PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Transcutaneous electrical acupoint stimulation combined with electroacupuncture for rapid recovery of patients after laparotomy for gastrointestinal surgery: A study protocol for a randomized controlled trial
AUTHORS	Li, Hao; Wen, Qian; Lu, Lingyun; Hu, Hangqi; He, Ying; Zhou, Yaming; Wu, Xiaoting; Li, Ning

VERSION 1 – REVIEW

REVIEWER	Wells, Cameron Iain The University of Auckland
REVIEW RETURNED	29-Jun-2021

GENERAL COMMENTS	Thank you for the opportunity to review this article for BMJ Open titled “Transcutaneous electrical acupoint stimulation combined with electroacupuncture for rapid recovery of patients after laparotomy for gastrointestinal surgery: A study protocol for a randomized controlled trial” by Li et al. I have included my comments to the authors below. Kind regards, Dr Cameron Wells Department of Surgery The University of Auckland, New Zealand cameron.wells@auckland.ac.nz Comments to authors: This is a study protocol for a prospective, three-arm, single-blind randomised sham-controlled trial investigating postoperative electroacupuncture (EA) vs. postoperative EA + transcutaneous electrical acupoint stimulation (TEAS) vs. usual care, in patients undergoing surgery for colorectal or gastric cancer. The primary aim of this study is to determine the effects of EA and TEAS on the time to “first postoperative spontaneous anal exhaust” – presumably this refers to first passage of flatus. I have several comments regarding this protocol, which I have listed below: 1. The absence of a sham control is a major limitation of this study, particularly given previous evidence has suggested up to a third of the effect of electrostimulation studies on GI symptoms

	may be due to placebo responses or effects (https://doi.org/10.1111/ner.13092). Multiple previous studies have described the use of sham EA and TEAS controls (e.g. https://doi.org/10.1136/acupmed-2013-010490, https://doi.org/10.1053/j.gastro.2012.10.050, https://doi.org/10.1155/2018/7341920) , and I cannot see a clear reason why the authors did not include a sham control arm in this trial. The authors should at the very least discuss this in the manuscript as a major limitation of their trial, though I would suggest that they reconsider their study design as they appear to still be very early on in recruitment. 2. This study was preregistered on the Chinese Clinical Trial Registry (ChiCTR2100045646), however on the online registration form it states that patients with hepatobiliary, renal, and bladder tumours will also be included. This is not mentioned in the manuscript and the authors should mention and clarify this discrepancy. 3. This article is powered based on a primary outcome of time to first flatus. This is not a useful clinical outcome as it is highly variable, subjective, and does not correlate well with overall recovery of GI function. The authors should consider using a validated outcome such as GI-2 (composite outcome of time to first defaecation and time to tolerance of oral diet) as their primary outcome. This has been shown to correlate with post-operative gut transit, and can be determined from the data already being collected in the study. (for further details see van Bree et al, Annals of surgery. 2014 Apr 1;259(4):708-14.) 4. Several of the secondary outcomes, including “postoperative complications”, “medication use” and “treatment modality acceptability” need further detail regarding how they will be defined and measured. 5. Further detail should be reported regarding how the three groups will be compared. The current statistical plan of using t-tests and Wilcoxon rank sum tests is inappropriate as these can only compare two groups. 6. There are many mentions/claims of the efficacy of EA/TEAS throughout the introduction and discussion of the manuscript that are currently unreferenced. References should be added to support these claims. Minor comments: 1. In statistical analyses, it states “All data will be collected by statisticians” – does this mean that statisticians are the ones collecting the data from patients (?!) or are all the analyses going to be done by statisticians? 2. The authors may wish to consider rephrasing the primary outcome to clarify this definition: “first postoperative spontaneous anal exhaust” could be changed to “first passage of flatus”?

	3. Presumably some patients will have a stoma formed at the time of the operation. How will these patients be accounted for in the analysis? 4. How many patients are in the preliminary sample that informed the power analysis? Are these data being included in the larger RCT?

