A Phase II, Randomized, Controlled Trial of Acupuncture for Reduction of Postcolectomy Ileus

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ABSTRACT

Purpose. Postoperative ileus (POI) prolongs hospital stay and increases risk of postoperative complications. We conducted a randomized, sham-controlled trial to evaluate whether acupuncture reduces POI more effectively than sham acupuncture.

Methods. Colon cancer patients undergoing elective colectomy were randomized to receive 30 min of true or sham acupuncture twice daily during their first 3 postoperative days. GI-3 (the later of the following two events: time that the patient first tolerated solid food, AND time that the patient first passed flatus OR a bowel movement) and GI-2 (the later of the following two events: time patient first tolerated solid food AND time patient first passed a bowel movement) were determined. Pain, nausea, vomiting, and use of pain medications were evaluated daily for the first 3 postoperative days.

Results. Ninety patients were randomized. Eighty-one received the allocated intervention: 39 in the true acupuncture group and 42 in the sham acupuncture group, all evaluated for the primary endpoint. The mean time to GI-3 was 149 h [standard deviation (SD) 71 h] and 146 (SD 62 h) after surgery for the acupuncture group and the sham acupuncture group (difference between means −2 h; 95 % confidence interval −31, 26; $p = 0.9$). No significant

differences were found between groups for secondary endpoints.

Conclusions. True acupuncture as provided in this study did not reduce POI more significantly than sham acupuncture. The study was limited by a standard deviation much larger than expected, suggesting that a study with a larger sample size might be required.

INTRODUCTION

Postoperative ileus (POI) is a common problem after major abdominal surgery. POI is characterized by transient bowel dysfunction and reduced motility that impairs effective transit of intestinal contents. Prompt recovery of bowel function after colorectal surgery is of major importance, not only to the wellbeing of patients, but also to health care costs, because prolonged ileus can lead to other complications that prolong hospital stay.

Successful management of POI has been a challenge. Much research in the past few decades has sought to find effective treatment modalities. Epidural local anesthetics, prokinetic agents, and opioid antagonists have been shown to improve recovery time of intestinal function but are associated with significant costs.^{1–5} Laparoscopic surgery also may reduce recovery time, but it involves training, equipment, and capital investment on the part of the health care institution.⁶ Despite the availability and cost of multiple treatment options, POI is still reported in approximately 15 % of patients undergoing partial bowel resection or 3 % of total abdominal hysterectomy patients.⁷

Acupuncture is a minimally invasive integrative oncology modality.⁸ It has been shown to improve GI motility in laparotomy animal models.^{9–12} In addition, several clinical studies of its effects on GI motility in the settings of

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healthy volunteers, diabetic gastroparesis, transabdominal hysterectomy, and abdominal surgery have been reported. However, the study designs were not rigorous, the selection of primary endpoint problematic, or the description of randomization inadequate in these studies.^{13–18}

Therefore, because the efficacy of acupuncture in the treatment of postoperative ileus remains inconclusive, we conducted a randomized, controlled trial to compare the effect of true versus sham electroacupuncture in reducing postoperative ileus.

METHODS

Study Design

The study was a single-center, prospective, randomized, sham-controlled, intervention study. The study was approved by the institutional review board at Memorial Sloan-Kettering Cancer Center (MSKCC). The primary objective of this phase II trial was to determine whether the observed reduction of postoperative ileus by acupuncture is large enough to warrant a Phase III trial of acupuncture for postoperative recovery after colorectal surgery. The effects of acupuncture in ameliorating other postoperative symptoms such as pain, nausea and vomiting were also evaluated.

Study Population

The inclusion criteria were: age older than 19–64 years and scheduled to undergo elective resection of biopsy proven or suspected colorectal cancer. The exclusion criteria were: history of major abdominal or pelvic surgery, laparoscopic procedure, epidural anesthesia, acupuncture treatment within the past 4 weeks, contraindications to use of electrical stimulation (pacemaker or implantable cardioverter defibrillator), previous serious adverse event with acupuncture. Study participants with the following intraoperative events also were excluded: resection incorporating the upper GI tract, gross fecal spillage, need to leave nasogastric tube in postoperatively, decision to give epidural anesthesia postoperatively, and complications during surgery requiring direct postoperative transfer to intensive care unit.

