Original Article

A randomized controlled trial of Chinese traditional medicine Dachengqi Decoction in the treatment of postoperative intestinal function recovery

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Background: Intestinal dysfunction is not conducive to the recovery of patients after surgery. It is particularly important to restore the intestinal function as soon as possible. In recent years, ultrasonic drug penetration therapy as a new type of non-invasive therapy has been used to solve this problem, but its efficacy has not been confirmed.

Methods: Single-centre, parallel, randomized controlled clinical trial in China that included 184 patients undergoing laparoscopic gastrointestinal surgery. Ninety-one participants were randomly assigned to low-frequency ultrasound and electric pulses for transdermal drug delivery with Dachengqi Decoction (DCQD) (intervention group), and 90 were assigned to the control group after laparoscopic gastrointestinal surgery. The primary outcome was time to first flatus after surgery (by patient's subjective feeling). Secondary outcomes assessed the recovery time of bowel movement, time of the first defecation, postoperative gastrointestinal complications (e.g., nausea, vomit, and bloating), days of hospitalization and treatment costs.

Results: Of 184 patients, 181 (98.4%) completed the trial. The sociodemographic characteristics and efficiency data were comparable in the two groups at baseline. The intervention group had a shorter mean time of bowel movement recovery than the control group [29.4 h (IQR, 22.0–35.0 h) *vs.* 33.7 h (IQR, 24.0–40.0 h; P=0.005)] and a shorter mean time to first flatus after surgery [35.8 h (IQR, 23.1–46.6 h) *vs.* 46.7 h (IQR, 25.9–61.3 h; P=0.012)]. Postoperative gastrointestinal reactions (e.g., nausea, vomit, and bloating) occurred in 28.6% in the intervention group and 43.3% in the control group (P=0.038). Two patients in the intervention group had electrical tingling sensations, and one patient had a skin rash during the treatment. There were no significant differences in the occurrence rates of AEs or SAE, days of hospitalization and treatment costs between the two groups.

Conclusions: Low-frequency ultrasound and electric pulses for transdermal drug delivery with DCQD can shorten the time of bowel movement recovery and accelerate first anal exhaust after laparoscopic gastrointestinal surgery.

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Keywords: Low-frequency ultrasound; transdermal drug delivery; Dachengqi decoction; intestinal function recovery

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Introduction

Postoperative ileus is a significant problem especially after open abdominal surgery via laparotomy and this has reduced since the introduction of laparoscopic surgery. Despite the advancement in laparoscopic surgery, paralytic ileus remains an issue in major complex gastrointestinal surgery due to long operative duration and considerable surgical trauma. The pathogenesis of post-operative ileus involves inhibitory neural reflexes and inflammatory mediators released from the site of injury. The varying degrees of inhibitory function of gastrointestinal motility after surgery may result in the symptoms of abdominal distension, nausea, vomiting, and even intestinal obstruction (1).

The recovery process of gastrointestinal function after surgery mainly includes intestinal paralysis, irregular peristalsis and return to normal motility. It is generally believed that recovery occurs in the first or second day for intestinal paralysis, second to third day for irregular peristalsis, and third to forth day for normal motility (2). The later the recovery of gastrointestinal function, the more severe the pathophysiological changes, such as intestinal effusion, water-electrolyte imbalance, and infection occur. Therefore, it is particularly important to restore the intestinal function of patients after surgery as soon as possible. At present, early oral feeding, ambulation, hot abdominal physiotherapy, anal enema, and Chinese medicine or treatment are commonly used clinically to help patients' intestinal function recovery. In recent years, ultrasonic drug penetration therapy as a new type of non-invasive therapy has been used to solve this problem.

Ultrasound conductance drug penetration therapy (3) is a combination of laser micro-hole technology, ultrasonic transdermal technology, and iontophoresis technology that achieves targeted and fixed-rate precise target drug delivery technology (4,5), which process is simple, safe and non-invasive (6). According to Chinese medicine, DCQD can promote the secretion of Gastrokin, improve disorders of gastric electric rhythm after surgery, reduce the incidence of gastrointestinal motility, and promote the recovery of gastrointestinal motility (7). However, due to the bitter taste of DCQD, oral drinking has limited its clinical application. Therefore, the external form of DCQD as a patch has been developed and combined with the ultrasonic conductivity meter to penetrate the medicine through the abdominal wall; however, this method's efficacy has not been confirmed.

Thus, a parallel randomized controlled clinical trial was designed to evaluate the effect of low frequency ultrasonic transdermal delivery system with DCQD in postoperative intestinal function recovery on patients after laparoscopic gastrointestinal surgery. We present the following article in accordance with the CONSORT reporting checklist (8) (available at http://dx.doi.org/10.21037/tcr-19-2671).

Methods

Study design and setting

This single-center and parallel randomized controlled clinical trial took place in the Department of General Surgery of Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences in Guangzhou, China. Enrolment occurred between July 1, 2017, and December 31, 2017. This study was approved by the Ethics Committee of Guangdong Provincial People's Hospital (No. GDRE2016429H) and was carried out in adherence with the Declaration of Helsinki (as revised in 2013). All patients involved in the study provided written informed consent.