REVIEWER	Abuelnaga, Mohamed E Suez Canal University, anesthesia, critical care and pain management
REVIEW RETURNED	04-Jul-2021

GENERAL COMMENTS	Dear respectable authors, thank you for this important protocol, but please try to consider the following points: 1- Will TEAS stimulation will add to the analgesic effect of electrical acupuncture, please explain your rationale 2-page 5 line 4 : is there is any rationale for choosing specific points for TEAS stimulation, please explain 3-in the introduction section, please explain the rationale behind choosing every acupuncture point and add reference confirming this rationale(like what was written about P6 point) on page 8 lines 17-19 4-page 8 lines 35-43 :(Currently, EA is the most common acupuncture scheme for ..... has relatively limited clinical application) : please add a reference 5- page 8 lines 44-51 : you assumed that combining TEAS and EA will be more beneficial than using only one of them , but you should add previous publications that support the idea that each method of stimulation has a beneficial effect 6- Page 12 lines 6-30: add references for acupoints locations 7-page 13 lines 4-20: please add the intensity, frequency, and duration of stimulation 8- Page 13 lines 53-56 :(The observer will be assessments and visits for participants after each treatment) please rephrase the sentence 9- in the statistical analysis section: please add the test that will be used to assess normality. 10-page 15 line 38 :(The patients and the public were not involved in the planning and design of this study) , please rephrase the sentence

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:
Reviewer Name: Dr. Cameron Iain Wells
Institution and Country: The University of Auckland, New Zealand

1.The absence of a sham control is a major limitation of this study, particularly given previous evidence has suggested up to a third of the effect of electrostimulation studies on GI symptoms may be due to placebo responses or effects (https://doi.org/10.1111/ner.13092). Multiple previous studies have described the use of sham EA and TEAS controls (e.g. https://doi.org/10.1136/acupmed-2013-010490, https://doi.org/10.1053/j.gastro.2012.10.050, https://doi.org/10.1155/2018/7341920) , and I cannot see a

clear reason why the authors did not include a sham control arm in this trial. The authors should at the very least discuss this in the manuscript as a major limitation of their trial, though I would suggest that they reconsider their study design as they appear to still be very early on in recruitment.

Response:Thank you for reminding us of this problem, which is very professional. We have changed the last item in "Strengths and Limitations of this study" to "This trial did not include a sham control arm, the analysis of the placebo response or effect was lacking ", and we described it in the discussion section. （ Strengths and Limitations of this study section 4,line 3-4,page 4; DISCUSSION section, line 9-15, page14 ）
In the trial design phase, we also considered this problem. Due to our team participated in a multi-center clinical study of electroacupuncture(EA) for Chronic Severe Functional Constipation, 1075 patients were involved in this study, the results revealed that the sham electroacupuncture(SA) although have some placebo effect, but EA might have greater benefits than SA[1], which is consistent with prior studies for gastrointestinal symptoms using shallow needling at non-acupoints (control) that showed EA's superiority over SA [2, 3]. Therefore, the sham control group was not included in this study design after discussion by our research team.
Nevertheless, we still think your suggestion is very good. However, since the trial has been carried out for more than 5 months now, we cannot change the study protocol again. As a result, the absence of a sham control has become a major limitation of this study .In future studies, we will fully consider the setting of the sham control group.
[1]Liu Z, Yan S, Wu J, et al. Acupuncture for Chronic Severe Functional Constipation: A Randomized Trial. Ann Intern Med 2016;165(11):761-69. doi: 10.7326/m15-3118
[2]Ng SS, Leung WW, Mak TW, Hon SS, Li JC, Wong CY, et al. Electroacupuncture reduces duration of postoperative ileus after laparoscopic surgery for colorectal cancer. Gastroenterology. 2013;144:307-313. doi:10.1053/j.gastro.2012.10.050
[3]Wang CP, Kao CH, Chen WK, Lo WY, Hsieh CL. A single-blinded, randomized pilot study evaluating effects of electroacupuncture in diabetic patients with symptoms suggestive of gastroparesis. J Altern Complement Med. 2008;14:833-9. doi:10.1089/acm.2008.0107

2.This study was preregistered on the Chinese Clinical Trial Registry (ChiCTR2100045646), however on the online registration form it states that patients with hepatobiliary, renal, and bladder tumours will also be included. This is not mentioned in the manuscript and the authors should mention and clarify this discrepancy.

