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Review Article

Clinical Evidence for Association of Electroacupuncture with Improved Colorectal Postoperative Gastrointestinal Function Recovery: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Studies on the efficacy of electroacupuncture (EA) on postoperative gastrointestinal function (PGIF) recovery in colorectal cancer (CRC) patients have been increasing, but the findings are inconsistent. To evaluate the effectiveness and safety of EA on PGIF recovery in patients with CRC based on existing randomized controlled trials (RCTs) and assess whether the current evidence is conclusive by trial sequential analysis (TSA). **Materials and Methods:** PubMed, Embase (Ovid), Medline, Cochrane Library, Chinese Biomedical Literature Database, VIP Database for Chinese Technical Periodicals, China National Knowledge Infrastructure, and Wanfang) were searched for RCTs published from inception to November 6, 2022. RCTs in which EA was compared with sham control (sham electroacupuncture, SA) or usual care (UC) for managing PGIF recovery in patients with CRC were included. Following the preferred reporting items for systematic reviews and meta-analyses, two reviewers independently extracted data as well as assessed the risk of bias using the cochrane risk of bias tool (ROB 2.0) and the certainty of evidence using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework. Data were screened and extracted independently using predesigned forms. Data were pooled using a random-effects model. **Results:** Sixteen studies, including 1290 patients with CRC that showed PGIF recovery met the inclusion criteria. The meta-analysis revealed that compared with the UC group, EA + UC group showed a significant improvement in the time to first flatus (MD: -14.59, 95% CI: -22.75 to -6.43, $P < 0.01$), time to first defecation (MD: -20.28, 95% CI: -28.14 to -12.42, $P < 0.01$), and time to first bowel sounds (MD: -11.79, 95% CI: -18.97 to -4.60, $P < 0.01$). The TSA confirmed the better treatment outcomes of EA compared with UC. Compared with the SA group, EA + UC group showed a significant improvement in the time to first flatus (MD: -10.48, 95% CI: [-13.74, -7.21], $P < 0.01$) and time to first defecation (MD: -10.72, 95% CI: [-20.14, -1.30], $P = 0.03$), and the improvement in time to first bowel sounds (MD: -5.41, 95% CI -12.43 to 1.60, $P = 0.13$) was similar. The TSA indicated there might be false positive results and further studies with a larger overall sample size are deemed necessary. The reported adverse events related to acupuncture were less serious. **Conclusion:** EA has great potential to accelerate the recovery of PGIF for patients with CRC. RCTs with usual care control was sufficient. Additional pre-registered and sham-controlled RCTs are still needed to validate the safety and efficacy of EA.

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1. Introduction

Cancer is the second leading cause of death, and colorectal cancer (CRC) ranks third among the most common cancers [1]. Surgical resection is the most common CRC treatment, but there can be postoperative complications, including postoperative gastrointestinal function (PGIF) in about 50% of patients [2, 3]. The acute gastrointestinal (GI) dysfunction after surgery performs as the postoperative ileus (POI) [4-6], which results in a high rate of morbidity and mortality and increases healthcare expenditures [2, 7-9]. At present, various psychological and drug therapies are used to treat postoperative gastrointestinal dysfunction (PGID) and complications [10, 11]. However, the optimal one with high efficacy, safety and cost-effectiveness has not been found [3, 12]. How to prevent and effectively treat POI has become a challenge.

Acupuncture is widely accented as an effective treatment for various PGIF diseases [13, 14]. Its efficacy in treating POI, however, is controversial, and related data are increasing. Electroacupuncture (EA) at acupoints, has been proven to accelerate colon movement and promote colon contraction through parasympathetic nerve and cholinergic pathways [15-17]. Several randomized controlled trials (RCTs) revealed that EA could stimulate the recovery of bowel function and shorten the hospital stay after colorectal surgery [18, 19]. Previous meta-analysis [20, 21] demonstrated that acupuncture could improve POI with low-to-moderate quality evidence. Nevertheless, systematic review of EA's efficacy on PGID in patients with CRC is lacking. In addition, the results of previous studies were controversial [18, 19, 22-25]. This review aims to evaluate the effectiveness and safety of EA on PGIF recovery in patients with CRC based on existing RCTs and to determine whether EA is conclusive in improving PGIF.