Participants

Patients were eligible if they were aged 18–70 years old, underwent elective laparoscopic gastrointestinal surgery, and if the operation time did not exceed six hours. Exclusion criteria included pregnant or lactating women, emergency surgery, extensive metastases of intra-abdominal gastrointestinal tumors or extensive intra-abdominal adhesions, severe abdominal infections, acute complete intestinal obstruction, required colostomy or small intestine ostomy that did not allow for evaluation of bowel exhaust or defecation, severe cardiovascular and haematopoietic diseases, diabetes with poor glycaemic control (fasting blood glucose >8 mmol/L), alanine aminotransferase (ALT) > normal upper limit 1.5 times or creatinine (CREA) > normal upper limit, body mass index (BMI >30 or <15), pacemakers, artificial stents and artificial valves, severe complications or serious infections or unconsciousness on the first postoperative day, use of drugs that affected gastrointestinal motility within one week before surgery, and inclusion in another trial within 4 weeks prior to enrolment.

Sample size estimation and randomization

Sample size estimation was performed according to the superiority trial design by PASS 11 software. According to the literature results, the postoperative flatus time was 53.6±10.7 and 62.9±11.4 h in the intervention group and

the blank control group, respectively. We set the equal ratio k=1, the superiority boundary value Δ as four hours, type I error α=0.025 and type II error β=0.20; thus, it could be concluded that there were 60 patients in each group. With an expulsion rate of 20% and a specific expected rejection rate of 6%, 92 patients were enrolled in one group for the study. The data manager used SAS (Statistical Analysis System) to create the randomization sequence with a 1:1 allocation ratio. Two professional physician assistants were arranged to implement patient enrolment, treatment, data collection, and recording. Surgeons who performed the surgery were unaware of treatment allocation throughout the trial.

Interventions

Briefly, patients in the intervention group received low-frequency ultrasound and electric pulses for transdermal drug delivery with DCQD treatment after the operation. DCQD is composed of *Da Huang* (*Radix et Rhizoma Rhei*), *Houpu* (*Cortex Magnoliae Officinalis*), *Zhi Shi* (*Fructus Aurantii Immaturus*) and *Mang Xiao* (*Natrii Sulphas*). Materials and drugs were provided by "Beijing Noah Tongzhou Medical Technology Co, Ltd." and included the NAVA-01TD ultrasound conductivity meter (*Figure S1*), ultrasound conductance gel patches, and DCQD patches, as shown in (*Figure S2*). Patients in the intervention group received the treatment within six hours after the operation, and the DCQD patch was placed on the left abdomen of the patients (*Figure S3*). Each treatment lasted for 30 minutes, and the DCQD patch was kept in the patient's abdomen for two hours. The procedure was performed once on the day of surgery and twice daily after the first day after surgery until the patient complained of first flatus. The control group received similar conventional treatment that excluded low-frequency ultrasound and electric pulses for transdermal drug delivery with DCQD treatment.

Outcomes

The primary outcome was defined as the time to first flatus by the patient's subjective feeling after surgery. The secondary outcomes assessed the recovery time of bowel movement (by auscultation of bowel sounds once every 4 hours; if two consecutive results ≥4 times per minute; next, the bowel movement was determined to be recovered), time of the first defecation, postoperative gastrointestinal complications (e.g., nausea, vomit, and bloating), days of hospitalization and treatment costs. We evaluated vital signs, such as body temperature, pulse, and arterial blood pressure, and serum tests, including ALT, AST, CREA, and CRP, before surgery and at days one, three and five after surgery. Adverse events (AEs) and serious adverse events (SAE) were recorded in the Case Report Form (CRF).

Statistical analysis

All statistical tests used two-sided tests (except for special instructions). Quantitative data was statistically described using case number, mean, standard deviation, median, upper and lower quartiles, and 95% confidence intervals. The *t*-test was used to compare the difference between the mean measurements of the standard measurement data and the rank sum test. Qualitative data was statistically described using various types of cases and percentages. A comparative analysis of the two groups before and after treatment within the groups or between the groups used the χ^2 test, Fisher's exact test or rank sum test. The efficiency of measured data was analyzed based on a full analysis set (FAS) and per protocol set (PPS), while safety measures were examined in the safety set (SS). According to the unilateral, there was a 97.5% confidence interval upper limit and the superiority boundary (Δ) between the two groups, whether the efficacy of the intervention group was better than that of the control group was evaluated. If the upper limit of the 97.5% confidence interval of the two groups was <-Δ, then the effect of the intervention group was better than that of the control group. If the upper limit of the 97.5% confidence interval of the two groups was ≥-Δ, the curative effect of the intervention group could not be indicated.

Results

Study population

During the study period, 351 patients were screened for eligibility and 184 were randomized (*Figure 1*). Subsequent exclusion of the 3 randomized patients due to laparotomy, great omentum resection only, or small intestine ostomy left 91 patients in the intervention group and 90 in the control group. *Table 1* compares the patients' characteristics between the groups, which were well-balanced.

