PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Pretreatment with transcutaneous electrical acupoint stimulation to prevent postoperative ileus in patients undergoing laparoscopic colon surgery: study protocol for a randomized controlled trial
AUTHORS	Wang, Jian; Li, Dongli; Tang, Wei; Guo, Jun; Chen, Wenting; Yong, Yue; Song, Wei; Yu, Guijie; Feng, Rui; Yuan, Lan; Fu, Guoqiang; Song, Jiangang; Fan, Lihua

VERSION 1 - REVIEW

REVIEWER	Cameron Wells and Greg O'Grady University of Auckland, New Zealand
REVIEW RETURNED	01-Jun-2019

GENERAL COMMENTS	This is a study protocol for a prospective, double-blind, randomized sham-controlled trial investigating pre-operative transcutaneous electroacupoint stimulation (TEAS) in patients undergoing laparoscopic distal colonic and rectal surgery. The primary aim of this study is to determine the effect of pre-operative TEAS on the time for clinical recovery of GI function post-operatively. The authors are to be commended for undertaking this prospective study, and for selecting a sham-controlled design. I have several comments regarding this protocol, which I have listed below: Major comments: 1. The authors have stated that for inclusion, patients must be undergoing laparoscopic descending colon and rectal cancer surgery (Page 6, Line 125). Why have patients undergoing right-sided colonic resections, and middle/low rectal resections been excluded? 2. Presumably some patients will have a diverting ileostomy formed at the time of the operation. How will these patients be accounted for in the analysis? Will the time for stoma output be treated as the time of first defaecation? Is a sub-group analysis of these patients planned? 3. The authors should also report time to GI-2 (composite outcome of time to first defecation and time to tolerance of oral diet) as a primary outcome, as 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. There are several errors in grammar and phrasing of common phrases in the manuscript, particularly with frequent changes in tense between past/future. I would suggest that the manuscript be proof-read and reviewed with this in mind. 5. The authors' conclusions in the discussion regarding the benefits of TEAS remain unproven until the study is completed and an effect of TEAS has been demonstrated. These should be re-worded, as it appears the authors are assuming the results of the trial will be positive. 6. The authors should provide a more detailed pre-specified analysis plan including which statistical tests they intend to use for primary/secondary outcomes, and which variables they will include in the multivariate analysis. Minor comments: 1. The authors may wish to include a reference to recent evidence suggesting pre-operative parasympathetic stimulation is more effective than post-operative – see http://dx.doi.org/10.1136/gutjnl-2018-317263 2. The objective of this study is technically not to improve gastrointestinal motor function (Page 6, Line 114) but to assess the effect of TEAS on clinical recovery of bowel function. 3. On Page 7, Line 158, the authors have stated that non-opaque envelopes will be used. This means the envelope is transparent. Presumably this is a typo – please clarify. 4. In order for readers to double-check the power calculation on Page 8, Line 162, could the authors please clarify whether the 62+/-19h reported refers to mean and standard error or standard deviation? The authors may also wish to reference the pilot cohort used for this calculation, if published. 5. Please clarify if patients receiving the active TEAS intervention are able to feel the sensation being applied. 6. Page 7, Line 149: Please clarify the term "post-operative anal exhaust time", which is not standard in the ileus literature – presumably this is time to first flatus? 7. Page 10, Line 217: The patient and public involvement section should either be re-worded or removed, as having a clinical advisory panel technically does not qualify as PPI.

REVIEWER	Stephen Chapman University of Leeds, United Kingdom
REVIEW RETURNED	23-Oct-2019