2. Materials and Methods

2.1. Literature Search Strategy

We registered our protocol on the PROSPERO (CRD42022363663) [26] and reported our study following the preferred reporting items for systematic reviews and meta-analyses 2020 (PRISMA-2020) guidelines [27] and the extension statement for acupuncture (PRISMA-A) [28] in the supplement. The following eight databases were searched, from their inception to November 6, 2022 for chinese and english articles: PubMed, Embase (Ovid), Medline, Cochrane Library, CBM, CNKI, Wanfang, and VIP. eTable1 in the supplementary file provides details on the search strategy.

2.2. Inclusion and Exclusion Criteria

The participants were patients with CRC, colon cancer or rectal cancer, who had undergone cancer surgery and were over 18 years old. The experimental interventions were EA and the control was sham interventions or usual care (UC). We also included trials comparing EA plus usual care (UC or non-intervention) with usual care alone. Main outcome(s) were recovery of PGI function included time to first flatus, and time to the first defecation, time to first bowel sounds. Secondary outcome(s) were length of hospital stay; postoperative pain; postoperative nausea and vomiting (PONV); postoperative abdominal distention and postoperative fatigue. Only RCTs that used EA to treat PGI function were included. We excluded articles that are not available in full text and other forms of publications, such as letters, comments, and conference abstracts; The researches for which we could not obtain complete data were not considered. Articles that used the same patient data or duplicate articles were not considered. The eligible trials met the following PICOS (participants, interventions, comparisons, outcomes, and study design) criteria. eTable2 in the supplementary file provides details on the summary of excluded studies with reason.

2.3. Data Extraction

Two researchers (HXX and LMC) independently selected the studies, collected the data, and imported the determined studies into EndNote 20. The third researcher (LYW) resolved any disagreements or problems. First, we excluded articles with the same data. Next, we excluded uncorrelated research by reading the title and abstract. Then, the rest studies were read in detail to determine the finally included ones. Microsoft Excel (2016) spreadsheets were used to enter the data for each included study. Including the study ID, nation, sample size, type of surgery, intervention time, study design, acupuncture points and the outcomes.

2.4. Quality Assessment

Two reviewers (HXX and LMC) independently used e cochrane Risk of Bias (ROB) tool 2.0 to assess the risk of bias [29] of the included studies. We graded the certainty of evidence using GRADE (Grading of Recommendations Assessment, Development, and Evaluation) according to (GRADE handbook). Disagreements between HXX and LMC were resolved by the third researcher (LYW). Our system review has been checked according to AMSTAR 2 [30]. According to the standards for reporting interventions in clinical trials of acupuncture (STRICTA) [31], we evaluated the description of the acupuncture treatment regimen of each study.

2.5. Strategy for Data Synthesis

Meta-analysis was conducted when there were comparisons reporting similar outcomes. We used R3.6.3 for data analysis. Whenever available, continuous data were presented as mean difference (MD) with 95% CI, and dichotomous data were presented as relative risk (RR) with 95% CI. Standardized mean differences (SMDs) with 95% CIs were calculated for studies using different outcome scales, and mean differences (MDs) with 95% CIs were calculated for studies using the same outcome scale [32]. The heterogeneity was considered low, moderate, or high for I^2 values of less than 50%, 50% to 74%, and 75% or greater, respectively [33]. Given the conceptual heterogeneity in RCTs of acupuncture, a random effect model should be used. Eggers tests were performed when more than 10 studies with the same outcome were included in the analysis to detect publication bias [34]. If the heterogeneity was considerable, we would conduct subgroup analysis. The sensitivity analyses were conducted to assess robustness of the synthesized results. Trial sequential analysis (TSA) was conducted to determine whether the optimal information size was reached in the included trials and whether the cumulative data was adequately powered to evaluate outcomes. TSA software 0.9.5.10 beta (Copenhagen Trial Unit, Denmark) was used [35,

36]. An optimal information size was considered as a 2-sided 5% risk of a type I error or a 20% risk of a type II error (power of 80%).