Response: Thank you for reminding us of this， I am very sorry that due to my personal mistake during registration, the inclusion criteria of "resection of stomach or colorectal tumor under general anesthesia" was incorrectly filled into "resection of hepatobiliary, gastrointestinal, kidney or bladder tumor under general anesthesia". Now I have applied for and completed the modification in Chinese Clinical Trial Registry.

3.This article is powered based on a primary outcome of time to first flatus. This is not a useful clinical outcome as it is highly variable, subjective, and does not correlate well with overall recovery of GI function. The authors should consider using a validated outcome such as GI-2 (composite outcome of time to first defaecation and time to tolerance of oral diet) as their primary outcome. This has been shown to correlate with post-operative gut transit, and can be determined from the data already being collected in the study. (for further details see van Bree et al, Annals of surgery. 2014 Apr 1;259(4):708-14.)

Response: Thank you for this useful comment, which is a very good suggestion. We have revised the

primary outcome to GI-2 (composite outcome of time to first defaecation and time to tolerance of oral diet). （OUTCOME MEASURES section 1, line 2-4, page 11）
We add GI-2 as a primary outcome outcome to the original protocol after recruitment of the study had already begun. GI-2 is a time indicator, which will be calculated from two existing outcomes (time to first defaecation and time to tolerance of oral diet). There will be no harm to subjects, no additional cost and no more work. （OUTCOME MEASURES section 3, line 15-18, page 11）
According to the main outcome indicators, we recalculated the sample size and adjusted the proportion of assumed lost follow-up, and the total number of included patients remained unchanged. （Sample size calculation section, line 7-18, page 12）

4.Several of the secondary outcomes, including “postoperative complications”, “medication use” and “treatment modality acceptability” need further detail regarding how they will be defined and measured.

Response: Thank you for this useful comment. We have described the secondary outcomes in more detail in our manuscript. （OUTCOME MEASURES section 2, line 6-14, page 11）
The secondary outcomes include the time of first passage of flatus, time to first defaecation , time to tolerance of a solid diet, time to first ambulation, hospital duration from operation to discharge, pain and nausea vomiting scores on the VAS (from 0 [no at all] to 10 [the worst]), medication use(name, frequency and dosage of analgesic drugs and antiemetic agents), incidence of postoperative complications(include intra-abdominal infection, intestinal ischemia and necrosis, anastomotic leak, pulmonary infection, etc), and evaluation of treatment modality acceptability(classified into five grades: very acceptable, moderately acceptable, somewhat acceptable, moderately unacceptable, and totally unacceptable). Participants will be visited and evaluated by efficacy evaluators at the end of each treatment.

5.Further detail should be reported regarding how the three groups will be compared. The current statistical plan of using t-tests and Wilcoxon rank sum tests is inappropriate as these can only compare two groups.

Response: Thank you for reminding us of this problem. We have revised this part. （Statistical analysis section, line 20-22, line 1-6 , page 12-13）
Data analysis will be performed using the intention processing principle in SPSS 22.0. Statistical results will be reported using a two-sided test, with statistical significance being set at P-value < 0.05. Continuous variables will be expressed as: mean (SD), median (interquartile range (IQR)), or minimum and maximum. For comparisons between treatment groups, analyses of variance (ANOVAs) will be used for normally distributed variables, and the Kruskal–Wallis H test will be used for non-normally distributed variables. Categorical variables will be expressed as numbers (%), and will be analyzed via chi-square tests for between-group comparisons.

6.There are many mentions/claims of the efficacy of EA/TEAS throughout the introduction and discussion of the manuscript that are currently unreferenced. References should be added to support these claims.

