

Effect of acupuncture on postoperative ileus after laparoscopic elective colorectal surgery: A prospective, randomised, controlled trial

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Summary

Background Postoperative ileus after colorectal surgery is a frequent problem that significantly delays recovery, increases perioperative costs, and negatively impacts on daily life, physical and psychosocial functioning, and well-being. We investigated the effect of acupuncture at different single acupoint combined with standard care on postoperative ileus.

Methods In this single-centre, three-arm, prospective, randomised trial, we enrolled patients with primary colorectal cancer undergoing elective colorectal resection at Cancer Hospital Chinese Academy of Medical Science in Beijing, China. Patients were randomly assigned (1:1:1) to receive either electroacupuncture (EA) at ST36 or ST25 combined with standard care (two EA groups) once daily from post-operative days 1–4, or standard care alone (standard care group). The co-primary outcomes were time to first flatus and time to defecation assessed in the intention-to-treat population. This study is registered with Chictr.org.cn, ChiCTR1900027466.

Finding Between Nov 15, 2019, and Sep 30, 2020, 129 patients were assessed for eligibility, 105 patients (35 patients per group) were enrolled and included in the intention-to-treat analysis. After receiving EA at ST36, the time to first flatus and defecation were shorter (between-group difference -10.98 [97.5% CI -21.41 to -0.56], $p = 0.02$ for flatus; -25.41 [-47.89 to -2.93], $p = 0.02$ for defecation). However, we did not observe a significant difference in time to first flatus and defecation between the EA at ST25 group and standard care group (between-group difference -5.54 [97.5% CI -15.78 to 4.70], $p = 0.26$ for flatus; -17.69 [-40.33 to 4.95], $p = 0.08$ for defecation). There were no serious adverse events.

Interpretation Compared with standard care alone, standard care combined with EA at ST36, but not ST25, significantly enhances bowel function recovery in a postoperative setting to patients with colorectal cancer with laparoscopic elective colorectal resection.

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Keywords: Acupuncture; Colorectal surgery; Enhanced recovery; Laparoscopy; Postoperative ileus

Introduction

Postoperative ileus (POI) is a block of coordinated bowel motility after surgery and is considered an often-

unavoidable consequence of abdominal or retroperitoneal surgery.¹ During the past decade, although the management of POI has changed from a ‘supportive’ to ‘active’ strategy aimed at identifying, preventing, and treating all perioperative factors contributing to POI, the reported duration is still as long as 4 days.² Therefore, it is clearly associated with prolonged hospital stay,

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Research in context

Evidence before this study

Using the key words “Postoperative ileus” (POI) and “acupuncture”, we searched PubMed for articles published between Jan 1, 1947 and May 16, 2019. There was only one well-designed prospective study evaluating the effect of electroacupuncture on POI after laparoscopic surgery for colonic and upper rectal cancer. Despite that the study showed a beneficial effect of electroacupuncture, this evidence had some limitations. Based on the consensus developed by the American Society for the Promotion of Recovery and the Perioperative Quality Initiative emphasising that there is a paucity of research on the management of POI under the ERAS pathway, studies that include a wider population and combined with ERAS pathway are urgently needed.

Added value of this study

This single-centre, assessor and statistician-blinded trial addressed the above limitations by showing that, compared with standard care alone, electroacupuncture at ST36, but not ST25, had beneficial effects on reducing the time to first flatus and the time to first defecation. The overall morbidity rate was 6.7%, with no significant difference among groups in overall post-operative complications.

Implications of all the available evidence

Compared with standard care alone, combined standard care with electroacupuncture at ST36 significantly enhances bowel function recovery in a postoperative setting to patients with colorectal cancer after resection. Since ERAS combined with laparoscopy surgery has been shown to have a synergistic effect in enhancing recovery and are the best perioperative strategy after laparoscopic surgery for colon disease, the finding is of vital significance to clinical work, as minimally invasive surgeries with the ERAS pathway continue to increase in popularity.

increasing costs, and higher 30-day readmission rate.³ Due to inability to fulfil social roles and obligations and curtailment of normal social activities, POI had a profound negative impact on daily life, physical and psychosocial functioning, and wellbeing.

With the implementation of minimally invasive surgery and the emergence of enhanced recovery protocols (ERAS), patient’s physical conditions have been improved, reflected in shortened hospitalisation and reduced costs.⁴ However, the improvement is still insufficient, and often requires combination with pharmacological treatments, such as prokinetics and opioid antagonists. Alvimopan, a peripherally acting μ -opioid receptor antagonist, is the only pharmacological treatment approved by the Food and Drug Administration in

the United States (FDA),⁵ but it is not approved in China. In addition, the clinical benefit of alvimopan was most apparent in a subgroup of patients who received opioids for post-operative pain management.⁶ With the increasing use of opioid-sparing postoperative analgesia, the role of alvimopan in alleviation of POI might be limited. Therefore, a more safe and effective treatment is urgently needed.

Because acupuncture is garnering increased attention as an effective treatment for postoperative gastrointestinal symptoms and gut motility disorders,^{7,8} one important issue is whether acupoint choice influences POI. In regard to two types of acupoints, recent animal studies have suggested acupoints in the abdominal area delay bowel motility, whereas acupoints on lower limbs promote it.⁹ In fact, Zusanli (stomach meridian ST36) located on the lower limbs as the “He Point” of stomach and Tianshu (stomach meridian ST25) located on the abdomen as the “Mu Point” of the large intestine, are the most commonly used acupoints for treating gastrointestinal disease in clinical practice, which is inconsistent with basic research. In addition, as laparoscopic surgery with the ERAS pathway is increasingly used, patients have less pain, lower opioid requirements, and a shorter recovery time. Although a previous study found acupuncture could reduce the duration of POI,¹⁰ it is unclear if acupuncture will have an additive effect for the current patient group. Therefore, the present study was conducted to assess the efficacy of electroacupuncture (EA) at different acupoint in reducing the duration of POI after laparoscopic colorectal surgery with ERAS pathway. We hypothesised that EA under the ERAS pathway could further accelerate recovery of gut function after colorectal surgery.