3. Results and Discussion

3.1. Description of Included Trials

16 RCTs [18, 19, 22-25, 37-46] of EA on PGIF recovery in patients with CRC were included (eFigure 1 in the supplement). Seven studies [18, 19, 22-25, 40] were published in english, and nine studies were published in chinese. Two studies [22, 24] were performed in the USA, 13 in China mainland, one in Hong Kong [18]. (eTable 3, study IDs 1-16). All studies used parallel design. 13 studies were two-armed, and three studies were three-armed. The sample size is between 30 and 248. The included studies comprised 1239 cancer patients (mean age 45 to 68 years). The patients were diagnosed with CRC in 14 studies, colon cancer in two studies [23, 44]. The experimental interventions included EA + UC. The control was SA in four studies, and was UC (no acupuncture) in 12 studies. There were different types of operations (open, laparoscopic, open and/or laparoscopic). In most studies, the recovery of PGIF was evaluated, including time to first flatus, time to defecation, time to first bowel movement, and length of hospital stay; in part of studies, other symptoms, including postoperative pain, PONV, abdominal distension, or fatigue were measured.

3.2. Risk of Bias

In 16 studies, one RCT [41] were at high ROB, 12 showed some concerns, and three [18, 19, 25] were at low ROB. The randomization process was not mentioned in the high-ROB study. In most studies, randomization methods and allocation concealment were applied in an improper way, which led to a certain degree of potential selection bias. In four trials [18, 24, 25, 40], SA was established to blind the participants and accessors with low quality methodology. Two RCTs performed blinded evaluations, one with a textual narrative [24] and one with statistics [25]. Thus, the performance bias and detection bias were high. In addition, since not all studies had registered protocols, the biases in the confirmation and report of the determination results were high (eFigure2 in the supplement).

3.3. Primary Outcomes: Recovery of PGIF

3.3.1. Time to First Flatus

In four studies, the effect of EA on time to first bowel sounds was compared with that of SA [18, 24, 25, 40], meta-analysis showed superior effects of EA compared with SA on time to first flatus (n = 487, MD = -10.48, 95% CI [-13.74, -7.21], $P < 0.01$), with low heterogeneity ($I^2 = 0\%$) (Figure 1A). In 13 studies, EA+ UC was compared with UC alone. Meta-analysis showed superior effects of EA+UC compared with UC alone on time to first flatus (n = 913, MD = -14.59, 95% CI [-22.75, -6.43], $P < 0.01$), with high heterogeneity ($I^2 = 96\%$) (Figure 1B).

