PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Perioperative Patient-Controlled Regional Analgesia versus Patient-Controlled Intravenous Analgesia for Patients with Critical Limb Ischemia: A Study Protocol for a Randomized Controlled Trial
AUTHORS	Chen, Si; Xu, Zhonghuang; Liu, Hongju; Zhang, Yuelun; Zhang, Jiao; Chen, Yuexin; Zheng, Yuehong; Huang, Yuguang

VERSION 1 – REVIEW

REVIEWER	Wei Jiang Shanghai sixth hispital affiliated to Shanghai Jiaotong University, China.
REVIEW RETURNED	29-Mar-2020

GENERAL COMMENTS	This paper is a well-designed trial protocol and has good clinical significance. And I think that there are several points to be determined as the following: 1. It is necessary to determine whether the analgesic acquirement of surgical area could be covered by subgluteal sciatic nerve block, and whether additional femoral nerve block is necessary if the subgluteal sciatic nerve block could not meet the surgical needs. 2. Early activity after endovascular revascularization is beneficial to accelerate rehabilitation, so the motor block effects needed to be accessed in the PCRA group. 3. It is necessary to determine hether the loss of sensation in the nerve block group would affect the judgment of postoperative limb thrombosis and ischemic complications. 4. Because the sciatic nerve block is invasive manipulation, so the patients' satisfaction with these two analgesic methods also needed to be evaluated. 5. What is the proportion of open surgical to endovascular for patients with critical limb ischemia in the researchers' clinical center, and how to ensure the matching between these two groups with the relative small sample size. Otherwise, you could consider to recruit patients of one type popular surgery. 6. The section of "discussion" was missing.

REVIEWER	Yen-Chin Liu National Cheng Kung University, Department of Anesthesiology, Taiwan
REVIEW RETURNED	07-May-2020

GENERAL COMMENTS	The research protocol may need to describe clearer about: 1. The PCA analgesia duration before T1. The flowchart claimed that one week before T1. It means that the PCA duration from T0

	to T1 is one week. It will be too long for PCRA/PCIA. The authors need to clarify this point in the methods. 2. Please add the vascular ischemia degree, anesthesia method and surgery type as the confounding factors. Those factors also have impacts on pain. 3. About the participant consent: It will be good if add: a: IRB approval date and version (closer to research starting date will be better, IRB approval on 2017 and research start at 2020/05). b: inclusion and exclusion criteria may add to the consent for patients to know. c: only tel number was provided on the consent for patient consultaton. It is better for provide more details about IRB and PI information (e-mail...) for participant protection. 4. Highly recommend to register on ClinicalTrials.gov (a free database of privately and publicly funded clinical studies conducted around the world) for international link.

REVIEWER	Morihisa Hirota Tohoku Medical and Pharmaceutical University, Japan
REVIEW RETURNED	10-May-2020

GENERAL COMMENTS	This protocol is well written and the planned trial is interesting. However, there are several concerns in 'reporting checklist for protocol of a clinical trial', which should be corrected. 1. There is no description of relevant concomitant care for dropped participants from the trial. Checklist #11d 2. There is no description of a plan to collect data from dropped participants. Checklist #18b 3. Data monitoring is not described in detail. Checklist #21a 4. There is no description about data and safety monitoring committee in this protocol, which decides the suspension and the termination of the trial if needed due to severe or unexpected adverse event. Checklist #21b 5. The description about auditing is lacking. Checklist #23 6. There is no description about ancillary and post trial care in the protocol. Checklist #30

VERSION 1 – AUTHOR RESPONSE

Responses to the reviewers' comments:

Reviewer #1: This paper is a well-designed trial protocol and has good clinical significance. And I think that there are several points to be determined as the following:
Comment 1: It is necessary to determine whether the analgesic acquirement of surgical area could be covered by subgluteal sciatic nerve block, and whether additional femoral nerve block is necessary if the subgluteal sciatic nerve block could not meet the surgical needs.
Response: Thanks for this insightful comment. In this study, preoperative analgesia approaches will be established right after the baseline assessment (T0) and randomization. In other words, the interventions focus on the perioperative pain relief and reperfusion effect on the lower limb, but not the surgical need. Patients with critical limb ischemia (CLI) mainly suffer from intense pain that comes from ulcers and gangrene which locate on the lower extremity. From this point, we believe that continuous subgluteal sciatic nerve block could provide favorable analgesia as well as reperfusion effect. Surgical need is not a primary focus of this study although the continuous patient-controlled analgesia device will not be suspended during surgery. Anaesthesiologists will select anaesthesia method according to their clinical experience and technical standards, without any restriction from the

study. In our center, most endovascular revascularizations are completed under local anaesthesia and most open surgeries are operated under general anaesthesia. Thanks again for your comment, we've made it more specified in the manuscript to avoid further confusion.