GENERAL COMMENTS	Many thanks for the invitation to review this manuscript, which I very

	much enjoyed reading. The study protocol for a randomised controlled trial of electrical acupoint stimulation to prevent ileus is reported. The role of electro-acupuncture and acupuncture techniques for preventing ileus have been explored previously. The novelty introduced by the present study is the role of acupoint stimulation in the pre-operative period. The topic is important and represents an unmet clinical challenge. The study is appropriately registered, although there are some discrepancies between aspects of the present protocol and registration entry (see below). Since the study has commenced recruitment, the following comments invite essential discussion, rather than suggestions for change to the study itself. On the other hand, a number of these comments reflect important concerns with the study method. 1. Further detail is required to adequately describe the intervention. Since stimulation takes place for several days prior to surgery, does this implicate a role for the patient in attaching the acupoint leads/operating the stimulation equipment? If so, are any challenges with compliance anticipated and how may these be addressed? 2. Justification for the intervention schedule (30 mins x 2 for three days before surgery + once immediately prior to surgery) is required. Is this based on previous mechanistic data or is there a logistical argument for this choice. This should be considered in the discussion. 3. The primary outcome is time to first defecation. One of the secondary outcomes is time to first flatus. Since these are both measures of bowel recovery, how might they be interpreted together if conflicting results were found i.e. significant improvement in time to flatus, but not defecation. It this clinically meaningful and how would it be managed? 4. Another secondary outcome is post-operative complications, which is important in this setting. However the study follow-up period ceases at the time of discharge. This will likely miss a number of serious complications, including all cases of hospital readmission. 5. I note that the study includes only descending colonic and upper rectal surgery (middle and lower rectal surgery excluded). Differences in the rate of ileus between right and left sided resection have been reported previously, however the current inclusion represents a very limited cohort within the wider population of elective colorectal surgery. The scope for generalisability should be discussed. 6. The blinding status of the study requires further clarification. I note that the outcome assessor is blinded (nurse anaesthetist). However, the text suggests that efforts to blind patients are also undertaken. If so, please discuss the anticipated performance of blinding procedures. If the active stimulator provides a perceptible sensation, will this lead to unblinding irrespective of the visual blinding procedures described. 7. I note the inclusion of a patient advisory group. This is a strength, especially if patients are expected to self-facilitate the intervention

	(comment 1). It would be useful to explain how this group contribute to study-specific activities. At present, the description is fairly generic. 8. I note that the study is powered to test effectiveness according to previous pilot data. However in the discussion, the sample size is discussed as a limitation, implicating a larger, multi-centre study in the future. I agree, that a single-centre study may be limited in overall generalisability. However, this element of the discussion seems to confuse the study's aim. If the study is appropriately powered, an assessment of effectiveness should be possible. If not (i.e. if this is a pilot or feasibility study), then considerations of feasibility (i.e. relevant feasibility outcomes) would have been more appropriate. The role of this study in the overall programme of research should be clarified. 9. It is pleasing to see the study prospectively registered, as required. However, there are some discrepancies between the present protocol and registration entry. Specifically, the exclusion criteria (ASA and age limits) and outcomes (markers of inflammation). Furthermore, there is discrepancy in eligibility criteria between abstract and method (age). 10. The references seem appropriate and the figures are clearly understood.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Major comments:

1. The authors have stated that for inclusion, patients must be undergoing laparoscopic descending colon and rectal cancer surgery (Page 6, Line 125). Why have patients undergoing right-sided colonic resections, and middle/low rectal resections been excluded?

Response: The differences between RCC and LCRC on complication rates, length of stay, frequent morbidity, overall cost and incidence of infections after surgery has been reported. [Hinojosa M.W., Konyalian V.R., Murrell Z.A., Varela J.E., Stamos M.J., and Nguyen N.T.: Outcomes of right and left colectomy at academic centers. Am Surg 2007; 73: pp. 945-948]. In fact, the rate of ileus between right and left sided resection do exist [Kummer, A., et al., Enhanced Recovery Pathway for Right and Left Colectomy: Comparison of Functional Recovery. World J Surg, 2016. 40(10): p. 2519-27. PMID:27194560]. In order to facilitate the promotion of therapeutic techniques, common surgical conditions in clinical practice should be included. This has been proofed in the manuscript.

