BMJ Open Effectiveness and safety of acupuncture and moxibustion for defecation dysfunction after sphincter-preserving surgery for rectal cancer: protocol for systematic review and meta-analysis

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ABSTRACT

Introduction Defecation dysfunction (DD) is one of the most common complications following sphincter-preserving surgery for rectal cancer. And there is no effective treatment of DD after sphincter-preserving surgery for rectal cancer. Although some studies suggested that acupuncture and moxibustion (AM) is effective and safe for DD after sphincter-preserving surgery for rectal cancer, lacking strong evidence, for instance, the relevant systematic review, meta-analysis and randomised controlled trial (RCT) of a large, multicentre sample, makes the effects and safety remain uncertain. The present protocol is described for a systematic review and meta-analysis to investigate the effectiveness and safety of AM for DD after sphincter-preserving surgery for rectal cancer.

Methods and analysis We will search nine online databases from inception to 1 October 2019; the language of included trials will not be restricted. This study will include RCTs that performed AM as the main method of the experimental group for patients with DD after sphincter-preserving surgery for rectal cancer. Two of the researchers will independently select the studies, conduct risk of bias assessment and extract the data. We will use the fixed-effects model or random-effects model of RevMan V.5.2 software to analyse data synthesis. The risk ratios with 95% CIs and weighted mean differences or standardised mean differences with 95% CIs will be used to present the data synthesis outcome of dichotomous data respectively and the continuous data. Evidence quality of outcome will be assessed by using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.

Ethics and dissemination Ethical approval is not required in this secondary research evidence, and we will publish the results of this study in a journal or concerned conferences.

Trial registration number CRD42019140097.

INTRODUCTION

Rectal cancer is the most common malignant tumour of the digestive system, and its incidence is gradually increasing.¹ It is now the

Strengths and limitations of this study

- This review will be the first study of the systematic review and meta-analysis, aims for the effectiveness and safety of acupuncture and moxibustion (AM) therapies for adult patients with defecation dysfunction after sphincter-preserving surgery for rectal cancer.
- We will use the GRADE system to assess evidence quality of the outcomes, which would help clinicians and patients decide whether or not to choose AM therapy.
- Rating the efficacy–effectiveness spectrum of trials included in the systematic review has the potential to display how close current evidence is to ‘real-world’ practice. But it might not be completed as a result of an insufficient number of eligible studies.

third-highest tumour in the world and occurs mostly in middle-aged and elderly people over 50 years old.² Transabdominal anterior resection (Dixon surgery), laparoscopic surgery or stoma closure were considered as the preferred treatment for patients with rectal cancer, which can retain physiological anus benefit to improve the quality of life and avoid abdominal wall ostomy.³ However, after the sphincter-preserving surgery, up to 90% of patients will have a subsequent change in bowel habit,^{4–6} such as the functional capacity, the filling and co-ordination of the rectum, and these wide-ranging symptoms collectively are known as defecation dysfunction (DD) after sphincter-preserving surgery for rectal cancer, DD is the most serious symptom which can decrease patients’ life quality sharply. Some studies have found that the main causes of DD may be anatomical damage,^{7 8} nerve damage,^{9 10} sphincter damage,¹¹ rectal dynamic change^{12 13} and

the effects of preoperative chemoradiotherapy.^{14 15} DD is most evident in the initial period after surgery and will continue for 1–2 years. Worse still, this series of defecation disorder syndromes might accompany patients through their life, and bring about harm to their daily life and social activities.

Thus, how to improve the function of defecation after sphincter-preserving surgery for rectal cancer has become a challenge that clinicians and patients face. The feasible measures for anterior resection syndrome can be divided into precautionary and therapeutic methods. Unsatisfactory effect of precautionary methods leads to few clinical applications, such as isolate and protect the extramural nerves of the intestine,¹⁶ twist the new mesentery 180 degrees¹⁷ and so on. Also, because the therapeutic methods require a complex process, long course and unstable efficacy, patients with DD may not endure or complete the treatment,^{18 19} for example, defecation function training,²⁰ biofeedback therapy¹⁸ and so on.

As a traditional Chinese medicine therapy, acupuncture and moxibustion (AM) has the unique capability of performing holistic treatment. Some studies demonstrated that AM is an effective and safe therapy for DD,^{21–28} and the mechanism of AM for DD may be due to the regulation of the intestinal nervous system,^{29–32} promotion of the secretion of gastrin and motilin,³³ and the improvement the blood circulation of the rectum,³² and so on. However, the discrepancies among the studies of effectiveness and safety of AM for DD still require strong evidence to settle, such as the systematic review, meta-analysis or randomised controlled trial (RCT) of a large, multicentre sample.