Comment 2: Early activity after endovascular revascularization is beneficial to accelerate rehabilitation, so the motor block effects needed to be accessed in the PCRA group.
Response: Thank you for the valuable comment. On the one hand, in this study, CLI patients who are in stage 6 according to Rutherford symptom classification system1 are included. Most of them have already lost at least partial motor function for a relatively long time, and postoperative motor function improvement is not their main requirement. On the other hand, Ropivacaine is a long-acting regional anesthetic that blocks nerve fibers involved in pain transmission to a greater degree than those controlling motor functions2, a low concentration ropivacaine of 0.2% may result in satisfactory pain control yet mild motor block in this study. However, your comment is very constructive. Early activities are beneficial to accelerate rehabilitation. For CLI patients, postoperative activities can be engaged after 12~24h immobilization. Motor block assessment is of great importance to prevent falling. We've added Bromage motor blockade score3 in the PCRA group (page 14, in "Trail safety"). The assessment will be done everyday after the establishment of the subgluteal sciatic block. Thanks again for this valuable comment.

Comment 3: It is necessary to determine hether the loss of sensation in the nerve block group would affect the judgment of postoperative limb thrombosis and ischemic complications.
Response: Thanks very much for this insightful comment. As the continuous nerve block may decrease pain and sensation, it is necessary for nurses and doctors to detect postoperative limb thrombosis and ischemic complications in time through close clinical observation. Other than pain, manifestations such as swelling, redness or skin temperature alteration would help us determine postoperative ischemic complications. Moreover, patients' dorsalis pedis artery pulse will be examined everyday after the revascularization treatment. If ischemic complications are suspected, ultrasound or other radiographic examinations will be carried out for the purpose of timely diagnosis and treatment.

Comment 4: Because the sciatic nerve block is invasive manipulation, so the patients' satisfaction with these two analgesic methods also needed to be evaluated.
Response: Thank you for this constructive comment. We agree that the continuous sciatic nerve block is invasive, therefore patient's satisfaction with these two analgesia approaches should be evaluated. In PUMCH, it is a general procedure to take in-patients' satisfaction survey on the day they are discharged. One of the many items allows patients to describe their satisfaction in medical procedures according to the experience in hospital using a 11-point scale from 0 to 10, with 0 defined as extremely dissatisfied and 10 defined as vastly satisfied. We have added patient satisfaction as one of the secondary outcomes at time point T1 and T2. Corresponding modification on the Chinese Clinical Trial Registry has also been made.

Comment 5: What is the proportion of open surgical to endovascular for patients with critical limb ischemia in the researchers' clinical center, and how to ensure the matching between these two groups with the relative small sample size. Otherwise, you could consider to recruit patients of one type popular surgery.
Response: Thanks for the valuable suggestion. In our center, the proportion of endovascular revascularization is more than 70% based on the previous experiences. We totally agree that the type of revascularization treatment may influence the primary outcome, that is, NRS. Nevertheless, it will not bias the estimate of the treatment effect in our study because of the randomization allocation. Even we mix different revascularization treatment type, the proportion of each type should be balanced in group I and group R after randomization. Furthermore, we will specially check the

proportion of the different treatment type in the description of baseline characteristics and adjust the unbalance in the analyses to ensure the randomization.
As stated above, the type of revascularization treatment is not a confounder in our study, but it may serve as an effect-modifier of the treatment effect. To explore the potential heterogeneity from revascularization treatment type, we will conduct a post-hoc subgroup analysis by the type of revascularization treatment and assess whether the effect of analgesia will differ in endovascular revascularization and open surgery.
Another reason for not limiting the patients in one single surgical type is because of the consideration of generalizability. If we limit our patients in one group, it will remain unclear whether our findings can be applied in another practice situation where the proportion of endovascular revascularization is different with ours.
Thanks again for your insightful suggestion. We have made a clearer statement in the manuscript (page 17, in “statistical analyses”), thanks for pointing this out.

Comment 6: The section of “discussion” was missing.
Response: Thank you for the suggestion and careful review. Since discussion is not a required item according to the submission guideline of BMJ Open, we integrated our discussion into the introduction section in the original manuscript. However, we agree it is better to have a separate discussion section. We have modified the introduction section and added a short discussion paragraph following the Ethics and dissemination section (page 19-20) mainly to discuss the application and reference value of this study.

