], tension-type headache [38], migraine [39, 40], and osteoarthritis of the knee [41] in which acupuncture and sham acupuncture were not different in efficacy but both were superior to no treatment or standard of care. In April 2006, the German health authorities decided to reimburse for acupuncture for low back pain and osteoarthritis of the knee (but not for headache or other types of osteoarthritis) based on the beneficial effects over no treatment or standard of care and its potential cost savings [42–44].

We had hoped that removing patients who had responded to sham acupuncture during the 3 week run-in phase of the trial would diminish the response rate to sham acupuncture during the second 3 week phase of the trial and, therefore, widen the gap between acupuncture responders and sham acupuncture responders. However, our results do not show a widening of the gap. In fact, contrary to expectations, the difference between acupuncture responders and sham acupuncture responders actually narrowed for our primary outcome measure (IBS-GIS) and the IBS-SSS. Our findings support other studies that have also failed to find increased efficiency in detecting intervention-placebo differences with the removal of placebo responders during a run-in phase [45, 46].

Our study had several limitations. First, 6 treatments of acupuncture over 3 weeks may have been insufficient to achieve maximum effect from acupuncture. Second, this study was nested in a larger study designed to evaluate the effects of patient-practitioner interaction in IBS. Thus, a run-in phase occurred prior to randomization between acupuncture and sham acupuncture, which had a significant drop-out rate and thereby decreased the power of our study. Also, some might object to our manualized approach to acupuncture treatment and argue for either a full standardized protocol or a totally flexible protocol. We feel that our manualized procedure is as close to actual clinical practice as reproducibility will allow. Last, there is debate in the acupuncture literature if sham acupuncture, although indistinguishable from acupuncture, is indeed ineffective. The mechanism of acupuncture is unknown and sham acupuncture may be a less effective form of acupuncture [47].

In summary, although our study failed to show a statistically significant superiority of acupuncture over sham acupuncture in the treatment of IBS, patients receiving both acupuncture and sham acupuncture improved significantly compared to waitlist control.