Inclusion criteria 2# (Page 6, Line 124) has been reworded: "Patients undergoing elective laparoscopic colonic surgery and upper rectal resection (such as left colectomy, right colectomy, and anterior resection of the upper part of the rectum and lower part of the sigmoid)."
Exclusion criteria 1# (Page 6, Line 131) has been reworded: "Middle and lower rectal resection, total/proctocolectomy or the need for complex endoscopic surgery"

2. Presumably some patients will have a diverting ileostomy formed at the time of the operation. How will these patients be accounted for in the analysis? Will the time for stoma output be treated as the time of first defaecation? Is a sub-group analysis of these patients planned?

Response: Thank you for your suggestion, which we should consider carefully. Subgroup analysis will be selected for adoption. We will conduct a preliminary analysis of the records in the following experiments. If a large number of patients undergoing diverting ileostomy, it is necessary to conduct subgroup analysis. In fact, diverting ileostomy was rarely performed in our center, so we tend to exclude this situation in this protocol. It has been rewarded description for Exclusion criteria 2# (Page 6, Line 133) “Need for abdominal wall fistula, gastrointestinal fistula, fistula surgery or stoma creation”

3. The authors should also report time to GI-2 (composite outcome of time to first defecation and time to tolerance of oral diet) as a primary outcome, as 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: We agree with the reviewer that GI-2 is an important outcome, and it will be added as a secondary outcome. We explained on why we chosen GI-2 in the discussion (Page11, Line 266): “Two indicators that are widely used to assess bowel movement will be used in this study. Time to first defecation will be the primary outcome and time to first flatus will be one of the secondary outcomes. There is a possibility that we may observe conflicting results (i.e., significant improvement in time to flatus, but not defecation). Because flatus can vary considerably between patients, clinical trials support the time to tolerance of oral diet and GI-2 (defined as the later of the following two events: time to first tolerance of solid food and time to first bowel movement) as supplementary secondary outcomes to measure the recovery time of GI function and these will be used in this study”

4. There are several errors in grammar and phrasing of common phrases in the manuscript, particularly with frequent changes in tense between past/future. I would suggest that the manuscript be proof-read and reviewed with this in mind.

Response: the manuscript has been proof-read

5. The authors’ conclusions in the discussion regarding the benefits of TEAS remain unproven until the study is completed and an effect of TEAS has been demonstrated. These should be re-worded, as it appears the authors are assuming the results of the trial will be positive.

Response: Conclusions in the discussion has been re-worded (Page12, Line289): “We hypothesize that pretreatment with TEAS could improve recovery of gastrointestinal function in patients undergoing laparoscopic surgery. If this study provides positive results, it will be possible to recommend this pretreatment strategy for patients undergoing abdominal surgery. Relevant cost-effectiveness studies are also worthy of consideration.”

6. The authors should provide a more detailed pre-specified analysis plan including which statistical tests they intend to use for primary/secondary outcomes, and which variables they will include in the multivariate analysis.

Response: Statistical methods are more detailed (Page 8, Line 179): “Data for continuous variables (i.e., first defecation time, first passage of flatus, time to tolerance of oral diet, time to walking independently, length of hospital stay) will be reported using the mean and standard deviation (M± SD) for normally distributed data or median (range) for skewed data. Data for categorical variables will be expressed as a number (percentage). Intergroup differences will be assessed using the Student’s t-test or Mann-Whitney U test. Outcomes such as time to first flatus, time to tolerance of oral diet, GI-2 and time to walking independently will be included in multiple linear regression to identify independent predictors that affect length of hospital stay. The significance level will be set at 5%. All data will be analyzed using SPSS 17.0 software or other appropriate statistical software packages.”

Minor comments:

1. The authors may wish to include a reference to recent evidence suggesting pre-operative parasympathetic stimulation is more effective than post-operative – see http://dx.doi.org/10.1136/gutjnl-2018-317263

Response: This reference has been included, it provides us a strong evidence for our view.

2. The objective of this study is technically not to improve gastrointestinal motor function (Page 6, Line 114) but to assess the effect of TEAS on clinical recovery of bowel function.

Response: This has been proofed in the manuscript.

3. On Page 7, Line 158, the authors have stated that non-opaque envelopes will be used. This means the envelope is transparent. Presumably this is a typo – please clarify.