Outcomes assessment

Primary outcomes

Postoperative time to first flatus differed significantly

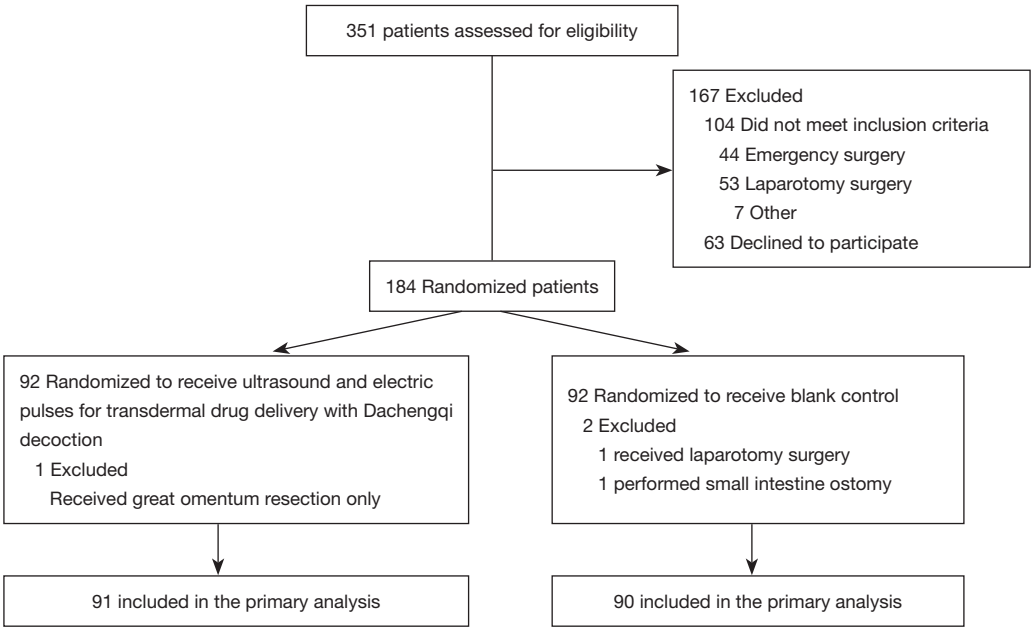

Figure 1 Population flowchart of intervention treatment to laparoscopic gastrointestinal surgery patients.

Table 1 Baseline characteristics

Terms	Event	Intervention group (n=91)	Control group (n=90)	Test statistics	P value
Gender (%)	Male	52 (57.14)	47 (52.22)	0.44	0.506
	Female	39 (42.86)	43 (47.78)		
Age(year)	Mean (SD)	58.0 (10.2)	60.0 (10.1)	1.56	0.119
BMI (kg/m^2)	Mean (SD)	22.8 (3.5)	22.3 (3.6)	0.07	0.337
Preoperative complications	No	63 (69.23)	56 (62.22)	0.99	0.321
	Yes	28 (30.77)	34 (37.78)		
History of abdominal surgery	Yes	11	13	0.218	0.640
	No	80	77		
ASA Grade	I	38	28	2.480	0.369
	II	52	60		
	III	1	2		
Surgical site	Gastric	25	28	0.594	0.922
	Intestinal	1	1		
	Colonic	48	46		
	Rectal	17	15		
Operation time (min)	Mean (SD)	234.0 (67.6)	231.1 (61.6)	0.845	0.635
Intraoperative blood loss (mL)	Mean (SD)	43.3 (39.0)	46.7 (54.8)	0.887	0.763

Table 2 Primary outcome and secondary exploratory outcomes

Index	Classification	Group intervention (n=91)	Group control (n=90)	Test[#] statistics	P value
Time of anal first exhaust (hour)	Mean (SD)	35.82 (17.57)	46.67 (27.60)	2.51	0.012
First defecation time after operation (day)	Mean (SD)	3.3 (1.6)	3.3 (1.8)	–0.15[a]	0.880
Time of bowel movement recovery (hour)	Mean (SD)	29.4 (11.3)	33.7 (12.8)	2.80[a]	0.005
Intestinal obstruction	No	89 (97.8)	86 (95.6)	–[b]	0.444
	Yes	2 (2.2)	4 (4.4)		
Number of intravenous infusion days (day)	Mean (SD)	5.6 (2.7)	5.9 (3.0)	0.69	0.488
Postoperative hospital stayed (day)	Mean (SD)	6.4 (2.8)	6.9 (3.1)	0.87	0.385
Hospitalization costs (Ten thousand RMB)	Mean (SD)	6.68 (2.27)	6.81 (1.71)	0.54	0.590

[#], t-test. [a], used the rank sum test; [b], used the exact probability method.