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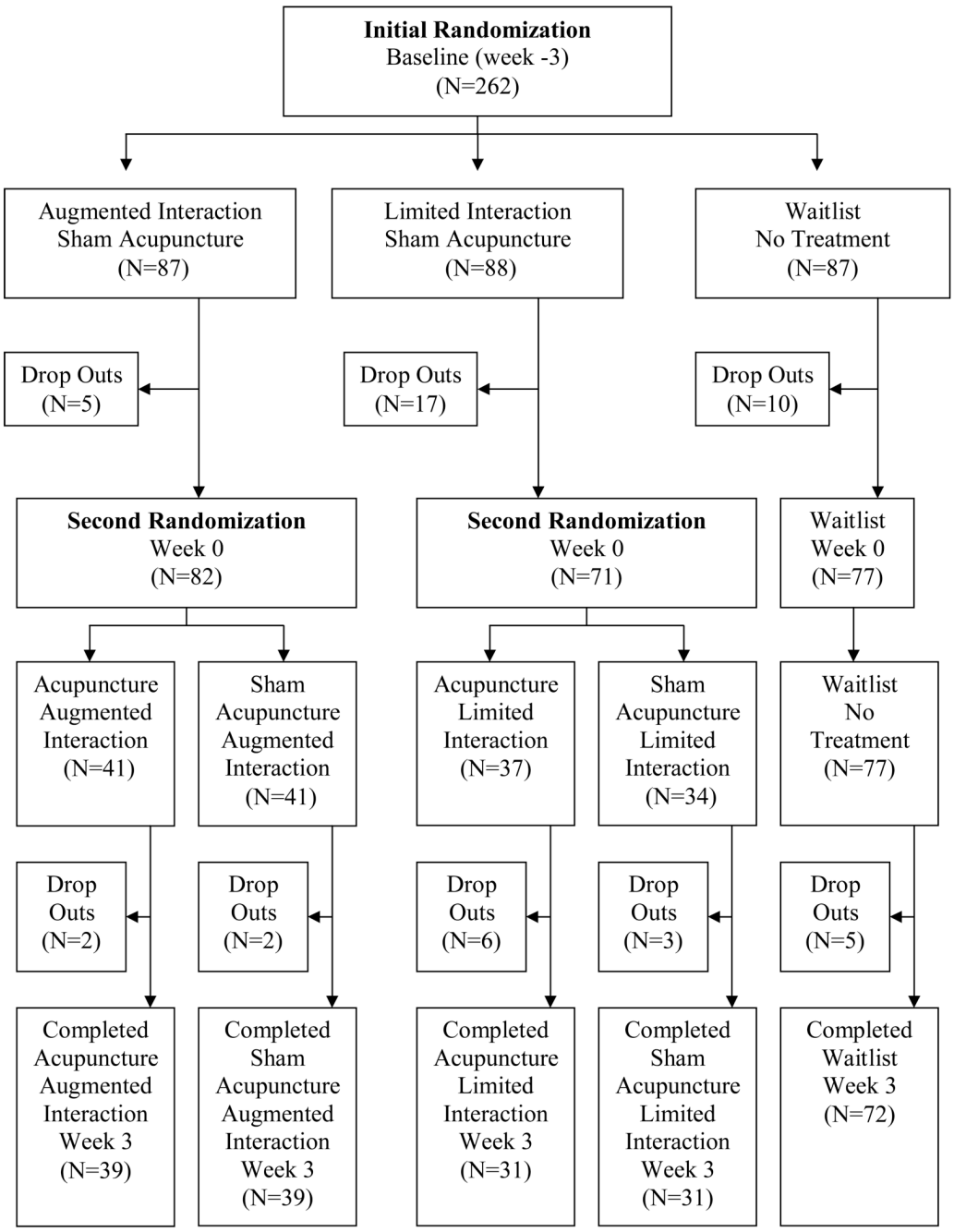