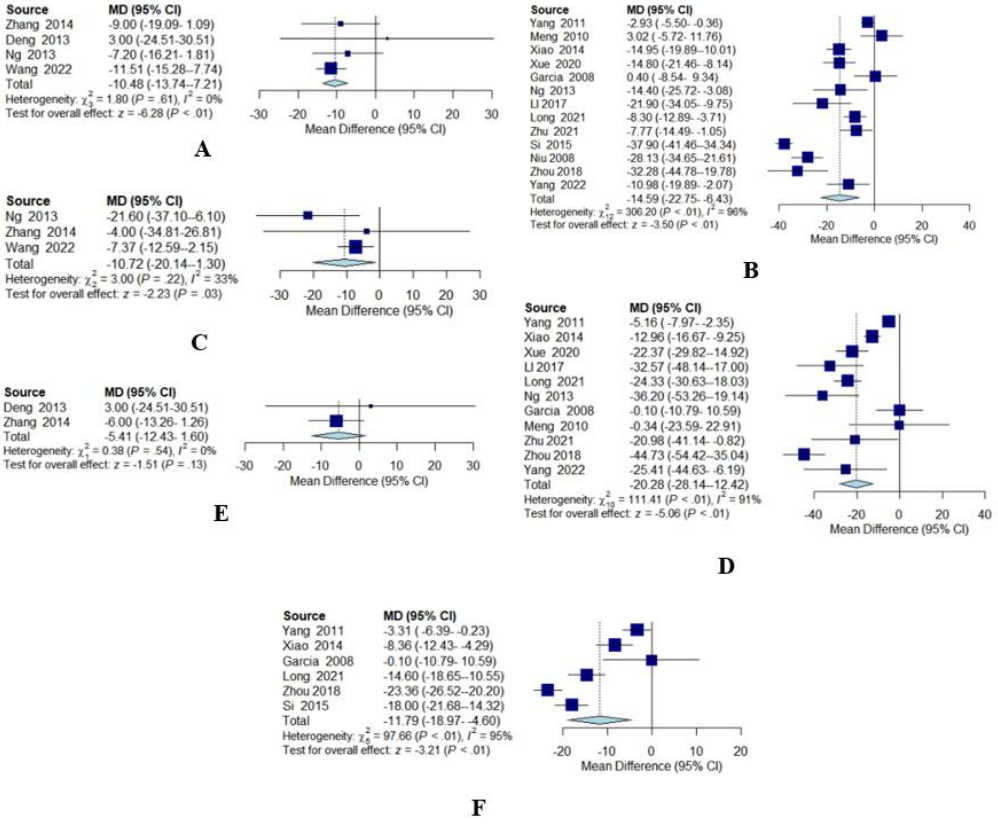

FIGURE 1: Forest plot of **A)** EA versus SA for time to first flatus; **B)** EA + UC versus UC for time to first flatus; **C)** EA versus SA for time to first defecation; **D)** EA + UC versus UC for time to first defecation; **E)** EA versus SA for time to first bowel sounds; **F)** EA + UC versus UC for time to first bowel sounds. EA: electroacupuncture; SA: sham electroacupuncture; UC: usual care.

3.3.2. Time to First Defecation

In three studies, the effect of EA on time to first defecation was compared with that of SA [18, 25, 40], meta-analysis showed superior effects of EA compared with SA on time to first defecation (n = 342, MD =-10.72, 95% CI [-20.14, -1.30], $P = 0.03$), with low heterogeneity ($I^2 = 33\%$) (Figure 1C). In 12 studies, EA+ UC was compared with UC alone. Meta-analysis shows superior effects of EA+UC compared with UC alone on time to first defecation (n = 819, MD = -20.28, 95% CI [-28.14, -12.42], $P < 0.01$), with high heterogeneity ($I^2 = 91\%$) (Figure 1D).

3.3.3. Time to First Bowel Sounds

Two studies where the effect of EA on the time to first bowel sounds was compared with that of SA [18, 40], meta-analysis failed to show superior effects of EA than SA on time to first bowel sounds (n = 129, MD = -5.41, 95% CI [-12.43, 1.60], $P = 0.13$), with low heterogeneity ($I^2 = 0\%$) (Figure 1E). In seven studies, EA+ UC was compared with UC alone. Meta-analysis showed superior effects of EA+UC compared with UC alone on time to first bowel sounds (n = 388, MD = -11.79, 95% CI [-18.97, -4.60], $P < 0.01$), with high heterogeneity ($I^2 = 95\%$) (Figure 1F).

3.4. Secondary Outcomes

On pain scores two days after surgery, meta-analysis showed superior effects of EA compared with SA (n = 358, MD = -0.72, 95% CI [-0.99, -0.45], $P < 0.01$), EA+UC compared with UC alone (n = 266, MD = -0.99, 95% CI [-1.66, -0.31], $P < 0.01$), with low heterogeneity ($I^2 = 0\%$). Besides, as to the outcomes of hospital stay, PONV, abdominal distension, postoperative fatigue, the meta-analysis failed to show superior effects of EA than UC or SA (eFigure3 in the supplement).

3.4.1 Postoperative Complications and Safety of Acupuncture

Postoperative complications, such as postoperative infection, prolonged ileus, acute gastric dilatation, or GI disorder, were measured in eight studies [18, 19, 22, 23, 25, 38, 43, 45], which occurred in 63/516 individuals in the EA group and 66/181 in the control group. Adverse events of included studies are shown (eTable 3 in the supplement). Only in two studies [19, 46], adverse events of EA were reported. Related adverse reactions were mild and transient, including bleeding at the acupuncture site, numbness or pain during EA, etc. Seven studies [18, 22, 23, 25, 38, 43, 46] reported that no adverse events occurred during the study period. Six studies did not report adverse reactions.

3.4.2. Subgroup Analysis

We conducted pre-planned subgroup meta-analyses for PGIF comparison between EA and UC groups. The subgroups include the type of cancer, the type of surgery and the frequency of intervention. In the aspect of surgery type (eFigure 4 in the supplement), the pooled result of time to first flatus indicated that laparoscopic surgery (4 studies) was favorable, with reduced heterogeneity and increased effect size (MD = -17.17, 95% CI [-24.92, -9.42], $I^2 = 62\%$). The pooled result of time to first defecation also indicated that laparoscopic surgery (4 studies) was favorable, with reduced heterogeneity and increased effect size (MD = -32.31, 95% CI [-45.20, -19.43], $I^2 = 78\%$). In addition, the pooled result of time to first bowel sounds indicated laparoscopic surgery (1 study) was favorable, with increased effect size (MD = -23.36, 95% CI [-26.52, -20.20]) (eFigure 4 in the supplement). Therefore, the difference in the surgery type may be responsible for some of the observed heterogeneity.