Hence, it is necessary to assess the issue and design this systematic review and meta-analysis to determine the effectiveness and safety of AM for patients with DD based on the latest evidence.

METHODS

Criteria for inclusion

1. Patients (aged ≥ 18 years) with DD after sphincter-preserving surgery for rectal cancer diagnosed by the Rome III or IV diagnosis criteria for DD.
2. The experimental group is defined as electroacupuncture, floating needle, fine needle and so on, or moxibustion at acupoints or trigger points. Besides, AM plus other interventions will also be included.
3. The control group that will include non-AM techniques, such as placebo control or other active therapies, is eligible. The acupoint numbers, retaining time and frequency, and treatment sessions will not be limited.
4. We assess the outcome indicators based on some studies concerning the variation in postoperative bowel dysfunction after rectal cancer surgery^{34 35} in this protocol.

Primary outcomes

1. Change in quality-of-life score from baseline to the last available follow-up, measured using the EORTC QLQ-C30.³⁴ A multicentre study collecting symptoms and quality of life in patients with low rectal cancer showed that a higher LARS score was associated with a lower quality of life.³⁴
2. Change in low anterior resection syndrome scale (LARS) scores from baseline to the last available follow-up. The scores of the five individual questions are added up to a total score of 0 to 42 points. The LARS score allows the categorisation of patients into three groups: no LARS (0–20 points), minor LARS (21–29 points) and major LARS (30–42 points). The score has previously been thoroughly validated in a large international study where several psychometric properties of the instrument were evaluated.^{35 36}

Secondary outcomes

1. Wexner, Vaizey, memorial Sloan Kettering Cancer Center, the American medical system faecal incontinence scores and so on.¹³
2. The incidence rate of adverse events.
3. We extract outcomes at all time points measured in the included trials. We plan to pool available data into short-term (up to 2 weeks), medium-term (2 to 6 weeks) and long-term (more than 6 weeks) outcomes, when data are available.
5. We will include RCTs that randomly divided the subjects into two groups, regardless of whether the blind method was used or not. Multiple-arm trials that fit in the mentioned criteria are eligible. The data of the first period of crossover trials will also be included.

Criteria for exclusion

1. The experiment group that does not contain the needle and moxibustion will be excluded.
2. The study comparing different forms of AM, such as acupuncture versus moxibustion, will be excluded.
3. Animal experiment, review and non-RCTs will be excluded.

Search methods for identification of studies

Electronic searches

From the inception to 1 October 2019, the following databases will be searched: EMBASE, the Cochrane Library, PubMed, Web of Science, Surveillance, Epidemiology and End Results (SEER), Chinese Biomedical Literature Database (CBM), Wanfang Database (WF), the Chongqing VIP (VIP) and Chinese National Knowledge Infrastructure (CNKI). The searching strategy of PubMed is presented in [table 1](#).

Searching other resources

We will search the National Institutes of Health (NIH) clinical registry Clinical Trials, International Clinical Trials Registry Platform (ICTRP), Australian New Zealand Clinical Trials Registry, and Chinese clinical registry to find the unpublished or ongoing trial data.

Table 1 Search strategy used in PubMed database

Number	Search items
#1	randomized controlled trial [All Fields]
#2	controlled clinical trial [All Fields]
#3	randomized [All Fields]
#4	randomised [All Fields]
#5	placebo [All Fields]
#6	randomly [All Fields]
#7	trial [All Fields]
#8	groups [All Fields]
#9	or/#1–#8
#10	rectal OR rectum [All Fields]
#11	cancer OR carcinoma OR neoplasms [All Fields]
#12	#10 AND #11
#13	constipation [All Fields]
#14	dyschezia OR obstipation OR constipation OR constipated OR astriction OR costive OR costiveness OR defecation OR defecatory OR defecate OR belly-bound OR oppilated OR oppilate OR oppilation OR Cacation OR 'bowel movement' OR 'hard stool' OR 'lumpy stool' OR constipat* OR 'impacted stool' OR 'rock-like stool' OR Impaction OR obstipation OR evacuation [All Fields]
#15	delayed bowel movement [All Fields]
#16	bowel AND (function* OR habit* OR movement* OR symptom* OR motility OR stool* [All Fields])
#17	colon transit [All Fields]
#18	intestin* AND (motility OR mobility OR peristalsis OR propulsion OR movement OR emptying [All Fields])
#19	diarrhea OR diarrhoea OR diarrh* [All Fields]
#20	or/#13–#19
#21	#12 AND #20
#22	acupuncture [All Fields]
#23	acupuncture therapy [All Fields]
#24	electroacupuncture [All Fields]
#25	electroacupuncture therapy [All Fields]
#26	manual acupuncture [All Fields]
#27	dry needle [All Fields]
#28	moxibustion [All Fields]
#29	acupoint [All Fields]
#30	or/#22–#29
#31	#9 AND #21 AND #30

