PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Acupuncture and PC6 stimulation for the prevention of postoperative nausea and vomiting in patients undergoing elective laparoscopic resection of colorectal cancer: a study protocol for a three-arm randomised pilot trial
AUTHORS	Kim, Kun Hyung; Kim, Dae Hun; Bae, Ji Min; Son, Gyung Mo; Kim, Kyung Hee; Hong, Seung Pyo; Yang, Gi Young; Kim, Hee Young

VERSION 1 - REVIEW

REVIEWER	Prof Simon Ng Division of Colorectal Surgery Department of Surgery The Chinese University of Hong Kong Hong Kong
REVIEW RETURNED	19-Sep-2016

GENERAL COMMENTS	This is a three-arm pilot randomized study that aims to investigate the efficacy of acupuncture plus PC6 wristband in the prevention of postoperative nausea and vomiting (PONV) in patients undergoing laparoscopic resection of colorectal cancer. Patients fulfilling the inclusion criteria will be randomized to receive: (A) acupuncture plus PC6 wristband; (B) PC6 wristband alone; and (C) no acupuncture or wristband (the control group). All patients will receive perioperative care based on a standardized ERAS protocol. The primary outcome of this study is the number of patients who experience moderate/severe nausea (at least 4 out of 10 on a severity numeric rating scale) at 24 hours after surgery. Secondary outcomes include pain scores, other postoperative recovery parameters, patient satisfaction, and quality of life at 2 weeks. This pilot study plans to recruit 60 patients (20 patients in each arm). No prospective sample size calculation was performed. It is hoped that the findings of this pilot study will inform a full-scale randomized trial. This pilot study commenced on 1 January 2016, and as of 13 July 2016, 41 patients have been enrolled. The researchers are to be commended for their effort to provide scientific evidence to clarify the role of acupuncture and PC6 wristband in the treatment of PONV. The research question and study objectives are clearly expressed. The research methodology is sound. The researchers have explained why they don't include a placebo/sham acupuncture group in this study. The primary and secondary outcomes of this study are clearly defined. The strengths and weaknesses of this study have also been discussed. The protocol is generally well-written. However, I have a few comments and questions for the researchers.

	1. The incidence of PONV after laparoscopic colorectal surgery within an ERAS program is indeed quite low. In the LAFA trial, the discharge criterion of 'absence of nausea' was achieved at postoperative day 1 in all groups (Vlug et al. Ann Surg 2011). In the current pilot study, all patients will receive ERAS plus a standardized protocol to prevent PONV. If the incidence of PONV after laparoscopic colorectal surgery is so low, the researchers would need a very large sample size in order to have enough power to show a significant difference between the intervention arms (acupuncture and/or PC6 wristband) and the control arm, which may not be feasible. What is the incidence of PONV after laparoscopic colorectal surgery within an ERAS protocol in the researchers' institute? 2. In the inclusion/exclusion criteria, conversion to laparotomy is not mentioned. Will converted cases be excluded from the study? 3. It is mentioned in the protocol that the outcome assessors will be blinded to the treatment allocation. However, the wristbands will be visible to them during the assessment on the first two postoperative days. Are they covered? 4. The number of patients who experience moderate/severe nausea at 24 hours after surgery is chosen as the primary outcome measure. Why don't the researchers choose the exact numeric rating scale or the nausea severity as a primary outcome? 5. I think hospital stay is a very important clinical outcome parameter, and it should be included as a secondary outcome measure.

REVIEWER	Saeed Shoar Icahn School of Medicine at Mount Sinai, NY, USA
REVIEW RETURNED	27-Sep-2016

GENERAL COMMENTS	The study is not novel as there a are a couple of randomized and non-randomized trials in the literature. Moreover, I wonder why the authors fail to blind the patients and the research staff to the groups.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Comment 1: The incidence of PONV after laparoscopic colorectal surgery within an ERAS program is indeed quite low. In the LAFA trial, the discharge criterion of 'absence of nausea' was achieved at postoperative day 1 in all groups (Vlug et al. Ann Surg 2011). In the current pilot study, all patients will receive ERAS plus a standardized protocol to prevent PONV. If the incidence of PONV after laparoscopic colorectal surgery is so low, the researchers would need a very large sample size in order to have enough power to show a significant difference between the intervention arms (acupuncture and/or PC6 wristband) and the control arm, which may not be feasible. What is the incidence of PONV after laparoscopic colorectal surgery within an ERAS protocol in the researchers' institute?