Response: The manuscript was proofread. It is a mistake spelling on Page 7, Line 165, should be: “a sealed envelope will be opened to determine to which group the patient has been assigned”

4. In order for readers to double-check the power calculation on Page 8, Line 162, could the authors please clarify whether the 62+/-19h reported refers to mean and standard error or standard deviation? The authors may also wish to reference the pilot cohort used for this calculation, if published.

Response: This 62+/-19h reported refers to mean and standard deviation, and it is a unpublished result from a preliminary study. Additional details on Page 8, Line 170 “According to Wang Jian and Song Jiangang's preliminary study of transcutaneous electrical acupoint stimulation pretreatment for prevention of postoperative ileus in patients undergoing laparoscopic colon surgery in Shuguang Hospital”

5. Please clarify if patients receiving the active TEAS intervention are able to feel the sensation being applied.

Response: This has been clarified (Page 8, Line192)：“For patients in the TEAS group, the Zusanli (ST-36), Shangjuxu (ST-37), Hegu (LI-4) and Neiguan (P-6) acupoints will be identified before electrical stimulation with surface electrodes (Figure 2). Selection of these acupoints is based on a consensus between the acupuncturists carrying out the study. The acupuncturist will stimulate these acupoints using a Han's acupoint nerve stimulator (HANS200A, Nanjing Jisheng Medical Technology Co., Ltd., Nanjing, China), at a frequency of 100 Hz. The intensity will be adjusted for each individual to maintain a slight twitching of the regional muscle and achieve De-Qi sensations, such as soreness, numbness, distention and heaviness. The STEAS group will receive a strong, but comfortable current for 30 s, and the current will then gradually vanish over the next 15 s. The participants will be told that they are receiving TEAS, but that sensation thresholds differ and that there may be no precise perception of current stimulation. Each session of acupoints treatment will last for 30 min. During the application of TEAS, patients will be required not to change the current settings themselves. A prompt beep at the end of TEAS will indicate the end of treatment.”

6. Page 7, Line 149: Please clarify the term “post-operative anal exhaust time”, which is not standard in the ileus literature – presumably this is time to first flatus?

Response: The manuscript was proofread. The standard literature should be “ time to first flatus”

7. Page 10, Line 217: The patient and public involvement section should either be re-worded or removed, as having a clinical advisory panel technically does not qualify as PPI.

Response: This part has been re-worded (Page 10, Line 236). “This study is currently in the recruitment phase. The participants will be able to access the study results through social media.”

Reviewer: 2

1. Further detail is required to adequately describe the intervention. Since stimulation takes place for several days prior to surgery, does this implicate a role for the patient in attaching the acupoint leads/operating the stimulation equipment? If so, are any challenges with compliance anticipated and how may these be addressed?

Response: The intervention has been further described (Page8,Line192):“For patients in the TEAS group, the Zusanli (ST-36), Shangjuxu (ST-37), Hegu (LI-4) and Neiguan (P-6) acupoints will be identified before electrical stimulation with surface electrodes (Figure 2). Selection of these acupoints is based on a consensus between the acupuncturists carrying out the study. The acupuncturist will stimulate these acupoints using a Han's acupoint nerve stimulator (HANS200A, Nanjing Jisheng Medical Technology Co., Ltd., Nanjing, China), at a frequency of 100 Hz. The intensity will be adjusted for each individual to maintain a slight twitching of the regional muscle and achieve De-Qi sensations, such as soreness, numbness, distention and heaviness. The STEAS group will receive a strong, but comfortable current for 30 s, and the current will then gradually vanish over the next 15 s. The participants will be told that they are receiving TEAS, but that sensation thresholds differ and that there may be no precise perception of current stimulation. Each session of acupoints treatment will last for 30 min. During the application of TEAS, patients will be required not to change the current settings themselves. A prompt beep at the end of TEAS will indicate the end of treatment.”