Table 3 Test of optimality for the main effective index (FAS/PPS population)

Time of first anal exhaust (hour)		Boundary value (h)	97.5% confidence interval for the mean difference (%)	
Group intervention	Group control		Lower limit	Upper limit
35.82	46.67	–4	–17.62	–4.07

Table 4 Comparison of postoperative gastrointestinal reactions in two groups

Index	Group intervention (n=91)	Group control (n=90)	Total (n=181)	Test statistics	P value
Postoperative gastrointestinal reactions				4.28	0.038
No (%)	65 (71.4)	51 (56.7)	116 (64.1)		
Yes (%)	26 (28.6)	39 (43.3)	65 (35.9)		

between the two groups: 35.8±17.6 h in the intervention group *vs.* 46.7±23.7 h in the control group, P=0.012 (*Table 2*). Regarding the superiority test for the main effective indicator, the 97.5% confidence interval for the mean difference was –4.0 (–17.26, –4.07), indicating that the intervention group was superior to control group, which was consistent with the PPS (Per-protocol set) results (*Table 3*).

Secondary outcomes

In the intervention group, the time of bowel movement recovery was 29.4 h (IQR, 22.0–35.0 h), which was significantly shorter than that of the control group (33.7 h, IQR, 24.0–40.0 h; P=0.005) (*Table 2*). Postoperative gastrointestinal reactions (e.g., nausea, vomit, and bloating) occurred in 28.6% in the intervention group and 43.3% in of the control group (P=0.038), which was determined to be an insignificant difference (*Table 4*).

The first postoperative defecation time was 3.3 days (IQR, 2.0–4.0 days) in the intervention group *vs.* 3.3 days (IQR, 2.0–4.0 days) for the control group (P=0.880). The incidence of intestinal obstruction was 2.2% in the intervention group and 4.4% in the control group (P=0.444). The impact of postoperative complications in the intervention group was 15.4% and 23.3% in the control group (P=0.176), which was determined to be an insignificant difference. Days of hospitalization and treatment costs were similar between the two groups (*Table 2*).

Changes from baseline over time in alanine aminotransferase, aspartate aminotransferase, C-reactive protein, and Creatinine within each group are illustrated in *Figure 2*, which demonstrated no significant difference. Vital signs (Body temperature, Heart rate, Systolic pressure, and Diastolic pressure) results were summarized in *Table S1*, and Serological examinations (WBC, HGB and PLT) were summarized in *Table S2*, which showed no significant

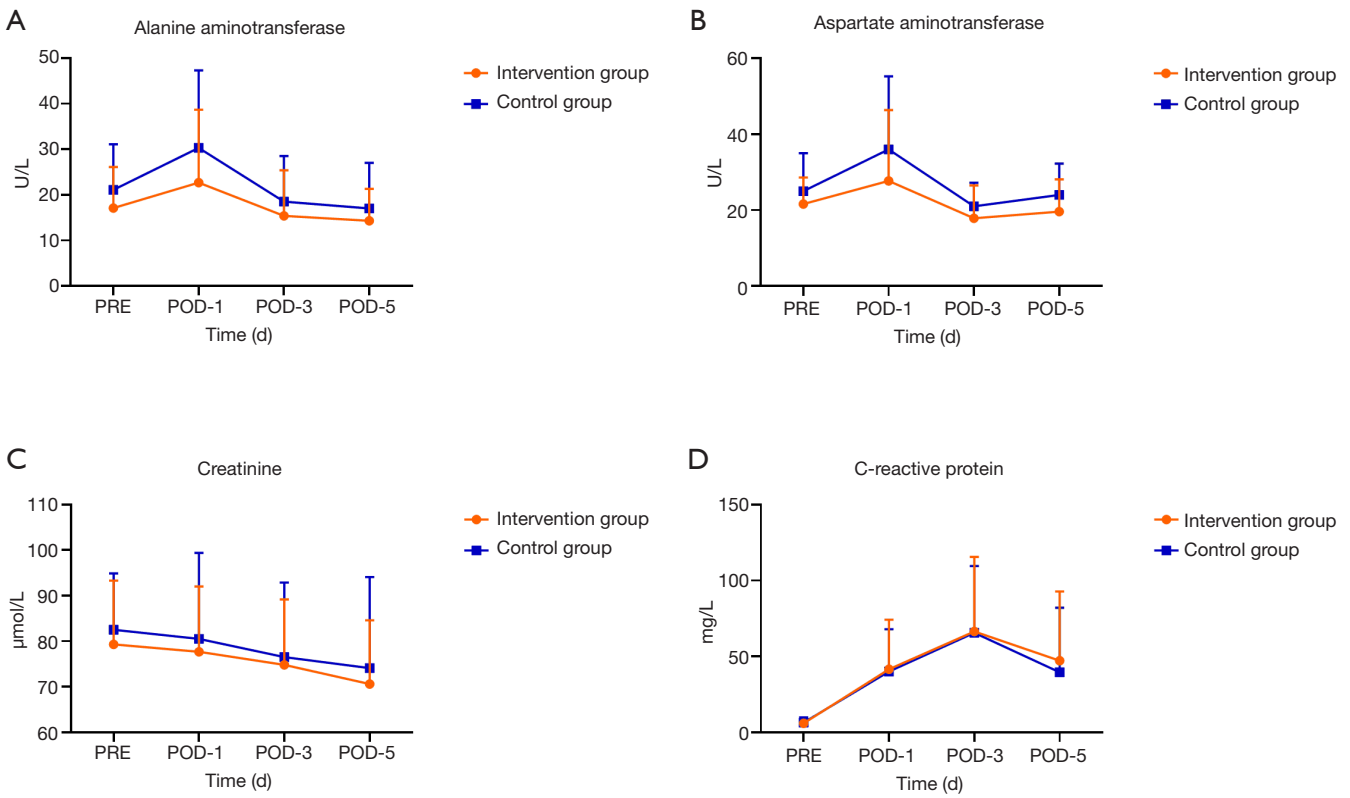

Figure 2 Changes in serum test indices from baseline over time. PRE, preoperative; POD-1, postoperative day first; POD-3, postoperative day third; POD-5, postoperative day fifth.

difference in the two groups.