Methods

Study design and participants

This single-centre, three-arm, prospective randomised trial was conducted in the inpatient departments of a tertiary hospital (Cancer Hospital Chinese Academy of Medical Science, Beijing) between Nov 15, 2019 and Sep 30, 2020. The study protocol was approved by the ethics committee (2019BZHYYL0207) and registered with the Chinese Clinical Trial Registry on Nov 14, 2019 (ChiCTR1900027466) (*Appendix study protocol*, supporting information). All patients provided written informed consent before enrolment.

Primary colorectal cancer patients with American Society of Anesthesiologists grading I–III aged at least 18 years undergoing elective segmental colorectal resection were considered for participation in the study. Exclusion criteria were a history of abdominal surgery, needing to be synchronised with other surgeries, conversion to open surgery, required postoperative

intensive care for more than 24 h, history of syncope or epilepsy, epidural anesthesia in surgery, taking drugs which affect bowel function within a month, and those with cardiac pacemakers. Patients participating in other clinical studies within the past 3 months or receiving acupuncture within a month were also excluded.

Randomisation and masking

The study protocol was explained to all enrolled patients before randomisation. After written informed consent was obtained, patients were allocated randomly (1:1:1) to the three arms: EA at ST36 with standard care, EA at ST25 with standard care, or standard care alone. Randomisation was performed shortly after surgery, with a random block size of six or nine. A randomisation sequence was created by a biostatistician who did not participate in the implementation or statistical analysis of trial. The assessor and statistician were blinded to treatment allocation throughout data collection and analysis.

Procedures and interventions

Electroacupuncture with standard care (EA groups).

To exploratively observe whether the effects of acupoints located on the abdomen or the lower limbs are different, this trial set two EA groups, in which patients received ST36 or ST25, respectively. All EA treatments were performed by two senior acupuncturists (length of services ≥ 5 years), who consistently applied the same standardised protocols. After identifying the location of acupoints (eFigure 1, eTable 1), sterile acupuncture needles (length 40 mm, diameter 0.30 mm; Hwato, Suzhou Medical Appliance Factory, China) were inserted, followed by 30s manipulation to acquire *Deqi* (a sensation of aching, soreness, swelling, heaviness, or numbness¹¹), and then a pair of electrodes from an electric stimulator (HANS-200A acupoint nerve stimulator, Nanjing Jisheng Medical Co, Ltd) were connected to the needle. The EA stimulation lasted for 30 min with a dilatational wave of 2/100 Hz and the electric current was gradually increased until the needle vibrates slightly. Patients in the two EA groups received one session of EA per day, in addition to the standardised postoperative management (described below) starting the first day postoperatively. The interventions were performed for 4 consecutive days or until discharge.

Standard care alone (standard care group). In the standard care group, the same postoperative management was applied without EA or any other postoperative intervention that might influence recovery of bowel function, including chewing gum, or adjuvant drugs. The postoperative management based on the Consensus on ERAS and guidelines for pathway management in China

(2018),¹² including multimodal analgesic, patient-controlled analgesia plus non-steroidal anti-inflammatory drugs, early oral feed, and early mobilisation (ie, stimulating patients to engage in physical activity instead of remaining in bed), which is comparable to the Western standardised ERAS (eTable 4). Patients were discharged provided that they had been weaned off intravenous fluids, had passed stool, were fully ambulant with oral analgesics, and had no evidence of complications.

Outcomes

The co-primary outcomes were time to first flatus and time to defecation, which were obtained from a patient diary (eTable 2) filled out once daily with assistance from an assessor, measured in minutes, from the time the laparoscopic surgery ended until the first observed passage of stool. EA was considered as an effective therapy only if both primary outcomes achieved significance.

Secondary outcomes included length of hospital stay, time to tolerated diet (liquid or semi-liquid food), use of analgesics, time to walking independently, incidence of nausea, vomiting, and abdominal distension, pain scores on visual analogue scale, and postoperative complications (Clavien–Dindo classification¹³). Extent of pain was reported by patients once daily on days 1 to 4 after resection. Adverse events were documented by patients and outcome assessors throughout the trial. All adverse events were categorised as treatment-related or non-treatment-related and followed up until resolution.

Moreover, we also observed the occurrence rate of different POI types which classified as early or late by Vather and colleagues.¹ Briefly, early POI was defined as absence of flatus or stool passage and inability to tolerate an oral diet between surgery and postoperative day 4. Late POI was defined as the initial development of symptoms (absence of flatus or stool passage and inability to tolerate an oral diet) after postoperative day 4. Late POI increases the incidence of postoperative complication and may predict a prolonged postoperative length of stay in patients undergoing colectomy. Therefore, in addition to shortening the recovery time of bowel function, whether EA can reduce the possibility of patients developing late POI may also have clinical significance. Two researchers analysed the diaries to establish whether patients had developed early or late ileus. The I-FEED (intake, feeling nauseated, emesis, physical examination, and duration of symptoms) classification was developed by an expert panel of international experts from anesthesia, nursing, nutrition, and surgery with expertise in Enhanced Recovery pathways and perioperative medicine during the second Perioperative Quality Initiative.¹⁴ We also assessed the postoperative gastrointestinal function measured by the I-FEED scoring system, which assigns 0 to 2 points for each of five components based on clinical presentation, then

categorises patients as having normal gastrointestinal function (scores of 0–2), postoperative gastrointestinal intolerance (scores of 3–5), or postoperative gastrointestinal dysfunction (scores of 6).