2. Justification for the intervention schedule (30 mins x 2 for three days before surgery + once immediately prior to surgery) is required. Is this based on previous mechanistic data or is there a logistical argument for this choice. This should be considered in the discussion.

Response: This has been clarified in discussion (Page10, Line245)：“This study has several strengths. Firstly, the intervention strategy of the protocol will be pretreatment with TEAS. Previous studies have shown that pretreatment has a prophylactic effect. For example, pretreatment with TEAS has been shown to improve pain treatment25,26 and to improve resuscitation after anesthesia, with reduction of postoperative nausea and vomiting27. Our previous studies have shown that postoperative treatment of patients who have undergone laparoscopic colon surgery with TEAS improves postoperative recovery28. It is, however, unclear whether preoperative TEAS can prevent POI. Studies suggest that early preoperative intervention may be more beneficial in regulating physiological functions and preventing gastrointestinal paralysis29. In an extension to these findings, the present study will help to determine whether TEAS pretreatment could improvement postoperative bowel paralysis.”

3. The primary outcome is time to first defecation. One of the secondary outcomes is time to first flatus. Since these are both measures of bowel recovery, how might they be interpreted together if conflicting results were found i.e. significant improvement in time to flatus, but not defecation. It this clinically meaningful and how would it be managed?

Response: The primary endpoint is time to first defecation. We set time to first flatus as one of the secondary outcomes, because flatus can vary considerably between patients. We also add a secondary endpoint GI-2 (defined as by the later of the following two events: time patient first tolerated solid food, and time patient first passed a bowel movement) to measure the recovery time of

GI function. [Deng, G., et al., A phase II, randomized, controlled trial of acupuncture for reduction of Postcolectomy Ileus. Annals of surgical oncology, 2013. 20(4): p. 1164-1169.].
We further explained the situation in our discussion (Page 11, Line 264): “Two indicators that are widely used to assess bowel movement will be used in this study. Time to first defecation will be the primary outcome and time to first flatus will be one of the secondary outcomes. There is a possibility that we may observe conflicting results (i.e., significant improvement in time to flatus, but not defecation). Because flatus can vary considerably between patients, clinical trials support the time to tolerance of oral diet and GI-2 (defined as the later of the following two events: time to first tolerance of solid food and time to first bowel movement) as supplementary secondary outcomes to measure the recovery time of GI function and these will be used in this study”

4. Another secondary outcome is post-operative complications, which is important in this setting. However the study follow-up period ceases at the time of discharge. This will likely miss a number of serious complications, including all cases of hospital readmission.

Response: Post-operative complications will be judged adopting the Clavien-Dindo classification [Dindo, D., N. Demartines, and P.A. Clavien, Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg, 2004. 240(2): p. 205-13. PMID: 15273542]. And the follow-up period has been clarified for at least 6 months (Page 7, Line 162).
To further clarify the specific criteria of “ Length of stay” and “discharge criteria”, we add the following (Page7, Line151): “length of hospital stay, defined as number of days from operation to discharge (d). Criteria for hospital discharge include stability of vital signs with no fever, achievement of flatus or defecation, ability to tolerate solid food without vomiting, control of postoperative pain, absence of other postoperative complications and ability to function at home independently or with home care provided.”

5. I note that the study includes only descending colonic and upper rectal surgery (middle and lower rectal surgery excluded). Differences in the rate of ileus between right and left sided resection have been reported previously, however the current inclusion represents a very limited cohort within the wider population of elective colorectal surgery. The scope for generalisability should be discussed.