Data collection and analysis

Selection of studies

The studies of electronic searches will be exported to EndNote software (V.X9). Publications obtained from other sources will also be imported to EndNote. After getting rid of the duplicates, two reviewers (GX and QX)

Figure 1 Process and results of studies selection.

will independently screen the titles and abstracts for potentially qualified studies in accordance with the selection criteria. If the studies cannot be showed from titles and abstracts, the full text will be screened. Data from the Clinical Research Registry will also be independently screened by (GX and QX) to remove published studies and include studies that have not been published and have not uploaded trial data. After screening, two reviewers cross-check. If inconsistent opinion exists, they will resolve it through discussion. If there are still disagreements, the decision will be made by a third reviewer (JK). The process and results of studies selection will be presented in a flow chart with figure 1.

If there are less than three RCTs of AM for DD that meet the inclusion and exclusion criteria, we will conduct a descriptive systematic review of the existing studies instead of a meta-analysis.

Data extraction and management

The standard data extraction form will be confirmed before data extraction. The following information from the included studies will be extracted by two reviewers (GX and QX): basic information (reference ID, including year of publication, publication source, the first author of the study, etc), characteristic of trial (number of groups, number of participants for treatment and control, method of randomisation, blinding, method of analysis, objectives of the study, etc), participants (total sample size, mean age, gender, ethnicity, country, diagnosis criteria, duration, etc), interventions and controls (information of caring, method of the AM intervention, number, frequency, and duration of AM treatment, name and type for control, additional treatment, etc), outcome measurements (LARS scores, quality-of-life score, and secondary outcome according to types of outcome measures, timeline for assessment, length of follow-up, etc) and so on. After extraction, two reviewers cross-check. The

disagreement between the two reviewers will be solved by discussion among all the reviewers. The extraction data will be listed in Excel 2016, and HL will check the data entered to ensure there are no errors.

Assessment of risk of bias in included studies

The quality of the included trials will be evaluated by two reviewers (QX and YF) using the Cochrane Collaboration's tool. Seven aspects including method of randomisation, allocation concealment, application of blind, outcome data integrity, selective reporting and other bias will be assessed.³⁷ For each aspect, we will use high risk, low risk or unclear of risk for the result of evaluation. The method of risk of bias tool of Cochrane Collaboration will be used for assessing the evaluation of study risk of bias. Moreover, our researchers will check the assessment results strictly and tackle the differences through discussions.

Measures of treatment effect

RevMan V.5.2 and STATA software will be used to synthesis all data. The risk ratios with 95% CIs and weighted mean differences or standardised mean differences with 95% CIs will be used to present the data synthesis outcome of dichotomous data and the continuous data, respectively.

Dealing with missing data

The authors of included studies with missing data will be contacted by mail or phone. If the corresponding author with missing data cannot be contacted, we will only conduct a narrative synthesis of the studies and synthesis the remaining studies.

Assessment of heterogeneity

We will use χ^2 test in forest plot using RevMan V.5.2 to assess the heterogeneity, and a p value less than 0.10 will be considered significant.³⁸ Besides, the impact of the heterogeneity on the meta-analysis will be quantified via calculating the I^2 value. A coarse guide for the explanation of I^2 is as follows: 0% to 40% means there might be no heterogeneity; 30% to 60% means moderate heterogeneity; 50% to 90% means extensive heterogeneity; 75% to 100% means important heterogeneity.³⁸ Moreover, the importance of the observation of I^2 depends on the following two aspects: size and direction of impact and strength of heterogeneity evidence (eg, p value from the χ^2 test, or a CI for I^2).³⁸

Data synthesis

Before synthesising the data, the units of outcome will be unified according the International System of Units. Next, we will import the clinical data into RevMan software (V.5.2) and perform data statistical analysis. The fixed-effects model will be used for data synthesis and analysis when the $I^2 < 40\%$. We will use the random-effects model to synthesise and analyse data when moderate heterogeneity is detected ($I^2 \geq 40\%$, $< 75\%$). If there is important heterogeneity with $I^2 \geq 75\%$ in the trials, meta-analysis could not be performed. If the heterogeneity with I^2

$\geq 40\%$ is detected, subgroup analysis and meta-regression will be conducted to identify the source of heterogeneity.