Response: Thank you for this useful comment. We have supplemented references as recommended. （INTRODUCTION section 7, line 17-20, page6;DISCUSSIONE section, line 8-10, page 14）
[1] Chen KB, Huang Y, Jin XL, et al. Electroacupuncture or transcutaneous electroacupuncture for postoperative ileus after abdominal surgery: A systematic review and meta-analysis. Int J Surg 2019;70:93-101. doi: 10.1016/j.ijsu.2019.08.034 [published Online First: 2019/09/09]
[2] Chen J, Zhang Y, Li X, et al. Efficacy of transcutaneous electrical acupoint stimulation combined with

general anesthesia for sedation and postoperative analgesia in minimally invasive lung cancer surgery: A randomized, double-blind, placebo-controlled trial. Thorac Cancer 2020;11(4):928-34. doi: 10.1111/1759-7714.13343 [published Online First: 2020/02/18]
[3] Hou L, Xu L, Shi Y, et al. Effect of electric acupoint stimulation on gastrointestinal hormones and motility among geriatric postoperative patients with gastrointestinal tumors. J Tradit Chin Med 2016;36(4):450-5. doi: 10.1016/s0254-6272(16)30061-9 [published Online First: 2017/05/02]
[4] Sun K, Xing T, Zhang F, et al. Perioperative Transcutaneous Electrical Acupoint Stimulation for Postoperative Pain Relief Following Laparoscopic Surgery: A Randomized Controlled Trial. Clin J Pain 2017;33(4):340-47. doi: 10.1097/ajp.0000000000000400 [published Online First: 2016/07/21]
[5] Ng SS, Leung WW, Mak TW, et al. Electroacupuncture reduces duration of postoperative ileus after laparoscopic surgery for colorectal cancer. Gastroenterology 2013;144(2):307-13.e1. doi: 10.1053/j.gastro.2012.10.050 [published Online First: 2012/11/13]
[6] Liu Z, Yan S, Wu J, et al. Acupuncture for Chronic Severe Functional Constipation: A Randomized Trial. Ann Intern Med 2016;165(11):761-69. doi: 10.7326/m15-3118 [published Online First: 2016/09/13]
[7] Wang CP, Kao CH, Chen WK, et al. A single-blinded, randomized pilot study evaluating effects of electroacupuncture in diabetic patients with symptoms suggestive of gastroparesis. J Altern Complement Med 2008;14(7):833-9. doi: 10.1089/acm.2008.0107 [published Online First: 2008/08/30]

Minor comments:
1.In statistical analyses, it states “All data will be collected by statisticians” – does this mean that statisticians are the ones collecting the data from patients (?!) or are all the analyses going to be done by statisticians?

Response: Thank you for reminding us of this problem. We have revised it. （Statistical analysis section, line 22, page 12）
All data will be collected by efficacy evaluators.

2.The authors may wish to consider rephrasing the primary outcome to clarify this definition: “first postoperative spontaneous anal exhaust” could be changed to “first passage of flatus”?

Response: Thank you for this useful comment. We have revised it. （ABSTRACT section 2, line 1-7, page 7; OUTCOME MEASURES section 2, line 6-7, page 11）

3.Presumably some patients will have a stoma formed at the time of the operation. How will these patients be accounted for in the analysis?

Response: Thanks for your careful consideration of this problem. We have changed the “first postoperative spontaneous anal exhaust” to “first passage of flatus” in our manuscript, and we can determine when these patients will resume defecation and flatus by looking at the amount of stool and gas in the stoma bag. These patients will be included in the same statistical analysis as those without the stoma.

4.How many patients are in the preliminary sample that informed the power analysis? Are these data being included in the larger RCT?