Statistical analysis

We designed our trial to determine whether there was a difference between each EA group and the standard care group in terms of the time to first flatus and time to defecation. A sample size calculation was performed based on previous trials^{10,15} and clinical experience. For the time to first flatus, the mean reduction was 16.8 h, favoring the EA group, with a standard deviation of 21.6 h. In January 2017, the FDA issued a guidance on ‘Multiple Endpoints in Clinical Trials’ stating that no multiplicity adjustment is necessary for co-primary endpoint.¹⁶ Therefore, considering the two-pairwise comparison (EA at ST36 compared with Standard care group, EA at ST 25 compared with Standard care group), α was only corrected to 0.025 to increase the power without regard to the co-primary outcomes. Based on these data, a group size of 35 patients was needed to detect a statistical difference, assuming a 10% dropout rate (2-sided significance level of 2.5%, power of 80%). For the time to first defecation, the mean reduction was 36 h, favouring the EA group, with a standard deviation of 45 h. Based on these data, a group size of 33 patients was needed. To ensure both primary outcomes were adequately powered, a total of 105 patients was ultimately included.

Categorical variables are presented as n (%) and continuous variables are presented as the mean (SD) or median (interquartile range, IQR). For the co-primary outcomes and key time to event secondary endpoints, considering the outcome are time-related and more intuitive to show changes, Kaplan–Meier analysis was used, with comparison of groups by the Breslow (Generalized Wilcoxon) test (*Appendix study protocol*, amendments). To be consistent with sample size calculation, two-sample t-test was also used as sensitivity analysis. The incidence of nausea, vomiting, and abdominal distension, the frequency of taking analgesics, the severity of pain, the occurrence rate of difference POI types, and the incidence of compliance were analysed with the Chi-square test or Mann-Whitney U test. Among the primary outcomes data, there was only one piece of missing data (patient forgot to record the time to first defecation). To make the results more conservative, we used the length of stay to replace it. For secondary outcomes, no imputation for missing data and the actual observed data were used to perform the analysis.

Analyses were performed in an intention-to-treat setting using IBM SPSS Statistics version 20 (IBM Corp, Armonk, NY). All tests applied were two-tailed, $p < 0.05$ was considered statistically significant. For the primary

outcomes, the p values were adjusted for multiple comparisons ($p < 0.025$) using Bonferroni correction.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to the data in the study and gave the final approval of the manuscript and agree to be accountable for all aspects of work.

Results

Patient characteristics

From Nov 15, 2019 to Sep 30, 2020, 129 patients with primary colorectal cancer were assessed for eligibility. Of these, 10 were excluded because they did not meet the inclusion criteria, and 14 declined to participate (**Figure 1**). The remaining 105 patients were randomly assigned to receive EA at ST36 with standard care ($n = 35$), EA at ST25 with standard care ($n = 35$), or standard care alone ($n = 35$). After randomisation, five patients (two patients in EA at ST25 group, three patients in EA at ST36 group) were unwilling to receive acupuncture during day 2 to 4 postoperatively, three patients (two patients in EA at ST25 group, one patient in EA at ST36 group) received Si-Mo-Tang (a Chinese patent medicine/prescription to enhance digestive function) that may interfere with the outcomes, and one patient in the standard care group requested to receive EA treatment. These nine patients were retained in the final analysis. Thus 35 patients per group were included in the intention-to-treat analyses.

Table 1 summarises demographic and baseline characteristics. There was no difference among groups regarding the usual risk factors for POI, such as male sex, age, body-mass index, or duration of surgery, which confirmed that the groups were well matched.

Effect of EA on first bowel movement

After receiving EA at ST36 with standard care, the time to first flatus and defecation were shorter (between-group difference -10.98 [97.5% CI -21.41 to -0.56], $p = 0.02$ for flatus; -25.41 [-47.89 to -2.93], $p = 0.02$ for defecation; **Table 2**). The hazard ratio for earlier first flatus after EA was 1.743 (97.5% CI 1.007–3.019, $p = 0.02$; **Figure 2**), and for first defecation after EA was 2.02 (97.5% CI 1.146–3.56, $p = 0.005$; **Figure 2**). Unlike EA at ST36 group, there was no significant difference in the time to first flatus and defecation between the EA at ST25 group and standard care group (between-group difference -5.54 [97.5% CI -15.78 to 4.70], $p = 0.26$ for flatus; -17.69 [-40.33 to 4.95], $p = 0.08$ for defecation; **Table 2**). Sensitivity analysis showed that the results of the two-sample t-test were consistent with the Kaplan–Meier analysis (eTable 6),