Patient accrual occurred from November 2006 to November 2009. Patients presented to the Colorectal Surgery Service at MSKCC were screened for eligibility. Informed consent was obtained from eligible patients before enrollment to the study.

Randomization

Full registration and randomization occurred after a subject was transferred from the Post Anesthesia Care Unit

to a patient floor. Randomization was accomplished in MSKCC's Clinical Research Database using blocks of random length. The use of telephone randomization and documentation by an independent entity using a secure database system ensures full randomization concealment; allocation could not be guessed before or changed after the patient was unambiguously registered on trial. Randomization was stratified by the need for stoma (yes/no).

Blinding

The patients, surgeons, nursing team, and evaluators taking data from patients were blinded to group assignment. Only the acupuncturists were aware of a patient's group assignment. All acupuncturists in this study were trained and experienced in providing true or sham electroacupuncture in randomized, patient, and evaluator-blind, controlled trials. Patients were asked about their beliefs concerning their treatment allocation at the end of the study to assess adequacy of blinding.

Intervention

All patients received a standardized postoperative care plan, which includes nursing orders, activity orders, DVT prophylaxis, antiemetics, analgesics, patient-controlled analgesia, dietary instructions, and discharge planning. Acupuncture or sham acupuncture was given twice daily for a total of 3 days starting on postoperative day 1. The two acupuncture sessions were separated by at least 4 h, given in the morning and late afternoon. Each session lasted approximately 30 min, starting from the moment the first needle was inserted and ending the moment the first needle was removed. The last treatment was given at the end of day 3 or day of discharge, whichever came first.

Single-use, sterilized, disposable, filiform acupuncture needles were used. These are made from stainless steel, 32 G in width, and ranged from 1/2" to 3" long. The acupuncture style and points used were based on traditional Chinese medicine and previous use in animal and human studies summarized in the "Introduction" section. During each acupuncture session, each patient received a total of 14 acupuncture needles at seven pairs of bilateral points (ST-36, PC-6, LI-4, SP-6, SP-9, ST-25, auricular shenmen) for 30 min. Electrical stimulation, 2 Hz, 0.5 msec square wave pulses, was applied to ST-36 (negative) and PC-6 (positive).

Sham acupuncture was performed on exactly the same points as true acupuncture. Acupuncturists taped a plastic guiding tube on the surface of the points to produce some discernible sensation and then immediately taped a real needle sideways parallel to the skin surface without needle insertion. The needles on the points for electroacupuncture

were connected to an electrostimulator with severed wires that did not deliver electrical current. The patient's eyes were covered so they were not able to observe the treatment directly. This sham acupuncture technique is thought to have low physiological activity and high patient credibility and has been validated and successfully implemented in a published randomized trial.¹⁹

All acupuncturists were employee members of the MSKCC Integrative Medicine Service, licensed by the State Education Department in New York, certified by the National Certification Commission for Acupuncture and Oriental Medicine and trained in human subjects research, and had a minimum of 3 years of practice experience plus training in working with cancer patients.

Outcome Evaluation

The primary endpoint was GI-3, defined by the later of the following two events: time that the patient first tolerated solid food, and time that the patient first passed flatus or a bowel movement. This choice conforms to industry standard as it is used in the pivotal trials of alvimopan, a peripherally acting μ -opioid antagonist approved by the FDA to prevent postoperative ileus.^{4,5} Four patients were missing time of first flatus. For these patients, only first bowel movement and first tolerated solid food were used to determine GI-3.

Because flatus can vary considerably between patients, a secondary end point GI-2 (defined as by the later of the following two events: time patient first tolerated solid food, and time patient first passed a bowel movement) was used to measure the recovery time of GI function. Other secondary endpoints included emetic episodes before GI recovery (GI-3), need for postoperative nasogastric (NG) tube reinsertion, postoperative pain and nausea, and opioid consumption in morphine equivalent. Pain and nausea were evaluated on a visual analogue scale (VAS), and the mean

scores from days 1–3 after surgery were compared between groups. Total morphine equivalent consumption before GI recovery (GI-3), and mean morphine equivalent consumption in the first 3 days following surgery were compared between groups.