Response: Thank you for this professional question. The trial feasibility has been examined in a pilot randomised trial of 120 patients，included 60 patients with laparotomy stomach tumor resection and 60 patients with laparotomy colon tumor resection. These data will not be included in the larger RCT. （

Strengths and limitations of this study section 2, line 17-19, page 3）

Reviewer 2:
Reviewer Name: Dr. Mohamed E Abuelnaga
Institution and Country: Suez Canal University, Egypt

1.Will TEAS stimulation will add to the analgesic effect of electrical acupuncture, please explain your rationale

Response: Thank you for your careful consideration of this. TEAS or EA have been shown in previous studies to reduce postoperative pain[1,2], but no studies have shown whether the combination of the two treatments increases the analgesic effect. This point will be recorded and analyzed in this study.
[1] Sun K, Xing T, Zhang F, et al. Perioperative Transcutaneous Electrical Acupoint Stimulation for Postoperative Pain Relief Following Laparoscopic Surgery: A Randomized Controlled Trial. Clin J Pain 2017;33(4):340-47. doi: 10.1097/ajp.0000000000000400
[2] Capodice JL, Parkhomenko E, Tran TY, et al. A Randomized, Double-Blind, Sham-Controlled Study Assessing Electroacupuncture for the Management of Postoperative Pain after Percutaneous Nephrolithotomy. Journal of endourology 2019;33(3):194-200. doi: 10.1089/end.2018.0665

2.page 5 line 4 : is there is any rationale for choosing specific points for TEAS stimulation, please explain

Response: Thank you for this useful comment, we explained this reason in the discussion section.（DISCUSSION section, line 3-7, page 14）
In this study, based on extensive clinical practice, TEAS will be applied to abdominal acupoints, which is safer than electroacupuncture based on acupuncture on the meridians of the distal extremities; moreover, the SP15 and ST21 chosen for abdominal surgery are unconventional incision positions that facilitate manipulation. Additionally, they are both antiemetic, promote gastrointestinal motility, and relieve abdominal pain.

3.in the introduction section, please explain the rationale behind choosing every acupuncture point and add reference confirming this rationale(like what was written about P6 point) on page 8 lines 17-19

Response: Thank you for reminding us of this, we have added this section and references.（INTRODUCTION section 4, line 12-17, page 5）
[1] Yang NN, Ye Y, Tian ZX, et al. Effects of electroacupuncture on the intestinal motility and local inflammation are modulated by acupoint selection and stimulation frequency in postoperative ileus mice. Neurogastroenterol Motil 2020;32(5):e13808. doi: 10.1111/nmo.13808 [published Online First: 2020/03/03]
[2] Jie Ma, Yunxiao Wang, Dan Fan, et al. Clinical Study of Acupoint Catgut Embedding in the treatment of Chronic Functional Constipation. Journal of Sichuan of Traditional Chinese Medicine 2015;33(10):161-162. [published Online First: 2015/10/15]
[3] SUN, Jian-hua. Clinical Observation of Acupuncture plus Flash Cupping for Gastroparesis in Senile Type 2 Diabetes. Shanghai J Acu-mox 2018;37(10):1132-1135. doi: 10.13460/j.issn.1005-0957.2018.10.1132 [published Online First: 2018/10/16]
[4] Zhang WB, Wu A, Litscher G, et al. Effects and mechanism of acupuncture based on the principle of meridians. Evid Based Complement Alternat Med 2013;2013:684027. doi: 10.1155/2013/684027 [published Online First: 2014/01/01]

4.page 8 lines 35-43 :(Currently, EA is the most common acupuncture scheme for ..... has relatively limited clinical application) : please add a reference

Response: Thank you for reminding us of this, we have added the reference.（INTRODUCTION section 7, line 17-18, page6）
[1] Chen KB, Huang Y, Jin XL, et al. Electroacupuncture or transcutaneous electroacupuncture for postoperative ileus after abdominal surgery: A systematic review and meta-analysis. Int J Surg 2019;70:93-101. doi: 10.1016/j.ijsu.2019.08.034 [published Online First: 2019/09/09]

5.page 8 lines 44-51 : you assumed that combining TEAS and EA will be more beneficial than using only one of them , but you should add previous publications that support the idea that each method of stimulation has a beneficial effect