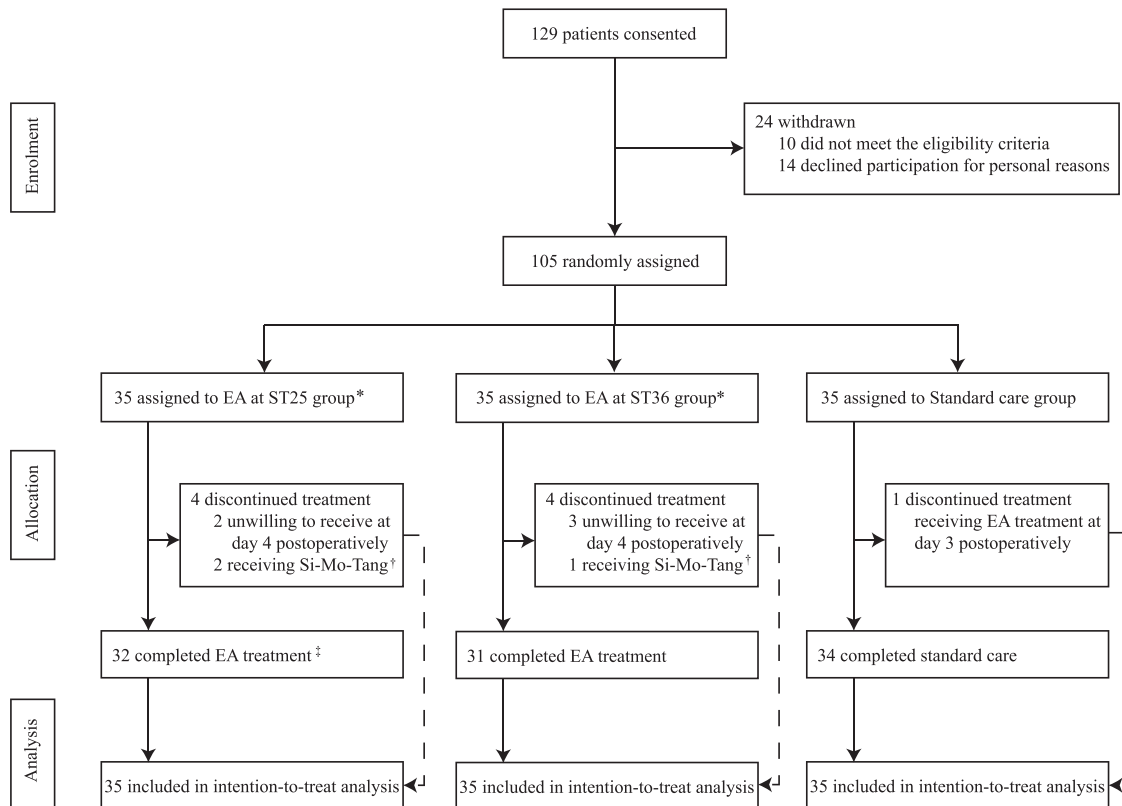


Figure 1. Trial profile. *EA at ST36 group: EA at ST36 (Zusanli) acupoint combined with standard care; EA at ST25 group: EA at ST25 (Tianshu) acupoint combined with standard care; Standard care group: standard care alone. † Si-Mo-Tang is decoction that may interfere with the outcomes. ‡ one patient received Si-Mo-Tang at day 6 postoperatively. At this time, they had received all EA treatments. EA=electroacupuncture.

reflecting the robustness of the results. When assessing the occurrence of different POI types, incidence of late POI was lower in the EA at ST36 group than in the standard care group ($p = 0.02$; Table 3), but it was similar between EA at ST25 group and the standard care group ($p = 0.43$; Table 3).

Compared with standard care alone, EA at ST36 or ST25 with standard care could significantly shorten the time to tolerance of a semi-liquid diet (Table 2). Patients in the EA at ST36 group, but not the EA at ST25 group, tolerated liquid food faster than standard care group (Table 2). There was no significant difference among groups in time to walk independently, length of hospital stay, use of analgesic, incidence of vomiting, or extent of pain, nausea and abdominal distension (Table 2 and 3). Among groups, the proportion of patients with I-FEED scores indicating normal postoperative gastrointestinal function, postoperative gastrointestinal intolerance, and postoperative gastrointestinal dysfunction were similar ($p = 0.19$; eTable 5).

During EA treatment, three patients had sensation (pain, soreness, or swelling) after the needle was removed (one in the ST25 group, two in the ST36 group, eTable 3). These events were mild, self-limiting, and

none required special medical interventions. There were no serious adverse events.

Perioperative complications

No deaths were observed in any group. 98 (93.3%) of the 105 patients were discharged uneventfully (Table 4), and there was no significant difference among groups in overall post-operative complications ($p = 0.24$ for EA at ST25 vs NA, $p = 0.99$ for EA at ST36 vs NA). Except for the patient experiencing anastomotic leakage (EA at ST36 group), who required redo surgery and had a Clavien-Dindo severity score of IIIa, and the patient experiencing intestinal adhesion (EA at ST36 group), who had a Clavien-Dindo severity score of IIIa, all the complications had a Clavien-Dindo severity score less than II.

Discussion

Postoperative ileus has historically been considered an unavoidable outcome of major abdominal surgery, which is associated with significant clinical and economic burdens. In this trial of EA for patients

Variable	EA at ST25 group (n = 35)	EA at ST36 group (n = 35)	Standard care group (n = 35)
Sex, n (%)			
Male	18 (51)	25 (71)	23 (66)
Female	17 (49)	10 (29)	12 (34)
Age, mean (SD), years	61.8 (11.0)	60.7 (12.7)	60.7 (10.5)
Body-mass index, mean (SD), kg/m ²	23.9 (3.2)	24.3 (2.4)	24.2 (2.9)
American Society of Anesthesiologists grade, n (%)			
I	2 (6)	2 (6)	0 (0)
II	31 (89)	33 (94)	35 (100)
III	2 (6)	0 (0)	0 (0)
Current smoker, n (%)	1 (3)	2 (6)	3 (9)
Diabetes, n (%)	4 (11)	3 (9)	5 (14)
Type of operation, n (%)			
colectomy	22 (63)	14 (40)	16 (46)
proctectomy	13 (37)	20 (57)	18 (51)
coloproctectomy	0 (0)	1 (3)	1 (3)
Duration of surgery, mean (SD), min	177.3 (61.5)	187.7 (59.4)	174.3 (54.0)
Intraoperative blood loss, median [IQR], mL	0 [0–30]	25 [0–30]	25 [0–30]
Use of self-controlled analgesia pump, n (%)	33 (94)	33 (94)	35 (100)

Table 1: Demographics and baseline characteristics.
SD: standard deviation, IQR: interquartile range.