Adverse events

Adverse events were reported for 26 of 91 patients (28.6%) and 39 of 90 patients (43.3%), while severe adverse events were reported for 11 of 91 patients (12.1%) and 14 of 90 patients (15.6%) in the intervention group and control group, respectively (*Table 5*). No patients died during the perioperative period, which was defined as extending from hospitalization to discharge for one week.

Discussion

To the best of our knowledge, this is the first randomized controlled clinical trial to evaluate low-frequency ultrasound and electric pulses for transdermal drug delivery with DCQD treatment for patients after a laparoscopic gastrointestinal surgery. This design reflects the daily practice of the combination of Chinese and Western medicine treatment options in many centers of China (9-12).

This trial found significant differences in the time of the recovery of bowel movement and time to first flatus after laparoscopic gastrointestinal surgery between the group with low-frequency ultrasound and electric pulses for transdermal drug delivery with DCQD and the control group. Previous studies suggested that DCQD can increase plasma motilin, enhance gastrointestinal motility, improve gastric dysrhythmia, and reduce gastroparesis after an abdominal surgery (13-15). In the current study, we did not routinely test the plasma motilin, but we found that postoperative time to first flatus did shorten about 10.9 h. In the Pan (16) review, it was found that DCQD can reduce capillary endothelial damage in acute pancreatitis-associated intestinal injury and the mechanism may be associated with the regulation of endothelial barrier function-associated proteins AQP-1, MMP9, and JAM-C. Thus, we speculated that the DCQD could accelerate the recovery of intestinal function by reducing inflammation (5,17,18).

Although the results showed no significant difference in terms of postoperative intestinal obstruction (POI) (19), the risk of adverse events associated with postoperative

Table 5 Adverse events and severe adverse events

Events	No. (%)	
	Group intervention (n=91)	Group control (n=90)
No. of patients with adverse events	26 (28.6)	39 (43.3)
Type of adverse events		
Nausea	4 (4.4)	1 (1.1)
Nausea/Vomiting	0	1 (1.1)
Mulligrubs/Ventosity	0	1 (1.1)
Ventosity	20 (22.0)	28 (31.1)
Ventosity/Nausea	2 (2.2)	5 (5.6)
Ventosity/Diarrhea	0	3 (3.3)
No. of infants with severe adverse events	11 (12.1)	14 (15.6)
Type of severe adverse events		
Anastomotic fistula	2 (2.2)	2 (2.2)
Incision infection	1 (1.1)	2 (2.2)
Lung infection	1 (1.1)	1 (1.1)
Abdominal infection	2 (2.2)	5 (5.6)
Heart failure	1 (1.1)	0
Postoperative bleeding	2 (2.2)	1 (1.1)
Intestinal obstruction	2 (2.2)	3 (3.3)

gastrointestinal reactions (nausea, vomit, bloating, and others) occurred in 28.6% of the tested patients in the intervention group and 43.3% in the control group (P=0.038), which was shown to be an insignificant difference. Meta-analysis involved 664 participants from five randomized trials suggesting that patients receiving a traditional Chinese medication method combined with a conventional therapy seemed to have improved outcomes compared with the patients receiving a standard treatment alone (OR 4.24; 95% CI, 2.83 to 6.36) (20), which still lacks the support of advantageous evidence.

Safety needs to be considered when implementing a treatment. The type of severe adverse events did not show a significant difference between the two groups, and it was usually thought to be associated with surgical quality (21,22). During the treatment course, there were three adverse events (3.3%) caused by intervention, where two patients had electrical tingling sensation during the treatment. After adjusting the frequency of treatment, they were able to tolerate the follow-up treatment. In 1 case, there was a skin rash due to the affixed electrode during surgery, which was also observed in areas where the electrocardiographic monitoring electrodes were placed. The reactions were considered as an allergy to the medical tape. The rest of the patients had no pruritus, swelling, ulceration, or other adverse reactions. In this study, we routinely detected changes from baseline over time in liver and kidney function before and after surgery. There was no significant difference between the two groups (P>0.05) concerning ALT, AST, CREA, and CRP. Studies showed that the DCQD could reduce the degree of liver and kidney function damage in rats (23,24). Therefore, we believe that low-frequency ultrasound conduction combined with DCQD would not affect the function of the liver and kidney.