Response:Thank you for this useful comment. We have supplemented references as recommended. （INTRODUCTION section 7, line 18-20, page6）
[1]. Chen J, Zhang Y, Li X, et al. Efficacy of transcutaneous electrical acupoint stimulation combined with general anesthesia for sedation and postoperative analgesia in minimally invasive lung cancer surgery: A randomized, double-blind, placebo-controlled trial. Thorac Cancer 2020;11(4):928-34. doi: 10.1111/1759-7714.13343 [published Online First: 2020/02/18]
[2]. Hou L, Xu L, Shi Y, et al. Effect of electric acupoint stimulation on gastrointestinal hormones and motility among geriatric postoperative patients with gastrointestinal tumors. J Tradit Chin Med 2016;36(4):450-5. doi: 10.1016/s0254-6272(16)30061-9 [published Online First: 2017/05/02]
[3]. Sun K, Xing T, Zhang F, et al. Perioperative Transcutaneous Electrical Acupoint Stimulation for Postoperative Pain Relief Following Laparoscopic Surgery: A Randomized Controlled Trial. Clin J Pain 2017;33(4):340-47. doi: 10.1097/ajp.0000000000000400 [published Online First: 2016/07/21]

6.Page 12 lines 6-30: add references for acupoints locations

Response: Thank you for this useful comment, we have added the reference.（INTERVENTION section 1, line 4-5, page 9）
All acupoints will be determined based on the National Standard of Nomenclature and Location of Acupuncture Points (GB/T 12346-2006).

7.page 13 lines 4-20: please add the intensity, frequency, and duration of stimulation

Response: Thank you for this useful comment. These information was mentioned in the second paragraph of the intervention section. （INTERVENTION section 1, line 10-13, page 9）
Regarding the electronic acupuncture treatment instrument (Hwato, SDZ-V, Suzhou Medical Supplies Factory Co., Ltd), the current frequency will be continuous wave 2 Hz, the current intensity will be measured in degrees as tolerated by the patient; moreover, the treatment duration will last 30 min (figure 2).

8.Page 13 lines 53-56 :(The observer will be assessments and visits for participants after each treatment) please rephrase the sentence

Response: Thank you for this useful comment. We have revised the sentence as requested. （OUTCOME MEASURES section 1, line 3-4, page 11；OUTCOME MEASURES section 2, line 13-14, page 11）
Participants will be visited and evaluated by efficacy evaluators at the end of each treatment.

9.in the statistical analysis section: please add the test that will be used to assess normality.

Response: Thank you for this useful comment. We have revised it as recommended. （Statistical analysis section, line 20-22, line 1-6 , page 12-13）
Data analysis will be performed using the intention processing principle in SPSS 22.0. Statistical results will be reported using a two-sided test, with statistical significance being set at P-value < 0.05. Continuous variables will be expressed as: mean (SD), median (interquartile range (IQR)), or minimum and maximum. For comparisons between treatment groups, analyses of variance (ANOVAs) will be used for normally distributed variables, and the Kruskal–Wallis H test will be used for non-normally distributed variables. Categorical variables will be expressed as numbers (%), and will be analyzed via chi-square tests for between-group comparisons.

10.page 15 line 38 :(The patients and the public were not involved in the planning and design of this study) , please rephrase the sentence

Response: Thank you for this useful comment. We have revised the sentence as requested. （Patient and public involvement section, line 8, page 13）
Patients and/or the public were not involved in study design or conduct of the study.

Other changes:
Due to the addition of some references and the change of the location of other references, we renumbered and arranged the references.
We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper.
In this letter we described exactly what amendments have been made to the manuscript text and where these can be viewed (e.g. Methods section, line 12, page 5).And all changes to the manuscript are indicated in the text by using track changes.
We appreciate for Editors/Reviewers' warm work earnestly, and hope that the correction will meet with approval.
Once again, thank you very much for your comments and suggestions.

VERSION 2 – REVIEW

REVIEWER	Wells, Cameron Iain The University of Auckland
REVIEW RETURNED	21-Sep-2021

GENERAL COMMENTS	The authors have satisfactorily addressed all of my previous comments. I wish them all the best with their study, and I look forward to reading the results.

REVIEWER	Abuelnaga, Mohamed E Suez Canal University, anesthesia, critical care and pain management
REVIEW RETURNED	07-Oct-2021

GENERAL COMMENTS	dear authors , thank you for your effort