Response to the comment 1: Thank you for your invaluable comments. Although there is no published report on the incidence of PONV in our hospital, we reviewed our sampled medical records to identify the number of patients who experienced PONV (due to lack of time resources, the complete records could not be reviewed). The gross incidence risk of PONV in patients underwent laparoscopic surgery

on the recent one year was 22.7% (28/123) (unpublished) in our hospital, which was much less than what we expected. Other controlled and uncontrolled studies in South Korea showed that proportion of patients experiencing PONV was 20.7 and 23.3 % when intravenous patient-controlled analgesia was used.[1,2] We will sincerely consider your comments and acknowledge your point that the relatively low baseline risk may require the large sample size when designing the future full-scale trial. Thank you.

Reference:
1. Choi YY, et al. Can intravenous patient-controlled analgesia be omitted in patients undergoing laparoscopic surgery for colorectal cancer? Ann Surg Treat Res 2015;88(2):86-91.
2. Oh BY, et al. Analgesic efficacy of ropivacaine wound infusion after laparoscopic colorectal surgery. Ann Surg Treat Res 2016;91(4):202-206.

Comment 2:In the inclusion/exclusion criteria, conversion to laparotomy is not mentioned. Will converted cases be excluded from the study?

Response to the comment 2: Yes, they will be excluded from the study process and the analysis. We will mention your comments in the methods section like this: “We will exclude patients if unexpected conversion to open surgery is occurred”.

Comment 3:It is mentioned in the protocol that the outcome assessors will be blinded to the treatment allocation. However, the wristbands will be visible to them during the assessment on the first two postoperative days. Are they covered?

Response to comment 3: Thank you for your comments. The wristband itself was not concealed in order not to make the patient discomfort by wearing additional cover on the band; therefore assessors may have been aware of the allocation results, although we made substantial efforts to conceal the allocation results to the assessors. Since we could not completely guarantee the blindness of assessors, the term “blinded” will be accordingly revised in the “Strengths and weakness of this study” and “methods” section.

Comment 4: The number of patients who experience moderate/severe nausea at 24 hours after surgery is chosen as the primary outcome measure. Why don’t the researchers choose the exact numeric rating scale or the nausea severity as a primary outcome?

Response to the comment 4:Thank you for your comments. It is sensible to keep consistency in terms of outcome measurements between a new trial and previous research literature, to enable new results to update the existing body of evidence. The Cochrane review of the PC6 stimulation for prevention of PONV employed the primary outcome as the number of patient who experienced vomiting or nausea. [1] A large-scale multicentre trial also used the number of patients (dichotomous variable) to measure PONV. [2] To make our results comparable and easy to combine with previous studies, we decided to use the dichotomized outcome. Nevertheless, your comment is still important because the actual score of measured nausea scale may be important for other researchers. We will open the raw data with the publication of the results and include the actual score of the nausea scale.

Reference:
1. Lee A, et al. Stimulation of the wrist acupuncture point PC6 for preventing postoperative nausea and vomiting. Cochrane Database Syst Rev 2015;11:CD003281.
2. Apfel CC, et al. A factorial trial of six interventions for the prevention of postoperative nausea and vomiting. N Engl J med 2004;350(24):2441-51.

Comment 5: I think hospital stay is a very important clinical outcome parameter, and it should be

included as a secondary outcome measure.

Response to the comment 5: Thank you for your comments. We completely agree with your comments. Hospital stay will be added as a secondary outcome.

Reviewer: 2

Comment 1-1: The study is not novel as there are a couple of randomized and non-randomized trials in the literature.
Comment 1-2: Moreover, I wonder why the authors fail to blind the patients and the research staff to the groups.

Response to the comment 1-1: Thank you for your comment. There are several randomized trials and systematic reviews with regard to the topic. However, what remains incompletely understood include the effects of PC6 stimulation within multimodal prophylaxis and the combined effects of PC6 and other acupuncture treatments. Previous systematic reviews called for future research on these gaps of the evidence. We clearly mentioned this in the background to justify the commencement of our trial.

Response to the comment 1-2: Thank you for your comment. The rationale of the lack of a placebo intervention group was already clarified in the manuscript. Because of our specific research question comparing active interventions, patients/practitioners were inevitably aware of allocation results. For the outcome assessors, we tried to conceal the allocation results. However, the wristband itself was not concealed in order not to make the patient discomfort by wearing additional cover on the band; therefore assessors may have been aware of the allocation results, although we made substantial efforts to conceal the allocation results to the assessors. Since we could not completely guarantee the blindness of assessors, the term “blinded” will be accordingly revised in the “Strengths and weakness of this study” and “methods” section. Thank you.

The authors have no conflict of interest to report.
We thank you in advance for your consideration of this manuscript.

VERSION 2 – REVIEW

REVIEWER	Prof Simon Ng Division of Colorectal Surgery Department of Surgery The Chinese University of Hong Kong Hong Kong
REVIEW RETURNED	10-Dec-2016

GENERAL COMMENTS	The authors have addressed all my concerns and questions in the revised manuscript. I would recommend BMJ Open to accept this manuscript in its present form.