In summary, low-frequency ultrasound and electric pulses for transdermal drug delivery with traditional Chinese medicine DCQD can improve abdominal distention symptoms in patients after laparoscopic gastrointestinal surgery and shorten the recovery time of the gastrointestinal function. The implementation process was simple, and the degree of patient cooperation was high; thus, it can be a strategy to enhance patient recovery after surgery.

Limitations

This study has several limitations. First, the trial was a single-center, randomized controlled clinical trial and not double-blinded, and thus there was a certain degree of bias. Further comprehensive verification and evidence from multi-center clinical studies are required. Second, it may be beneficial to have a placebo group in this study, where the low frequency ultrasonic transdermal delivery system with DCQD patch should be performed on a control group of patients without the treatment power on. Third, this study was a manifestation of the combination of Chinese and Western medicine treatment, and so although we achieved expected results in laparoscopic surgery patients, further studies are needed to prove the efficacy for laparotomy patients. Fourth, there were some heterogeneous types of surgical resection (gastric versus colorectal) in both arms of study, of which we have closely matched to reduce the bias. (Worth describing whether these were total/subtotal gastrectomy or right/left/subtotal colectomy, anterior resections etc. in *Table 1*).

Conclusions

The result of this study supported that low-frequency ultrasound and electric pulses for transdermal drug delivery with the DCQD can shorten the time of bowel movement recovery and accelerate time to first flatus after a laparoscopic gastrointestinal surgery. Furthermore, it is safe in clinical usage and has prospective clinical applications.

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Footnote

Reporting Checklist: The authors have completed the CONSORT reporting checklist. Available at http://dx.doi.org/10.21037/tcr-19-2671

Data Sharing Statement: Available at http://dx.doi.org/10.21037/tcr-19-2671

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr-19-2671). XF reports grants from the Research Fund of Guangdong Provincial People's Hospital (No. KY012019130), outside the submitted work. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Guangdong Provincial People's Hospital (No. GDRE2016429H) and informed consent was taken from all the patients.

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Supplementary

Figure S1 The NAVA-01TD ultrasound and electric pulses for transdermal drug delivery.

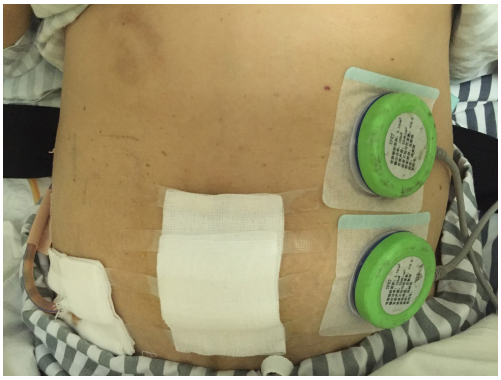

Figure S3 The Dachengqi Decoction patch paste position schematic.

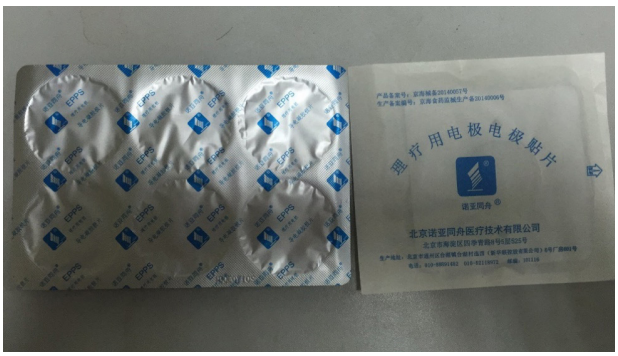

Figure S2 The Dachengqi Decoction patch.

Table S1 Analysis of vital signs results (SS population)