Figure 1. Flow of Patients through the Study

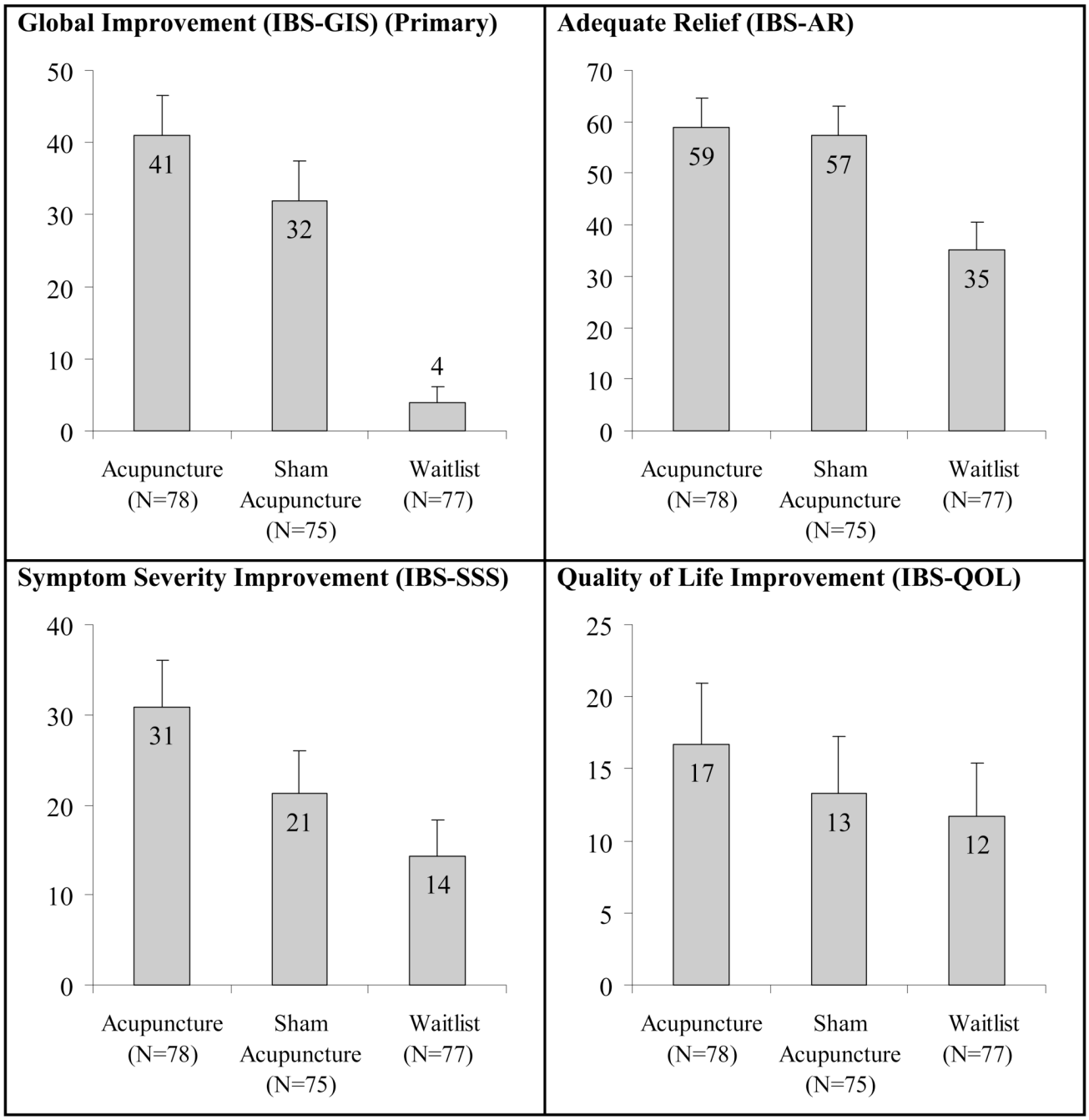

Figure 2. Percent of Patients who were Responders by Outcome Measure

Note. Error bars indicate standard errors. None of the acupuncture-sham acupuncture differences are statistically significant.

Table 1

Demographics and Baseline Symptoms

	Acupuncture (N=78)	Sham Acupuncture (N=75)	Waitlist (N=77)
Demographics			
Mean Age (SD)	37.5 (14.6)	38.9 (14.1)	39.0 (14.0)
Female	78	77	74
Caucasian	84	89	90
Married/Living Together	47	43	39
Graduated College	73	77	78
Employed	78	81	81
IBS Type and Duration			
Constipation	22	15	27
Diarrhea	21	32	24
Alternating	57	53	49
IBS for > 1 year	96	91	95
Baseline IBS Symtoms			
Mean IBS-SSS (SD)	199.3 (98.3)	200.5 (83.4)	240.3 (76.0)
Mean IBS-QOL (SD)	70.8 (17.3)	72.4 (17.6)	66.4 (17.3)
Psychiatric Symptoms			
Mean Anxiety (SD)	11.8 (9.0)	13.2 (9.3)	11.4 (9.9)
Mean Depression (SD)	3.5 (3.4)	3.9 (3.8)	3.5 (3.6)

Note. All values are percentages except where noted.

Table 2

Percent Responder Rates for the Primary and Secondary Outcome Measures by Patient-Practitioner Context

	Augmented		Limited		
	Acupuncture (N=41)	**Sham Acupuncture (N=41)**	**Acupuncture (N=37)**	**Sham Acupuncture (N=34)**	**Waitlist (N=77)**
IBS-GIS	49	39	32	24	4
IBS-AR	63	61	54	53	35
IBS-SSS	37	29	24	12	14
IBS-QOL	24	17	8	9	12

Note. Within each treatment condition (augmented and limited), none of the acupuncture-sham acupuncture differences were statistically significant.