Response:

The differences between RCC and LCRC on complication rates, length of stay, frequent morbidity, overall cost and incidence of infections after surgery has been reported. [Hinojosa M.W., Konyalian V.R., Murrell Z.A., Varela J.E., Stamos M.J., and Nguyen N.T.: Outcomes of right and left colectomy at academic centers. Am Surg 2007; 73: pp. 945-948]. In fact, the rate of ileus between right and left sided resection do exist [Kummer, A., et al., Enhanced Recovery Pathway for Right and Left Colectomy: Comparison of Functional Recovery. World J Surg, 2016. 40(10): p. 2519-27. PMID:27194560]. In order to facilitate the promotion of therapeutic techniques, common surgical conditions in clinical practice should be included. We made the following rewarded to the inclusion criteria and exclusion criteria:
Inclusion criteria 2# (Page 6, Line 124) has been reworded: Patients undergoing elective laparoscopic colonic surgery and upper rectal resection (such as left colectomy, right colectomy, and anterior resection of the upper part of the rectum and lower part of the sigmoid).
Exclusion criteria 1# (Page 6, Line 131) has been reworded: Middle and lower rectal resection, total/proctocolectomy or the need for complex endoscopic surgery

6. The blinding status of the study requires further clarification. I note that the outcome assessor is blinded (nurse anaesthetist). However, the text suggests that efforts to blind patients are also undertaken. If so, please discuss the anticipated performance of blinding procedures. If the active

stimulator provides a perceptible sensation, will this lead to unblinding irrespective of the visual blinding procedures described.

Response: It has been further clarified (Page 9, Line 199): “The STEAS group will receive a strong, but comfortable current for 30 s, and the current will then gradually vanish over the next 15 s. The participants will be told that they are receiving TEAS, but that sensation thresholds differ and that there may be no precise perception of current stimulation. Each session of acupoints treatment will last for 30 min. During the application of TEAS, patients will be required not to change the current settings themselves. A prompt beep at the end of TEAS will indicate the end of treatment.”
A study was cited [Rakel B, Cooper N, Adams HJ, et al. A new transient sham TENS device allows for investigator blinding while delivering a true placebo treatment. J Pain. 2010;11(3):230–238. doi:10.1016/j.jpain.2009.07.007]. It is about a sham TENS device shown that this method can promote the effect of blinding through eliminating expectation bias and clarifying the true efficacy of TEAS.

7. I note the inclusion of a patient advisory group. This is a strength, especially if patients are expected to self-facilitate the intervention (comment 1). It would be useful to explain how this group contribute to study-specific activities. At present, the description is fairly generic.

Response: Your profound views coincide with Review 1# (comment 7), through careful consideration, we re-worded this part of description (Page 10, Line 236). “This study is currently in the recruitment phase. The participants will be able to access the study results through social media.”

8. I note that the study is powered to test effectiveness according to previous pilot data. However in the discussion, the sample size is discussed as a limitation, implicating a larger, multi-centre study in the future. I agree, that a single-centre study may be limited in overall generalisability. However, this element of the discussion seems to confuse the study’s aim. If the study is appropriately powered, an assessment of effectiveness should be possible. If not (i.e. if this is a pilot or feasibility study), then considerations of feasibility (i.e. relevant feasibility outcomes) would have been more appropriate. The role of this study in the overall programme of research should be clarified.

Response: The manuscript was proofread. This part has been rewritten in the discussion (from Page 10, Line 245 to Line 286).
“This study has several strengths…… Furthermore, this study is a single-center trial and, because the therapeutic effect of TEAS may be affected by ethnicity and region, it will be necessary to conduct multi-center and large sample studies in the future.”

9. It is pleasing to see the study prospectively registered, as required. However, there are some discrepancies between the present protocol and registration entry. Specifically, the exclusion criteria (ASA and age limits) and outcomes (markers of inflammation). Furthermore, there is discrepancy in eligibility criteria between abstract and method (age).

Response: The manuscript was proofread. The differences of information between the protocol and registration entry has been updated as consistent.

10. The references seem appropriate and the figures are clearly understood.

Response: thank you.