Index	Classification	Statistics	Group intervention, 91	Group control, 90	Total
Body temperature (℃)	Pre-operation	Mean (SD)	36.61 (0.26)	36.65 (0.25)	36.63 (0.25)
		Median (Q1, Q3)	36.60 (36.50, 36.80)	36.60 (36.50, 36.80)	36.60 (36.50, 36.80)
		Min, Max	36.10, 37.30	36.20, 37.40	36.10, 37.40
	POD-1	Mean (SD)	36.93 (0.40)	36.91 (0.36)	36.92 (0.38)
		Median (Q1, Q3)	36.90 (36.70, 37.20)	36.80 (36.70, 37.10)	36.90 (36.70, 37.10)
		Min, Max	35.30, 38.40	36.10, 38.00	35.30, 38.40
	POD-2	Mean (SD)	36.80 (0.34)	36.84 (0.33)	36.82 (0.34)
		Median (Q1, Q3)	36.80 (36.50, 37.00)	36.80 (36.60, 37.00)	36.80 (36.60, 37.00)
		Min, Max	36.10, 38.40	36.10, 38.00	36.10, 38.40
	POD-3	Mean (SD)	36.73 (0.28)	36.72 (0.27)	36.73 (0.28)
		Median (Q1, Q3)	36.70 (36.50, 36.90)	36.70 (36.50, 36.90)	36.70 (36.50, 36.90)
		Min, Max	36.10, 37.80	36.00, 37.40	36.00, 37.80
	POD-4	Mean (SD)	36.55 (0.35)	36.62 (0.30)	36.58 (0.33)
		Median (Q1, Q3)	36.50 (36.30, 36.80)	36.60 (36.50, 36.80)	36.60 (36.40, 36.80)
		Min, Max	36.00, 37.80	36.00, 38.00	36.00, 38.00
Heart rate (times/ minute)	Pre-operation	Mean (SD)	79.11 (11.39)	80.37 (9.71)	79.73 (10.58)
		Median (Q1, Q3)	78.00 (72.00, 86.00)	79.50 (74.00, 88.00)	78.00 (72.00, 87.00)
		Min, Max	52.00, 113.00	60.00, 109.00	52.00, 113.00
	POD-1	Mean (SD)	83.24 (12.34)	81.21 (10.11)	82.23 (11.30)
		Median (Q1, Q3)	82.00 (76.00, 89.00)	80.00 (75.00, 88.00)	81.00 (75.00, 88.00)
		Min, Max	64.00, 140.00	62.00, 108.00	62.00, 140.00
	POD-2	Mean (SD)	84.58 (13.14)	81.82 (12.20)	83.20 (12.72)
		Median (Q1, Q3)	82.00 (76.00, 92.00)	80.00 (76.00, 88.00)	80.00 (76.00, 90.00)
		Min, Max	61.00, 128.00	38.00, 122.00	38.00, 128.00
	POD-3	Mean (SD)	82.87 (12.40)	81.93 (11.66)	82.40 (12.01)
		Median (Q1, Q3)	82.00 (76.00, 88.00)	80.00 (76.00, 88.00)	80.00 (76.00, 88.00)
		Min, Max	55.00, 124.00	60.00, 130.00	55.00, 130.00
	POD-4	Mean (SD)	79.77 (12.22)	78.01 (12.32)	78.91 (12.26)
		Median (Q1, Q3)	78.00 (72.00, 88.00)	78.00 (70.00, 86.00)	78.00 (71.00, 86.00)
		Min, Max	53.00, 112.00	51.00, 110.00	51.00, 112.00
Systolic pressure (mmHg)	Pre-operation	Mean (SD)	128.23 (16.54)	126.52 (15.64)	127.39 (16.08)
		Median (Q1, Q3)	125.00 (117.00, 141.00)	125.50 (116.00, 135.00)	125.00 (117.00, 139.00)
		Min, Max	98.00, 172.00	95.00, 182.00	95.00, 182.00
	POD-1	Mean (SD)	122.73 (17.60)	123.97 (20.79)	123.36 (19.22)
		Median (Q1, Q3)	120.00 (109.00, 136.00)	121.00 (108.00, 140.00)	121.00 (109.00, 138.00)
		Min, Max	90.00, 700.00	88.00, 186.00	88.00, 186.00
	POD-2	Mean (SD)	125.03 (17.00)	127.42 (15.74)	126.19 (16.38)
		Median (Q1, Q3)	125.00 (114.00, 135.00)	129.00 (118.00, 136.00)	127.00 (116.00, 135.00)
		Min, Max	94.00, 180.00	91.00, 164.00	91.00, 180.00
	POD-3	Mean (SD)	127.35 (16.02)	124.27 (16.32)	125.66 (16.17)
		Median (Q1, Q3)	127.00 (117.00, 138.00)	121.50 (113.00, 137.00)	123.00 (114.00, 137.00)
		Min, Max	99.00, 159.00	93.00, 162.00	93.00, 162.00
	POD-4	Mean (SD)	131.06 (20.89)	129.97 (17.59)	130.52 (19.20)
		Median (Q1, Q3)	127.00 (119.00, 147.00)	130.00 (116.50, 142.50)	129.00 (117.00, 143.00)
		Min, Max	88.00, 178.00	102.00, 167.00	88.00, 178.00
Diastolic pressure (mmHg)	Pre-operation	Mean (SD)	79.78 (10.03)	77.81 (9.70)	78.81 (9.89)
		Median (Q1, Q3)	78.00 (73.00, 86.00)	78.00 (71.00, 85.00)	78.00 (72.00, 85.00)
		Min, Max	57.00, 105.00	60.00, 106.00	57.00, 106.00
	POD-1	Mean (SD)	72.88 (10.96)	73.88 (12.78)	73.38 (11.88)
		Median (Q1, Q3)	73.00 (65.00, 81.00)	73.00 (64.00, 83.00)	73.00 (65.00, 82.00)
		Min, Max	52.00, 97.00	41.00, 113.00	41.00, 113.00
	POD-2	Mean (SD)	76.33 (9.57)	77.53 (14.97)	76.92 (12.46)
		Median (Q1, Q3)	77.00 (71.00, 81.00)	76.50 (71.00, 80.00)	77.00 (71.00, 80.00)
		Min, Max	59.00, 108.00	53.00, 168.00	53.00, 168.00
	POD-3	Mean (SD)	79.60 (9.81)	76.25 (9.95)	77.79 (9.98)
		Median (Q1, Q3)	79.00 (70.00, 87.00)	74.00 (69.00, 86.00)	78.00 (70.00, 86.00)
		Min, Max	60.00, 97.00	59.00, 99.00	59.00, 99.00
	POD-4	Mean (SD)	79.55 (10.67)	78.25 (9.31)	78.91 (9.97)
		Median (Q1, Q3)	78.00 (70.00, 88.00)	78.50 (71.00, 85.00)	78.00 (70.00, 86.00)
		Min, Max	58.00, 99.00	62.00, 95.00	58.00, 99.00

POD-1, postoperative day 1st; POD-2, postoperative day 2nd; POD-3, postoperative day 3rd; POD-4, postoperative day 4th.