3.4.3. Sensitivity Analysis

After excluding the high ROB-RCT, the overall effect of EA + UC in the remaining 11 studies remained as a significantly lower risk for the time to first flatus (MD = -10.42, 95% CI [-15.13, -5.72], $I^2 = 82\%$). Therefore, the high ROB studies were considered as one of the sources of heterogeneity. Furthermore, we performed a leave-one-out sensitivity analysis by iteratively removing one study at a time. Point estimates were within the 95%CI of the complete analysis for the primary outcomes (eFigure 5 in the supplement), which suggests the results were stable.

3.4.4. Publication Bias

Egger's tests for the primary outcomes were performed for EA versus UC (more than 10 studies). The *p*-values of the time to first flatus and time to first defecation versus the UC were 0.7705 and 0.07526, respectively (eFigure 6 in the supplement). This indicates that the risk of publication bias is low.

3.4.5. Certainty of Evidence

We extracted all outcomes (time to first flatus, time to first defecation, time to first bowel sounds, length of hospital stay, VAS (24h), VAS (48h), nausea, vomiting, fatigue day 1, fatigue day 2, abdominal distension) reported in 16 included RCTs. The results of the GRADE analysis showed that the total evidence quality of different outcome indicators was from low to high, which was conducive to our recommendation of the results. The reasons for downgrading were clarified with superscripts for every outcome (eTable 4 in the supplement). According to AMSTAR2, the funding sources of included studies were clarified (eTable 5 in the supplement).

In the included studies, the course and duration of acupuncture treatment are different (eTable 6 in the supplement). The semi-standardized acupuncture protocol was only adopted in one study (Studies 9), and in the rest studies, standardized approaches were used. The most frequently used acupoint was ST36 (16 studies, 93.75%), followed by ST37 (10 studies, 56.25%), LI4 (6 studies, 37.60%), ST25, SP6 (5 studies, 31.25%), ST39, PC6 (3 studies, 18.75%), and TE/ SJ6 (2 studies, 12.50%). Other acupoints were used only once (eTable 7 in the supplement). In all studies, EA was applied. According to the STRICTA criteria, the EA treatment protocols were reported (eTable 8 in the supplement).

3.4.6. TSA

The TSA was carried out for the reductions of time to first flatus, time to first defecation, and time to first bowel sounds. Due to the relatively high heterogeneity and bias in the trials, the random-effect model (BT) was employed [47]. The graphs of EA+ UC versus UC all showed that Z-curve crossed the trial sequential monitoring boundary and

conventional monitoring boundary, and surpassed the RIS axis, indicating that the evidence was conclusive for the efficacy of EA interventions for the recovery of PGIF of patients with CRC (Figure 2). The graphs of EA versus SA for time to first flatus and time to first defecation showed that Z-curve crossed the conventional monitoring boundary, and surpassed the RIS axis but did not cross the trial sequential monitoring boundary, indicating that there may be false positive results. The graphs of EA versus SA for time to first bowel sounds showed that although the cumulative Z-curve does not pass the traditional significance boundary and the sequential monitoring boundary of the adjusted confidence interval, it hasn't reached the RIS yet. So the non-significant result between the EA group and SA remains inconclusive (eFigure 7 in the supplement).