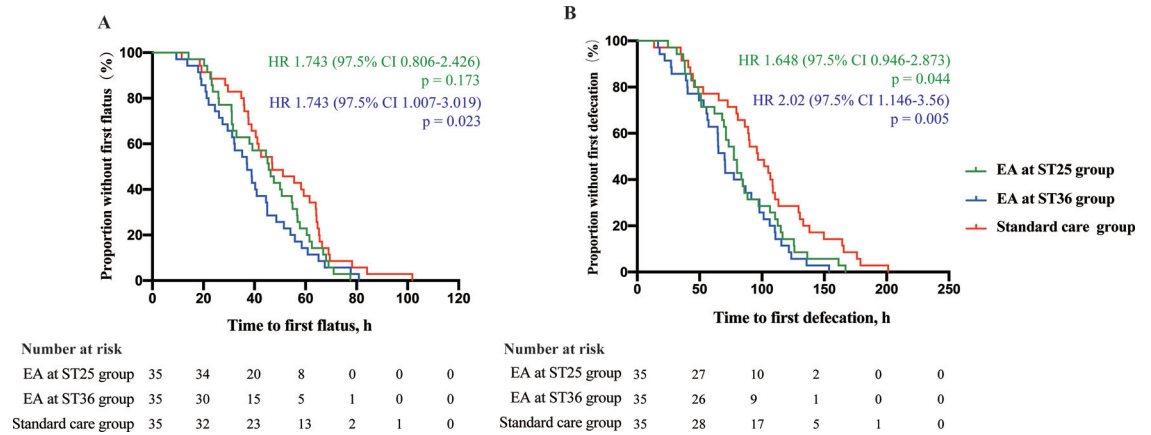


Figure 2. Kaplan–Meier curve. (A) Kaplan–Meier curve comparing time to first flatus; (B) Kaplan–Meier curve comparing time to first defecation. Hazard ratios (HRs) were estimated from Cox models. EA at ST36 group: electroacupuncture (EA) at ST36 (Zusanli) acupoint combined with standard care; EA at ST25 group: electroacupuncture at ST25 (Tianshu) acupoint combined with standard care; Standard care group: standard care alone. Among the primary outcomes data, there is only one missing data in EA at ST36 group (patient forgot to record). To make the results more conservative, we used the length of stay (later than first defecation) to replace it. Survival tables were shown in eTable 7 and 8.

undergoing elective segmental colorectal resection, we hypothesised that the addition of EA with the ERAS pathway could further improve patient outcomes, and then found a statistically significant improvement in shortening the time of recovery of gastrointestinal motility favouring the EA at ST36 group, with no significant improvement in the EA at ST25 group. ERAS combined with laparoscopy surgery has been shown to have a synergistic effect in enhancing recovery and are the best perioperative strategies after laparoscopic surgery for colon

disease.^{17,18} The finding that EA at ST36 with standard care was beneficial for POI patients is of vital significance to clinical work, as minimally invasive surgeries with the ERAS pathway continue to increase in popularity.

In this trial, the actual between-group differences of time to first flatus (10.98 h) and time to first defecation (25.41 h) were lower than the expected between-group differences used for sample size calculation (17 h for time to first flatus, 36 h for time to first defecation), which means the study power might be insufficient. It

Variable	Standard care group (n = 35)	EA at ST25 group (n = 35)	Mean difference (CI) ^d	p ^a	EA at ST36 group (n = 35)	Mean difference (CI) ^d	p ^a
Primary Outcomes							
Time to first flatus, h	50.10 ± 20.05	44.56 ± 17.23	-5.54 (-15.78 to 4.70)	0.26	39.12 ± 17.94	-10.98 (-21.41 to -0.56)	0.02
Time to first defecation, h	99.36 ± 46.1	81.67 ± 35.92	-17.69 (-40.33 to 4.95)	0.08	73.95 ± 35.24 ^b	-25.41 (-47.89 to -2.93)	0.02
Secondary Outcomes							
Time to tolerance of liquid diet ^c , h	87.98 ± 30.60	75.12 ± 19.46	-12.86 (-25.14 to -0.57)	0.09	73.86 ± 28.00	-14.12 (-28.44 to 0.20)	0.03
Time to tolerance of semi-liquid diet ^c , h	132.10 ± 36.83	109.93 ± 28.15	-22.17 (-39.20 to -5.14)	0.02	112.36 ± 40.77	-19.74 (-39.07 to -0.42)	0.03
Time to walk independently, h	46.09 ± 17.19	40.12 ± 13.26	-5.97 (-13.29 to 1.35)	0.17	49.77 ± 25.11	3.67 (-6.59 to 13.94)	0.52
Length of hospital stay ^c , h	172.53 ± 33.38	164.82 ± 26.05	-7.71 (-22.00 to 6.57)	0.37	170.92 ± 34.31	-1.61 (-17.88 to 14.65)	0.94

Table 2: Time to event outcomes.

Data are presented as mean ± SD.

^a The two electroacupuncture groups compared with Standard care group, respectively. Bold p-value indicates statistical difference ($p < 0.025$ for primary outcomes and $p < 0.05$ for others). Kaplan–Meier analysis was used, with comparison of groups by the Breslow (Generalized Wilcoxon) test.