Table S2 Analysis of Serological examinations (SS population)

Index	Classification	Statistics	Group intervention	Group control	Total
WBC (10^9/L)	Pre-operation	Mean (SD)	6.46 (1.87)	6.42 (2.20)	6.44 (2.04)
		Median (Q1, Q3)	6.22 (4.94, 7.64)	5.94 (4.94, 7.24)	6.11 (4.94, 7.51)
		Min, Max	3.37, 12.02	3.41, 18.22	3.37, 18.22
	POD-1	Mean (SD)	10.67 (3.56)	10.02 (2.91)	10.35 (3.26)
		Median (Q1, Q3)	10.05 (7.98, 12.61)	9.57 (7.50, 11.91)	9.82 (7.91, 12.14)
		Min, Max	4.60, 21.33	6.16, 18.45	4.60, 21.33
	POD-3	Mean (SD)	8.25 (2.68)	7.79 (2.60)	8.02 (2.65)
		Median (Q1, Q3)	8.09 (5.95, 9.93)	7.65 (5.82, 9.53)	7.87 (5.89, 9.85)
		Min, Max	3.79, 14.89	1.72, 16.96	1.72, 16.96
	POD-5	Mean (SD)	7.35 (3.06)	6.97 (2.46)	7.16 (2.77)
		Median (Q1, Q3)	6.68 (5.12, 8.87)	6.74 (5.44, 7.85)	6.70 (5.35, 8.12)
		Min, Max	3.00, 18.74	2.44, 15.50	2.44, 18.74
HGB (g/L)	Pre-operation	Mean (SD)	119.58 (25.00)	131.14 (119.17)	125.36 (86.05)
		Median (Q1, Q3)	123.00 (109.00, 137.00)	119.50 (104.00, 134.00)	121.00 (106.00, 135.00)
		Min, Max	10.00, 165.00	68.00, 1230.00	10.00, 1230.00
	POD-1	Mean (SD)	112.66 (18.81)	111.72 (20.06)	112.19 (19.39)
		Median (Q1, Q3)	116.00 (101.00, 129.00)	113.00 (100.00, 127.00)	114.00 (100.00, 127.00)
		Min, Max	70.00, 149.00	69.00, 159.00	69.00, 159.00
	POD-3	Mean (SD)	108.05 (18.04)	104.84 (19.95)	106.43 (19.03)
		Median (Q1, Q3)	108.50 (97.00, 118.50)	107.00 (91.00, 117.00)	108.00 (93.00, 118.00)
		Min, Max	66.00, 148.00	31.00, 153.00	31.00, 153.00
	POD-5	Mean (SD)	108.25 (18.14)	106.98 (18.79)	107.62 (18.39)
		Median (Q1, Q3)	109.00 (94.50, 120.50)	106.50 (95.50, 121.00)	108.00 (95.00, 121.00)
		Min, Max	69.00, 160.00	66.00, 147.00	66.00, 160.00
		N (n miss)	90 (1)	89 (1)	179 (2)
PLT (10^9/L)	Pre-operation	Mean (SD)	280.23 (119.69)	262.24 (90.86)	271.28 (106.42)
		Median (Q1, Q3)	252.00 (202.00, 328.00)	254.00 (205.00, 305.00)	254.00 (202.00, 315.00)
		Min, Max	25.00, 754.00	59.00, 517.00	25.00, 754.00
	POD-1	Mean (SD)	247.20 (88.10)	232.08 (81.62)	239.69 (85.04)
		Median (Q1, Q3)	231.50 (180.00, 302.00)	227.00 (176.00, 287.00)	229.00 (180.00, 288.00)
		Min, Max	93.00, 606.00	60.00, 425.00	60.00, 606.00
	POD-3	Mean (SD)	226.94 (90.18)	213.11 (74.89)	220.02 (82.93)
		Median (Q1, Q3)	210.00 (170.00, 268.00)	213.00 (162.00, 255.00)	210.00 (166.00, 260.00)
		Min, Max	93.00, 652.00	57.00, 446.00	57.00, 652.00
	POD-5	Mean (SD)	239.17 (85.97)	231.37 (79.00)	235.31 (82.28)
		Median (Q1, Q3)	226.00 (182.50, 286.50)	236.00 (171.00, 258.00)	230.00 (177.00, 280.00)
		Min, Max	85.00, 569.00	72.00, 445.00	72.00, 569.00

POD-1, postoperative day 1st; POD-3, postoperative day 3rd; POD-5, postoperative day 5th; WBC, white blood cell; HGB, Hemoglobin; PLT, Platelet.