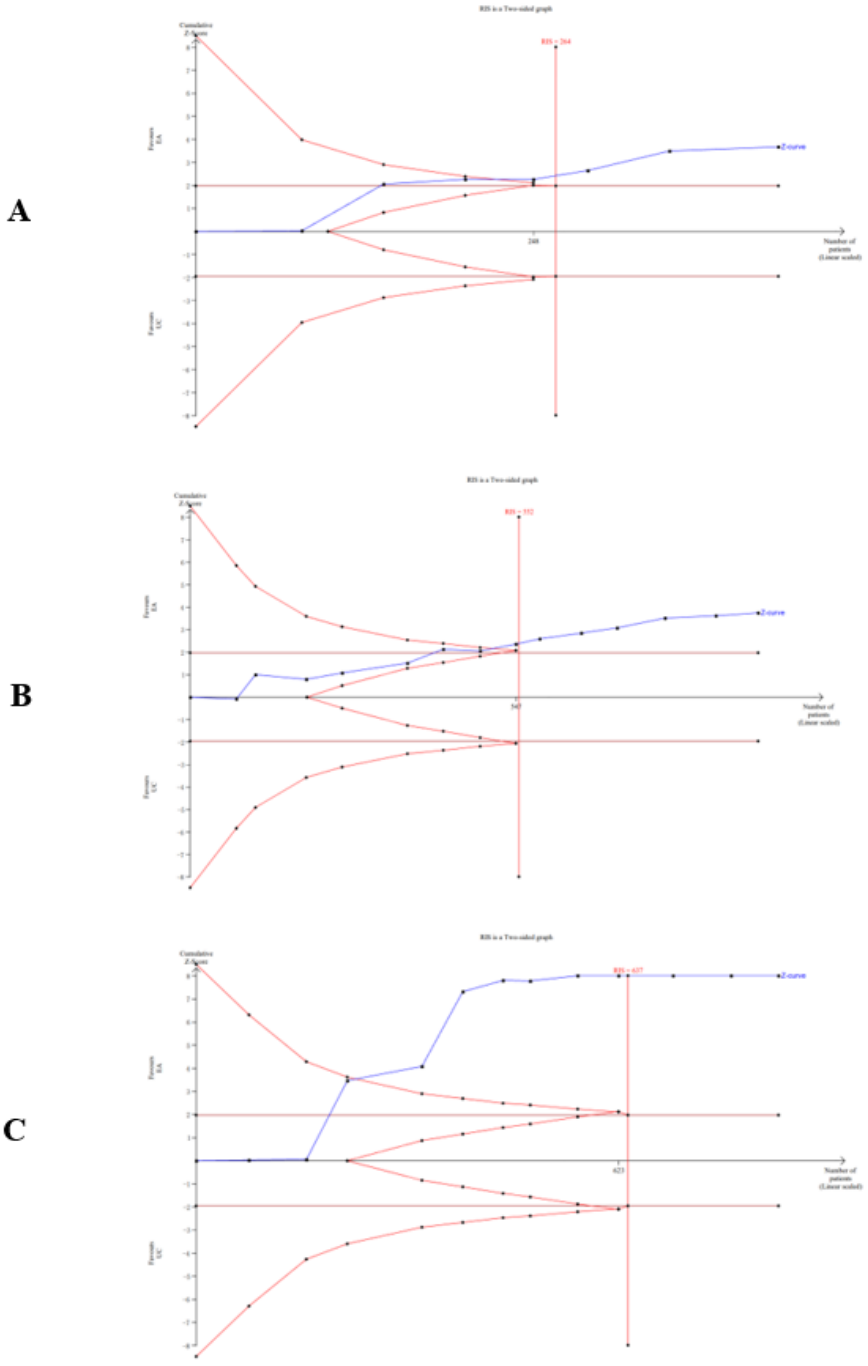

FIGURE 2: TSA of the EA versus UC.
A) EA + UC versus UC for time to first flatus; **B)** EA + UC versus UC for time to first defecation; **C)** EA + UC versus UC for time to first bowel sounds. EA: electroacupuncture; UC: usual care.

4. Discussion

To the best of our knowledge, this is the first systematic review of EA for PGIF in patients with CRC. 16 studies were included. It is still controversial whether EA can treat PGID in patients with CRC. Similar improvement effects of EA and SA on time to first bowel sounds in patients with CRC were found, possibly because of the small sample size (four studies). In 14 studies, EA+ UC was compared with UC alone. Twelve studies showed more favorable effects of EA+UC on the PGIF compared with UC alone. One study [23] admitted that the use of epidural anesthesia in most patients might reduce the possible effects of acupuncture by obstructing the afferent and efferent nerve pathways.

This review mainly indicated that EA has great potential to accelerate the PGIF recovery of patients with CRC. The details of the acupuncture treatment regimen varied greatly in different studies. The different acupuncture treatment protocols and the type of surgery may lead to the heterogeneity of therapeutic effects in different studies. The adverse reactions of EA were mild, and most were bleeding at needle sites, numbness or soreness. Although the certainty of the evidence is low to high due to poor methodological quality and great heterogeneity among studies, this review summarizes the existing RCT results concerning the effect of EA on PGIF in patients with CRC and points out the research gaps that need to be filled. EA could be extended in the postoperative recovery of CRC, and it is worth being translated into relevant clinical guidelines.