The reporting bias will be presented via a funnel plot when more than 10 trials are included.

Subgroup analysis and meta-regression

The subgroup analyses or meta-regression will be performed using STATA software to explore the potential sources of heterogeneity, according to the characteristics of the trial participants, different acupuncture therapies, quality of included studies, sample size and so on.

Sensitivity analysis

We will assess the stability of primary decision made in the review process by sensitivity analysis. And the several decision nodes in the process of the meta-analysis will be taken into consideration, such as low-quality studies, small sample size studies and so on. Also, we will present the results of the sensitivity analysis in summary tables. The risk of bias in the meta-analysis will be discussed as a result from the sensitivity analysis.

Evidence quality evaluation

Two reviewers will independently assess the quality of evidence for each outcome by using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.³⁹ Due to the GRADE rating standards, 'high', 'moderate', 'low' or 'very low' will be used to rate the evidence quality. The assessment of evidence quality mainly stems from the risk of bias, inconsistency, indirectness, imprecision, publication bias, large effect, dose response and all plausible confounding.^{39 40} We will also report the results of GRADE in a summary of findings table.⁴⁰

Efficacy–effectiveness spectrum analysis

Because the systematic review will include RCTs often characterised as designed with either a more explanatory or a more pragmatic approach, clinicians and patients need to know the characteristics of the included studies. Therefore, we will use the Efficacy–Effectiveness Spectrum scale⁴¹ with four domains (participant characteristics, trial setting, the flexibility of interventions and clinical relevance of interventions) to analyse the efficacy–effectiveness spectrum of each included trial.

Ethics and dissemination

Since this study is a secondary analysis of existing literature, ethical approval is not required. We will provide a systematical view and evidence of AM for DD, which will benefit clinical practice and further research. Also, we will publish our study in a peer-reviewed journal or distributed at relevant conferences.

Patient and public involvement

There was no patient or public that will be directly involved in this review. Only data already existent in the literature and the sources will be used for this study.

DISCUSSION

AM is a valuable heritage based on Chinese medical and scientific traditions which have distinct Chinese cultural and regional characteristics. Acupuncture is to pierce acupuncture needles into acupoints of the patients' body, combined with acupuncture manipulations such as twisting and lifting to treat diseases; moxibustion is to burn the moxa with acupoints to burn the skin within safe limits and use thermal stimulation to treat disease. More and more countries are treating AM as a complementary alternative therapy. AM has been proven to cure many diseases such as stress urinary incontinence,⁴² cancer pain,⁴³ migraine,⁴⁴ chronic stable angina⁴⁵ and so on. WHO also recommends a variety of dominant AM diseases. And many studies suggested that AM is a cost-effective intervention.^{46–50} In China and some Asian countries, AM, a distinctive medical resource, has been used to treat gastrointestinal disease.^{51–53} In western countries, AM has been accepted gradually as a major non-drug treatment. There were studies on the treatment of DD after sphincter-preserving surgery of rectal cancer by AM. Complete RCTs were conducted using only AM-related therapies or AM combined with biofeedback and so on in treatment groups, and the results of the studies all concluded that acupuncture was beneficial to DD, but the effectiveness of different studies varied. Therefore, we plan to study the effectiveness and safety of AM in the treatment of DD. If the results of the study prove that AM is a safe and effective treatment for DD, it will help improve the quality of life of patients with DD and save on medical expenses.

Limitations of research: (1) In order to ensure the quality of research, we have formulated strict standards for admission. But this may lead to a limited number of studies. It is recommended to increase the corresponding RCTs. (2) This study only included articles published in Chinese or English. Therefore, language bias is possible.

Contributors GX and FL conceived the review protocol and drafted the manuscript. LZ and HL revised the study design. GX, QX, HL and FY participated in the design of the search strategy and data extraction data set. GX, FL and JK formed the data synthesis and analysis plan. In practice, QZ and LZ will monitor each procedure of the review and are responsible for the quality control. All authors have read and approved the publication of the protocol.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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