Statistical Analyses

All statistical analyses were performed using Stata 11.1 (Stata Corp., College Station, TX) and were based on the intent-to-treat principle for all patients who had evaluable outcome data. Using previously published data, we estimated a standard deviation for GI-3 of approximately 24 h.⁵ We deemed a difference of 12 h to be clinically significant. Thus, a trial with 80 % power, a one-sided alpha of 10 %, and a difference of 12 h required 37 patients per group. We deemed acupuncture worthy of further study if a one-sided 90 % confidence interval excluded no difference between groups.

Per the study protocol, the primary endpoint of GI-3 was analyzed using a one-sided test at a 90 % significance level, and all other analyses were two-sided at a 95 % significance level. The primary endpoint, GI-3, was evaluated using a one-sided permutation test of difference in mean time to GI recovery taking into account randomization stratum. GI-2, pain score, nausea score, and morphine equivalent consumption were evaluated by using two-sided permutation tests of difference in means taking into account randomization stratum; the 95 % confidence intervals were produced via bootstrap methods. Between groups differences in NG tube reinsertion and emetic episodes were tested by Fisher's exact test.

RESULTS

A flow chart for the study is provided in Fig. 1. A total of 1,253 patients were screened. From these, 90 were found

FIG. 1 Study flow chart

TABLE 1 Patient characteristics data are median (IQR) or frequency (percent)

	Placebo (n = 44)	Acupuncture (n = 46)
Age (years)	59 (51, 70)	56 (50, 69)
Male	26 (59 %)	26 (57 %)
Randomization stratum		
Need for stoma	20 (45 %)	21 (46 %)
No need for stoma	24 (55 %)	25 (54 %)
Received acupuncture or sham treatment	42 (95 %)	39 (85 %)
No. of treatments		
1	3 (7 %)	2 (5 %)
2	2 (5 %)	2 (5 %)
3	3 (7 %)	3 (8 %)
4	7 (17 %)	5 (13 %)
5	9 (21 %)	3 (8 %)
6	18 (43 %)	24 (62 %)
Surgery duration (min)	234 (180, 273)	227 (172, 295)
Procedure (patients may undergo more than one procedure)		
Ileostomy/jejunostomy	13 (32 %)	16 (43 %)
Removal of colon	8 (20 %)	9 (24 %)
Partial removal of colon	20 (50 %)	21 (57 %)
Removal of rectum	11 (28 %)	8 (22 %)
Randomization assignment belief		
Acupuncture	12 (29 %)	19 (51 %)
Placebo	8 (20 %)	6 (16 %)
Unsure	21 (51 %)	12 (32 %)

eligible and were consented and randomized. Forty-six were allocated to the true acupuncture group, among whom 39 received allocated intervention and 7 withdrew before the first intervention. Forty-four patients were allocated to the sham acupuncture group, among whom 42 received allocated intervention and 2 withdrew before the first intervention. Thirty-nine patients in the acupuncture group

were evaluable for the primary endpoint and 42 in the sham acupuncture group. Patient characteristics are given in Table 1. Patient characteristics were well balanced between randomization group with respect to age and gender. The number of treatments received also was well balanced between treatment groups; 51 % of patients who received acupuncture believed that they were in the true acupuncture group, whereas only 29 % of patients in the sham acupuncture group believed that they received true acupuncture. This is close to statistical significance ($p = 0.064$, Fisher's exact test), suggesting that the blinding of sham treatment may have not been fully maintained throughout the study.

The mean time to GI-3 was 149 h [standard deviation (SD) 71 h] and 146 (SD 62 h) after surgery for the acupuncture group and the sham acupuncture group, respectively (Table 2). Because the mean time to GI-3 was longer in the acupuncture group than in the placebo group, it is clear that a one-sided confidence interval will not exclude no difference between groups and therefore that the trial has not met the criterion for declaring acupuncture worthy of further study. The difference between groups after adjusting for randomization stratum was -2 h (95 % confidence interval $-31, 26$; $p = 0.9$ based on a two-sided permutation test for difference in means). The upper bound of the confidence interval is a 26-h shorter duration of GI dysfunction in the acupuncture and, as such, the study does not rule out acupuncture having a clinically worthwhile effect on GI recovery. Given the extreme skew of the data, we conducted an exploratory analysis, repeating the main analysis using difference in median time to GI-3 recovery, but results were almost identical.