VERSION 2 – REVIEW

REVIEWER	Cameron Wells and Greg O'Grady The University of Auckland, New Zealand
REVIEW RETURNED	18-Dec-2019

GENERAL COMMENTS	Dear Adrian Aldcroft and BMJ Open Editorial Team, Thank you for the opportunity to re-review this revised article for BMJ Open titled “Pretreatment with transcutaneous electrical acupoint stimulation to prevent postoperative ileus in patients undergoing laparoscopic colon surgery: study protocol for a randomized controlled trial”. There are several clarifications which I believe need addressing before the procotol is suitable for publication; I have included my comments to the authors below. Kind regards, Dr Cameron Wells Comments to authors: This is a study protocol for a prospective, single-blind, randomized, sham-controlled trial investigating pre-operative transcutaneous electroacupoint stimulation (TEAS) in patients undergoing laparoscopic colon surgery. The authors are to be commended for conducting a sham-controlled trial in this setting. I have several comments regarding this protocol: 1. A previously submitted version of this protocol reported the study as double-blind, however the current version now describes the study as single-blind. Please clarify. Furthermore, will the treating surgical team and other staff involved in the patient’s care (i.e. nurses, other staff) be blinded to the treatment allocation? This is not stated in the manuscript. 2. Are patients receiving the active TEAS intervention are able to feel the sensation being applied? If so, this is an important limitation to the blinding process and should be described. 3. Inflammatory mediators will be measured pre-TEAS/STEAS treatment, and on post-operative days 1, 3, and 5. How will these samples be analysed, and what statistical analyses will be performed? The authors have stated that an aim of the study is to verify the anti-inflammatory effect of TEAS, however there are no analyses described regarding this aim. It may also be interesting to include a post-TEAS/STEAS but pre-operative sample, to determine whether there is a difference between groups at this timepoint. 4. The statistical analysis plan (lines 184-186) states that outcomes including time to first flatus, tolerance of an oral diet, GI-2 and time to mobilization will be included as co-variates in a regression model

	to determine predictors of length of hospital stay. This is a highly flawed analysis plan, as the clinical decision to discharge a patient is made based on all of these (highly inter-related) criteria – patients are usually not discharged until they are meeting these criteria. A regression model constructed with these variables would be highly unlikely to provide useful information and should be removed, as it does not contribute to the primary or secondary aims of the trial. 5. As currently written, exclusion criteria #6 implies that "patients with limbs" will be excluded – presumably this is not the case. Please amend accordingly. 6. Exclusion criteria #9 states that patients using centrally active analgesic drugs will be excluded – does this mean that patients receiving post-operative opiate analgesia will be excluded? This should be clarified. Also please clarify what "combined pain" in this line refers to. 7. Recent evidence has shown that the gastrointestinal tract is not paralysed post-operatively (see doi: 10.1002/bjs.10808), although GI transit is clearly impeded. Statements referring to "gastrointestinal paralysis" (lines 83, 90, 240, 251, 253) should be rephrased to avoid.

REVIEWER	Stephen Chapman University of Leeds, UK
REVIEW RETURNED	08-Dec-2019

GENERAL COMMENTS	I am grateful to the authors for their responses and I appreciate the opportunity to revisit this manuscript. In addressing the comments, a number of changes have been made to key aspects of study design, including eligibility criteria and outcome measures. Many of these make the study more clinically applicable. If the study has already begun (I understand that it has), the authors may wish to outline these interim changes in future reports. The study is not without some limitations, however these are discussed openly in the manuscript. The study question is important and incorporates good translational science which justifies the intervention. On balance, I think it will add constructively to the literature in this area.

VERSION 2 – AUTHOR RESPONSE

Reviewer #1:

Comment 1：

A previously submitted version of this protocol reported the study as double-blind, however the current version now describes the study as single-blind. Please clarify. Furthermore, will the treating surgical team and other staff involved in the patient's care (i.e. nurses, other staff) be blinded to the treatment allocation? This is not stated in the manuscript.

Answer：

We are very sorry for our incorrect writing, and we have re-written this part as “Single center，double-blinded，randomized…” on line 116.

It is really true as reviewer suggested that we further clarified the treatment allocation (on lines 166-167) as “The acupuncturist will be aware of the treatment group. Patients as well as the outcome investigator (nurse anesthetist) will be blinded to the treatment allocation.”

Comment 2：

Are patients receiving the active TEAS intervention are able to feel the sensation being applied? If so, this is an important limitation to the blinding process and should be described.