^b There is only one missing data in EA at ST36 group (patient forgot to record). To make the results more conservative, we used the length of stay (later than first defecation) to replace it.

^c There are three censored patients in time to tolerance of liquid diet (two in EA at ST36 group, one in Standard care group); There are 11 censored patients in time to tolerance of semi-liquid diet (six in EA at ST25 group, one in EA at ST36 group, four in Standard care group); There are one censored patient in length of hospital stay (EA at ST36 group).

^d For the confidence interval of mean difference, we used 97.5% in primary outcomes and 95% in secondary outcomes.

Variable	Standard care group (n = 35)	EA at ST25 group (n = 35)	p ^a	EA at ST36 group (n = 35)	p ^a
Any postoperative ileus, n (%)					
Early	2 (6)	5 (14)	0.43 ^b	9 (26)	0.02^b
Late	33 (94)	30 (86)		26 (74)	
Use of analgesic, n (%)	30 (86)	29(83)	0.74 ^b	26(74)	0.23 ^b
Vomiting, n (%)	6(17)	10(29)	0.26 ^b	4(11)	0.50 ^b
Nausea, n (%)	16(46)	15(43)	0.81 ^b	14(40)	0.63 ^b
Abdominal distension, n (%)	22(63)	27(77)	0.19 ^b	24(69)	0.62 ^b
Pain scores, median [IQR]					
POD1	20 [0–30]	30 [0–50]	0.32 ^c	30 [0–36.7]	0.90 ^c
POD2	20 [0–30]	20 [0–40]	0.57 ^c	20 [0–30]	0.56 ^c
POD3	10 [0–30]	10 [0–30]	0.94 ^c	0 [0–20]	0.14 ^c
POD4	20 [0–30]	10 [0–20]	0.54 ^c	10 [0–20]	0.07 ^c

Table 3: Others secondary outcomes.

IQR: interquartile range; POD: postoperative day.

^a The two electroacupuncture groups compared with NA group, respectively. Bold p-value indicates statistical difference.

^b Chi-square test and c Mann-Whitney U test.

is noted that the studies we referenced for the calculated sample size were conducted without the ERAS pathway. The strategy of combined ERAS program could have attenuated the surgical stress response to a certain extent that the EA did not have enough space to further improve clinical outcomes. Since a difference of 12h in time to event above that of the control group was

suggested to be clinically meaningful,¹⁹ the between-group differences in our trial were acceptable in clinical practice. These findings are consistent with a recent meta-analysis showing the safety and effect of EA for POI after surgery, in which results indicated that EA can shorten the time of first flatus and defecation by 11.6 h and 12.94 h, respectively.²⁰ Before our study, Ng

Variable	Standard care group (n = 35)	EA at ST25 group (n = 35)	p	EA at ST36 group (n = 35)	p
No complication, n (%)	32 (91)	35 (100)	0.24*	31 (89)	0.99*
I	2	0	0.08†	3	0.69†
II	1	0		0	
III	0	0		1	
IV	0	0		0	

Table 4: Post-operative complications.

Analyzed by *Chi-square test (Fisher's exact test) or † Mann-Whitney U test.

and colleagues completed an adequately powered, sham-controlled study to evaluate the effect of EA in recovering bowel mobility after laparoscopy for colorectal cancer.¹⁰ In this study, patients that received EA had shorter time to defecation than patients that received no acupuncture, the mean difference was 36.2 h, which is higher than ours. In addition to the combined use of ERAS program, our study used single acupoint in the acupuncture protocol, which may explain this phenomenon. It is agreed that the efficacy of acupuncture is related to the dose, including number of needles, point selection, and treatment time (duration and frequency).²¹ Although the use of a single acupoint may lead to a relatively limited efficacy, it still induced a positive therapeutic effect, and using single acupoint maybe reduced the potential for hospital-acquired infections.

When it comes to EA at ST25 group, the primary outcomes were not significant, which can be explained in several ways. Firstly, it is well known that acupuncture has regionally specific effects.^{22,23} Numerous studies have shown that stimulating acupoints in the abdominal area inhibits gastric, duodenal, jejunal, and proximal colonic motility by increasing sympathetic efferent fiber activity, and stimulating acupoints in the limb, which, by contrast, facilitates the above-mentioned gut motility by exciting vagal efferent fiber activity. For the distal colonic motility, stimulating acupoints in the limbs and abdomen both produced an augmented effect. Therefore, the opposite effect of ST25 between the proximal and distal colon might dilute its effect on gastrointestinal motility. Meanwhile, this body-region specificity was also supported by a systemic inflammation model, which showed that EA at ST36 but not ST25 can drive the vagal–adrenal anti-inflammatory axis in septic mice.²⁴ Furthermore, many human and animal studies have shown that the effect of EA is dose-dependent, and current intensity is an important factor. In a study investigating the relationship between current intensity and EA-induced analgesia in rat with colorectal distension, the effect of EA at ST36 emerged from 0.5 mA, while the effect of EA at PC6 (like ST25, with different segmental innervation with colon) showed no significant difference until 2mA.²⁵ According to the treatment records, the average current intensity of the two EA groups was 1.5 mA, lower than the current intensity threshold of acupoints with

different segmental innervation, which may explain why EA at ST25 did not work and is worthy of further study.