Results of secondary endpoint analyses are found in Table 2. There were no statistically significant differences in time to GI-2, any emetic episodes before GI recovery (GI-3), mean VAS pain score from days 1–3, mean VAS nausea score from days 1–3, mean morphine equivalent

TABLE 2 Primary and secondary endpoint results by treatment group

	Placebo (n = 42)	Acupuncture (n = 39)	Difference ^a	95 % CI for difference	p
Time to GI-3 (h)	146 (62)	149 (71)	−2	−31, 26	0.9
Time to GI-2 (h)	152 (60)	149 (71)	3	−26, 32	0.8
Mean VAS pain score, days 1–3	4.8 (2.3)	5 (1.9)	−0.2	−1.1, 0.7	0.7
Mean VAS nausea score, days 1–3	1.9 (2.3)	1.8 (1.8)	0.1	−0.7, 1	0.8
mean morphine equivalent (mg), days 1–3	122 (167)	101 (79)	22	−32, 75	0.6
Total morphine equivalent (mg)	205 (308)	179 (147)	25	−74, 125	0.8
Any emetic episodes	10 %	18 %	−8 %	−23 %, 7 %	0.3
NG tube reinsertion	10 %	10 %	−1 %	−14 %, 12 %	1

Values presented are mean (SD) or proportion

For all endpoints, a positive difference between groups indicates better outcome on acupuncture

^a Adjusted for randomization stratum

consumption from days 1–3, or total morphine equivalent consumption before GI recovery (GI-3). Rates of NG tube reinsertion did not differ (10 % in both groups, $p = 1$).

DISCUSSION

POI remains a clinical problem in patients undergoing abdominal or pelvic surgery, despite the advent of management pathways.⁷ Our randomized, sham-controlled, blinded trial of 90 patients undergoing colectomy for colon cancer did not demonstrate a significant difference between true and sham acupuncture in promoting recovery of gastrointestinal function. Compared with a previous study,¹⁸ our design was different in that we used sham-acupuncture as control (instead of usual care as control), provided more intensive interventions (twice daily instead of once daily acupuncture), used a shorter duration of intervention (3 days instead of 6 days), and had GI-3 as the primary endpoint (instead of having a bowel movement by 96 h after surgery).

There are several possible explanations for our findings. The first obvious possibility is that acupuncture, although may stimulate gastrointestinal motility as evidenced by animal studies, does not produce a large enough effect size to be clinically meaningful. Many other factors, in addition to gastrointestinal motility, probably impact POI. Another possibility is that our intervention regimen was not intensive enough or our acupuncture point selection was not optimal. However, any more intensive (more frequent, longer duration) intervention regimens are unlikely to be practical in the current postoperative care setting. Our acupuncture point selection derived from the consensus of previous preclinical and clinical studies that showed a positive effect, making suboptimal point selection less likely.

A third possibility is that sham acupuncture is not entirely inert. In this study, patients in the sham group still received skin stimulations from the tapping of the guided tube and were informed on the use of electrical stimulation. This possibility is supported by the report that in a randomized trial that a sham acupuncture device was superior to an inert pill for the treatment of pain.²⁰ It would be ideal to include a third group—a usual care control. Although true versus sham acupuncture may not differ significantly in their effects, both may be superior to usual care.

Several strengths of the reported study may be noted: randomized, controlled design; strict eligibility criteria; use of sham-intervention; all researchers and patients blinded except for the acupuncturist; the use of industry standard endpoints; and low attrition rate. Our study also has several weaknesses. Blinding in the sham group was not entirely successful. Only 29 % of patients in the sham acupuncture

group believed that they had received acupuncture, meaning that most of them had guessed correctly that they had received sham acupuncture. Yet, this would not change the final finding that acupuncture was not more effective than sham acupuncture in reducing POI, because blinding in the true acupuncture group was quite successful (51 % guessed right). If placebo effect contaminated the therapeutic effect, we would have seen even less difference between the two groups. Another limitation is that the standard deviation of the primary endpoint was much higher than anticipated: 62 and 71 h rather than the 24 h assumed in our sample size calculations. This suggests that our trial would have benefited from a larger sample size. The upper bound of the confidence interval of GI-3 is 26 h shorter in the acupuncture group and, as such, although not reaching statistical significance, the study does not entirely rule out acupuncture as an effective treatment for GI recovery. A definitive answer would require a larger study with ideally two control groups (sham acupuncture at nonacupuncture points and usual care).

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CONFLICT OF INTEREST No commercial interest is disclosed.

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