Answer：

In terms of the sensation, both groups could feel an electrical stimulation during the treatment. For the TEAS group, patients received a constant stimulation. Patients in the STEAS group received a transient placebo treatment (receive a current for 30 s, the current gradually decreases in the following 15 seconds. On lines 199-200). It has been shown in clinical trials that this sham method can promote the effect of blinding through eliminating expectation bias and providing a true efficacy of TEAS. [25. Rakel B, Cooper N, Adams HJ, et al. A new transient sham TENS device allows for investigator blinding while delivering a true placebo treatment. J Pain 2010;11(3):230-8. doi: 10.1016/j.jpain.2009.07.007] We further revised the description as “The participants of both groups will be told that they are receiving current stimulation” on lines 200-201.

Comment 3：

Inflammatory mediators will be measured pre-TEAS/STEAS treatment, and on post-operative days 1, 3, and 5. How will these samples be analysed, and what statistical analyses will be performed? The authors have stated that an aim of the study is to verify the anti-inflammatory effect of TEAS, however there are no analyses described regarding this aim. It may also be interesting to include a post-TEAS/STEAS but pre-operative sample, to determine whether there is a difference between groups at this timepoint.

Answer：

Considering the Reviewer’s suggestion, we have added an analysis describe “Intergroup differences in inflammatory mediators (at time points of pre-TEAS/STEAS treatment, and on post-operative days 1, 3, and 5) were assessed by two-way repeated measures analysis of variance with Bonferroni post hoc test.” (on lines 183-185)

The baseline for our trial was pre-TEAS/STEAS treatment. Due to the limitation of our time and budget, it is difficult for us to add another time point (post-TEAS/STEAS but pre-operative), and we are willing to accept your suggestion to improve in the future study.

Comment 4：

The statistical analysis plan (lines 184-186) states that outcomes including time to first flatus, tolerance of an oral diet, GI-2 and time to mobilization will be included as co-variates in a regression model to determine predictors of length of hospital stay. This is a highly flawed analysis plan, as the clinical decision to discharge a patient is made based on all of these (highly inter-related) criteria – patients are usually not discharged until they are meeting these criteria. A regression model constructed with these variables would be highly unlikely to provide useful information and should be removed, as it does not contribute to the primary or secondary aims of the trial.

Answer：

This part has been removed.

Comment 5：

As currently written, exclusion criteria #6 implies that “patients with limbs” will be excluded – presumably this is not the case. Please amend accordingly.

Answer：
Thank the reviewers for their valuable Suggestions. We have corrected the wrong expression on exclusion criteria #6. Exclusion criteria #6 is modified as “patients have a history of limb surgery, spinal surgery or nerve injury” on line 137.

Comment 6：
Exclusion criteria #9 states that patients using centrally active analgesic drugs will be excluded – does this mean that patients receiving post-operative opiate analgesia will be excluded? This should be clarified. Also please clarify what “combined pain” in this line refers to.
Answer：
We thank the reviewers for their constructive comments. I'm very sorry for the wrong expression. Exclusion criteria #9 has been modified as “Patients have one of the following conditions before surgery: chronic pain, drug addiction, or alcohol dependence” on lines141-142.

Comment 7：
Recent evidence has shown that the gastrointestinal tract is not paralysed post-operatively (see doi: 10.1002/bjs.10808), although GI transit is clearly impeded. Statements referring to “gastrointestinal paralysis” (lines 83, 90, 240, 251, 253) should be rephrased to avoid.

Answer：
We have re-written this part according to the Reviewer’s suggestion. On line 83, “leading to total gastrointestinal paralysis” were corrected as “leading to postoperative ileus over the entire intestinal tract. On lines 90, 240, 251, 253, the statements referring to “gastrointestinal paralysis” were corrected as “POI”.

VERSION 3 – REVIEW

REVIEWER	Cameron Wells and Greg O'Grady Department of Surgery The University of Auckland New Zealand
REVIEW RETURNED	28-Feb-2020

GENERAL COMMENTS	The authors have addressed all previous comments.