A meta-analysis of EA for GI function recovery after gynecological surgery showed that EA could be a promising strategy for the prevention and treatment of GI dysfunction after gynecological surgery, including shortening the time to first flatus, time to first defecation and time to first bowel sounds and decreasing the ratio of PONV within 24 h, which is aligned with our findings [48]. In addition, there is sufficient evidence that opioid analgesia can stimulate peripheral opioid receptors in the GI tract, which may aggravate POI after surgery [49-51]. However, it is difficult to determine whether the improvement of GI function is mainly due to the direct effect of EA on intestinal movement or the indirect effect that EA can relieve postoperative pain and promote walking.

A previous meta-analysis [14] focused on EA or transcutaneous EA for POI after abdominal surgery. This study combined different control methods (e.g., sham acupuncture, usual care) into a single control group, which may not be reasonable. Sham acupuncture is designed to eliminate the placebo effect, and usual care inevitably involves the placebo effect.

Compared with previous works [20, 21], detailed subgroup and sensitivity analysis were performed to find out the potential sources of heterogeneity and ensure the reliability and robustness of our findings. Besides the above advantage, firstly, this is the first systematic review concerning the effect of EA on PGIF recovery in patients with CRC. We concluded that EA was an effective supportive therapy for PGIF recovery after CRC surgery though the level of evidence was low-to-high. Secondly, two high-quality RCTs [19, 25] were included, reaching an optimal information size and power, which helped us finally confirm the effectiveness of EA versus usual care through TSA. Thirdly, most of the included trials provided sufficient details according to STRICTA criteria, which will enable the reader to properly evaluate these studies.

In this review, the standardized acupuncture protocol was used in 15 trials, and semi-standardized acupuncture protocol was only adopted in one study [41]. The most frequently used acupoints were Zusanli (ST36), Shangjuxu (ST37), Xiajuxu (ST39), Sanyinjiao (SP6) on legs; Tianshu (ST25) on the abdomen; Hegu (LI4) and Neiguan (PC6) on hands. These acupoints were used in three or more trials. As a relatively standardized manipulation, EA is more conducive to clinical promotion. Additional sham-controlled RCTs are still needed to validate the safety and efficacy of EA for PGIF recovery in patients with CRC. Future RCTs should still adhere to the STRICTA and CONSORT guidelines, properly describe random number generation and allocation concealment, and pre-registration trial protocol, blind outcome assessors, participants, and doctors, and clearly describe any adverse effects. Better methods for evaluating the success of blinding implementation are needed for blinded acupuncture RCTs. Bang *et al.* [52] developed a proposal of high quality blinding assessment tool for clinical trials, which should be widely used in the future.

5. Conclusion

EA has great potential to accelerate the recovery of PGIF for patients with CRC. RCTs with usual care control was sufficient. Additional pre-registered and sham-controlled RCTs are still needed to validate the safety and efficacy of EA.

Limitations

There are several limitations in this review that need to be considered. The main limitation is that the general methodology and reporting of the included studies were of poor and unsatisfactory quality, which affects the credibility of the research results. Secondly, there is a high heterogeneity among the included studies. The clinical characteristics of the patients and their treatments varied, including the dose and type of surgery. The pooled results also showed high statistical heterogeneity. Lastly, in the studies included in this review, long-term post-discharge functional recovery was not considered, and long-time follow-up was not conducted to assess any lasting effects of acupuncture.

Data Availability

None.

Conflicts of Interest

None.

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Author Contribution

Drs Wu and Zhou had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data

analysis. Drs Xu H, Chen L, Xu S and Gu contributed equally to this study. Concept and design: Wu, Zhou. Acquisition, analysis, or interpretation of data: Xu H, Chen L, Gu, Zhong, Li, Chen B, Zhu, Qi, Zhou, Wu. Drafting of the manuscript: Xu H, Chen L, Xu S. Critical revision of the manuscript for important intellectual content: Xu S, Huang, Liu, Qi, Wu. Statistical analysis: Wang, Li, Chen L, Zhu, Wu. Obtained funding: Wang, Gu, Zhou, Wu. Administrative, technical, or material support: Chen L, Gu, Li, Xu S. Supervision: Huang, Liu, Qi, Wu.

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