It is important to define specific parameters when evaluating a patient for POI. Traditionally, time to first flatus and time to first defecation are essential components in the assessment of gastrointestinal dysfunction and POI.¹ These outcomes are commonly accepted as the clinical endpoint of POI and valuable indexes for evaluating the effect of interventions.²⁶ However, studies found that flatus cannot be regarded as an insensitive parameter and passing flatus may rather mirror rectal emptying and therefore not necessarily adequately reflect recovery of effective gastrointestinal motility.²⁷ Therefore, another commonly used parameter, time to recover gastrointestinal function (GI-2) which is a two-component composite endpoint that includes time until the patient first tolerates solid food and the time to first defecation, was considered to best reflect recovery of gastrointestinal transit.²⁷ Since the clinical pathway of the hospital in which we conducted this trial does not require patients to tolerate a solid diet prior to discharge, and the time to resume diet can be influenced by the patient's perception (patients often refuse to advance to solid foods too early) and are easily manipulated by the attending clinician,²⁸ we ultimately chose the time to first flatus and time to first defecation as the co-primary outcomes. Instead of the time to tolerant solid diet, we evaluated the time to tolerant liquid or semi-liquid diet. Results showed that EA at either ST36 or ST25 resulted in a significantly faster time to tolerant liquid and semi-liquid diet compared with the standard care group, which reflects the potential effect of EA on promoting upper gastrointestinal transit.

Although the underlying therapeutic mechanism has not been fully elucidated, EA has been shown to protect interstitial cells of Cajal and regulate immunity,^{29,30} and regulate secretion of hormones related to small intestinal and colonic motility.³¹ Since the intestinal muscle inflammation resulting from perioperative bowel handling is accepted widely to play an important role in the pathogenesis of POI, extensive research focused on the anti-inflammatory mechanism of acupuncture, and proposed a relationship between the vagus nerve and an inhibitory feedback mechanism of the innate immune system. In mice, our previous study found that EA suppressed intestinal inflammation

and promoted gastrointestinal motility by activated α_7 nAChR-mediated cholinergic anti-inflammatory pathways in macrophages that reduced the production of inflammatory cytokines.³² The mechanism was also found in a human study that transcutaneous electrical acupoint stimulation applied in the lower limbs enhanced gastrointestinal functional recovery, which is associated with increased parasympathetic nerve tone and its anti-inflammatory actions.³³ Considering that most of the existing studies are aimed at lower limb acupoints, and the efficacy and underlying mechanisms of acupoints in the abdomen or limbs may be different, further research focusing on determining the specific mechanism of action is required.

Some limitations have to be discussed. First of all, due to the different area of acupoints and the nature of acupuncture, acupuncturists and patients were not blinded. The two EA groups received more attention for at least 25–30 min per each day as part of the acupuncture treatment compared with the standard care group. Therefore, the lack of blinding and longer patient contact time may affect the results. However, our study still could partially answer whether a strategy combined with acupuncture produces an acceptable degree of improvement that could inform everyday clinical practice. Secondly, this study included patients undergoing colonic or rectal surgery for colorectal cancer. It is not known whether the observed outcomes can be extrapolated to other elective and/or emergency abdominal operations. Thirdly, the sample size of 35 patients per group is underpowered, thus further studies with sufficient sample sizes are needed. Finally, the trial was conducted in a single centre with strict criteria. The extrapolation of the findings needs to be taken with caution.

In conclusion, this study presents evidence that EA at ST36 or ST25 can be safely administered in a postoperative setting to patients with colorectal cancer after resection, and that EA at ST36 in combination with standard care significantly enhances bowel function recovery, more robustly than standard care alone. Future studies should explore the underlying mechanism of acupuncture in treating POI.

Contributors

CZL is the guarantor for the article. CZL, JWY, JKS, YW, and WP designed the study. JKS, WP, QL, JWY, and SCZ recruited and followed up patients. GXS and JWY coordinated the study. Data analysis was done by SYY and JWY. YW, NNY, and LQW were responsible for study monitoring. The manuscript was prepared by JWY, YW, SYY and CZL, and revised by JKS, WP, JWY, SCZ, NNY, GXS and LQW. SYY and JWY take responsibility for the accuracy of the data analysis. All authors had full access to the data in the study and gave the final approval of the manuscript and agree to be accountable for all aspects of work.

Data sharing

De-identified individual clinical data will be made available to others upon request to the corresponding authors, only for research, non-commercial purposes to individuals affiliated with academic or public health institutions.

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Declaration of interests

We declare no competing interests.

Supplementary materials

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References

- Vather R, Trivedi S, Bissett I. Defining postoperative ileus: results of a systematic review and global survey. *J Gastrointest Surg*. 2013;17:962–972.
- Veldkamp R, Kuhry E, Hop WC, et al. Laparoscopic surgery versus open surgery for colon cancer: short-term outcomes of a randomised trial. *Lancet Oncol*. 2005;6:477–484.
- van Bree SH, Nemethova A, Cailotto C, et al. New therapeutic strategies for postoperative ileus. *Nat Rev Gastroenterol Hepatol*. 2012;9:675–683.
- Lee SM, Kang SB, Jang JH, et al. Early rehabilitation versus conventional care after laparoscopic rectal surgery: a prospective, randomised, controlled trial. *Surg Endosc*. 2013;27:3902–3909.
- Harbaugh CM, Al-Holou SN, Bander TS, et al. A statewide, community-based assessment of alvimopan's effect on surgical outcomes. *Ann Surg*. 2013;257:427–432.
- Büchler MW, Seiler CM, Monson JR, et al. Clinical trial: alvimopan for the management of post-operative ileus after abdominal surgery: results of an international randomised, double-blind, multicentre, placebo-controlled clinical study. *Aliment Pharmacol Ther*. 2008;28:312–325.
- Cheong KB, Zhang JP, Huang Y. The effectiveness of acupuncture in postoperative gastroparesis syndrome—a systematic review and meta-analysis. *Complement Ther Med*. 2014;22:767–786.
- Martin CS, Deverman SE, Norvell DC, et al. Randomised trial of acupuncture with antiemetics for reducing postoperative nausea in children. *Acta Anaesthesiol Scand*. 2019;63:292–297.
- Yu Z. Neuromechanism of acupuncture regulating gastrointestinal motility. *World J Gastroenterol*. 2020;26:3182–3200.
- Ng SS, Leung WW, Mak TW, et al. Electroacupuncture reduces duration of postoperative ileus after laparoscopic surgery for colorectal cancer. *Gastroenterology*. 2013;144:307–313. .e1.
- Zhou K, Fang J, Wang X, et al. Characterization of de qi with electroacupuncture at acupoints with different properties. *J Altern Complement Med*. 2011;11:1007–1013.
- Chinese society of surgery, Chinese society of anesthesiology. Consensus on ERAS and guidelines for pathway management in China (2018). *Chin J Anesthesiol*. 2018;38:8–13.
- Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg*. 2009;250:187–196.
- Hedrick TL, McEvoy MD, Mythen MMG, et al. American society for enhanced recovery and perioperative quality initiative joint consensus statement on postoperative gastrointestinal dysfunction within an enhanced recovery pathway for elective colorectal surgery. *Anesth Analg*. 2018;126:1896–1907.

- 15 Deng G, Wong WD, Guillem J, et al. A phase II, randomised, controlled trial of acupuncture for reduction of Postcolectomy Ileus. *Ann Surg Oncol*. 2013;20:1164–1169.
- 16 FDA Draft Guidance for Industry. Multiple endpoints in clinical trials (2017). Available at <https://www.fda.gov/media/102657/download>. Accessed 30 March 2022.
- 17 Lee TG, Kang SB, Kim DW, et al. Comparison of early mobilization and diet rehabilitation program with conventional care after laparoscopic colon surgery: a prospective randomised controlled trial. *Dis Colon Rectum*. 2011;54:21–28.
- 18 Vlug MS, Wind J, Hollmann MW, et al. Laparoscopy in combination with fast track multimodal management is the best perioperative strategy in patients undergoing colonic surgery: a randomised clinical trial (LAFA-study). *Ann Surg*. 2011;254:868–875.
- 19 Ghodraty MR, Rokhtabnak F, Dehghan HR, et al. Crystalloid versus colloid fluids for reduction of postoperative ileus after abdominal operation under combined general and epidural anesthesia. *Surgery*. 2017;162:1055–1062.
- 20 Liu Y, May BH, Zhang AL, et al. Acupuncture and related therapies for treatment of postoperative ileus in colorectal cancer: a systematic review and meta-analysis of randomised controlled trials. *Evid Based Complement Alternat Med*. 2018;2018: 3178472.
- 21 Pomeranz B, Berman B. *Scientific Basis of Acupuncture; Basics of Acupuncture*. Springer; 2003:7–86.
- 22 Noguchi E. Acupuncture regulates gut motility and secretion via nerve reflexes. *Auton Neurosci*. 2010;156:15–18.
- 23 Liang C, Wang KY, Gong MR, et al. Electro-acupuncture at ST37 and ST25 induce different effects on colonic motility via the enteric nervous system by affecting excitatory and inhibitory neurons. *Neurogastroenterol Motil*. 2018;30:e13318.
- 24 Liu S, Wang ZF, Su YS, et al. Somatotopic organization and intensity dependence in driving distinct NPY-expressing sympathetic pathways by electroacupuncture. *Neuron*. 2020;108:436–450. e7.
- 25 Yu L, Wang W, Li L, et al. Inhibition of electroacupuncture on nociceptive responses of dorsal horn neurons evoked by noxious colorectal distention in an intensity-dependent manner. *J Pain Res*. 2019;12:231–242.
- 26 Mattei P, Rombeau JL. Review of the pathophysiology and management of postoperative ileus. *World J Surg*. 2006;30:1382–1391.
- 27 van Bree SH, Bemelman WA, Hollmann MW, et al. Identification of clinical outcome measures for recovery of gastrointestinal motility in postoperative ileus. *Ann Surg*. 2014;259:708–714.
- 28 Jung SY, Chae HD, Kang UR, Kwak MA, Kim IH. Effect of acupuncture on postoperative ileus after distal gastrectomy for gastric cancer. *J Gastric Cancer*. 2017;17:11–20.
- 29 Liu M, Zhang S, Gai Y, et al. Changes in the interstitial cells of cajal and immunity in chronic psychological stress rats and therapeutic effects of acupuncture at the zusanli point (ST36). *Evid Based Complement Alternat Med*. 2016;2016: 1935372.
- 30 Deng J, Yang S, Yuan Q, et al. Acupuncture ameliorates postoperative ileus via IL-6-miR-19a-KIT axis to protect interstitial cells of cajal. *Am J Chin Med*. 2017;45:737–755.
- 31 Zhu X, Liu Z, Qu H, et al. The effect and mechanism of electroacupuncture at LI11 and ST37 on constipation in a rat model. *Acupunct Med*. 2016;34:194–200.
- 32 Yang NN, Yang JW, Ye Y, et al. Electroacupuncture ameliorates intestinal inflammation by activating $\alpha 7nAChR$ -mediated JAK2/STAT3 signaling pathway in postoperative ileus. *Theranostics*. 2021;11:4078–4089.
- 33 Gao W, Li W, Yan Y, et al. Transcutaneous electrical acupoint stimulation applied in lower limbs decreases the incidence of paralytic ileus after colorectal surgery: a multicenter randomized controlled trial. *Surgery*. 2021;170:1618–1626.