Reviewer #2: The research protocol may need to describe clearer about:
Comment 1: The PCA analgesia duration before T1. The flowchart claimed that one week before T1. It means that the PCA duration from T0 to T1 is one week. It will be too long for PCRA/PCIA. The authors need to clarify this point in the methods.
Response: Thanks for the careful review and this insightful comment. We apologize for our lack of consideration. Patients who suffer from CLI require revascularization treatment as soon as possible. In our center, the average duration from admission to revascularization is 3~5 days based on statistical data. Therefore, we have revised the flowchart according to your comment. It had also been stated in the intervention section (page 10).

Comment 2: Please add the vascular ischemia degree, anesthesia method and surgery type as the confounding factors. Those factors also have impacts on pain.
Response: Thanks for the valuable suggestion. Firstly, for vascular ischemia degree, patients only in stage 6 according to Rutherford symptom classification system are included in this study. The clinical description and objective criteria of the vascular ischemic degree are fully defined in the classification system4. Secondly, we agree with you that anaesthesia method and surgery type may have impacts on pain. However, since this is a randomized controlled study, if the randomization is achieved, theoretically all the prognostic factors of patients in both groups will be balanced. Therefore, prognostic factors from balanced groups will not produce any confounding effect. Nevertheless, it is still possible that unbalanced prognostic factors may exist between groups. In this study, there may be two possible reasons for causing this unbalance. One is due to random error caused by the relatively small sample size. We believe that this unbalance will not influence the result of research because the impact will be reflected in the confidence interval width of the primary outcome’s effect estimates. The other possible reason is due to errors in randomization, this will produce actual confounding effects. We expect that anaesthesia method and surgery type will not have a higher probability to produce unbalance between groups comparing to other variables, but we agree that if these variables were unbalanced between groups, they may introduce confounding effects in the estimates of the treatment effect. Hence, we will specially check variables such as anaesthesia method and surgery type in the description of baseline characteristics and adjust any unbalanced

variable using a multivariable method in the analysis. We have added this on page 16, in “Statistical analyses” section. Thanks again for the helpful suggestion.

Comment 3: About the participant consent: It will be good if add: a: IRB approval date and version (closer to research starting date will be better, IRB approval on 2017 and research start at 2020/05). b: inclusion and exclusion criteria may add to the consent for patients to know. c: only tel number was provided on the consent for patient consultaton. It is better for provide more details about IRB and PI information (e-mail...) for participant protection.
Response: Thank you for pointing these out. We have revised the consent form according to your suggestion. a: IRB approval date and version number have been added to the consent form. As you noted, the study was funded and ethically approved in 2017. By mid-2018, we have finished the pilot study. Then there was a two-year delay because of the maternity leave of a key research member. Although we believe there are no major changes from academic perspective on this study over the past three years and participants will not be at increased risk of ethical injury, we have applied for a follow-up ethics review to IRB. The consent and registry will be further updated after the follow-up review. b: The inclusion and exclusion criteria have been added to the consent form. c: We have added the E-mail address of PI and IRB to the consent form for patient consultation. Thanks again for your professional suggestion.

Comment 4: Highly recommend to register on ClinicalTrials.gov (a free database of privately and publicly funded clinical studies conducted around the world) for international link.
Response: Thanks for your suggestion. We have already registered out trial with Chinese Clinical Trial Registry (ChiCTR2000029298, 22 January 2020). Chinese Clinical Trail Registry is primary registry of The World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP). It has been endorsed by ICMJE and has equal power with clinicaltrials.gov regarding to the trial registration. ChiCTR is also acceptable registry according to submission guidelines of BMJ Open. We did not register our trial with clinicaltrials.gov because sometimes National Institutes of Health (NIH) recommends local investigators complete their protocols on local registries after they receive the submissions from mainland China.

Reviewer #3: This protocol is well written and the planned trial is interesting. However, there are several concerns in ‘reporting checklist for protocol of a clinical trial’, which should be corrected.
Comment 1: There is no description of relevant concomitant care for dropped participants from the trial. Checklist #11d
Response: Thanks for the careful review and constructive comment. According to checklist #11d, we’ve added the description of relevant concomitant care and interventions that are permitted or prohibited during the trial on page 10, in the section of “Intervention”. In addition, according to your valuable suggestion, we have modified the dropout criteria and added the description of remedial intervention for participants that dropped out from the trial (page 11, “Interventions”).

Comment 2: There is no description of a plan to collect data from dropped participants. Checklist #18b
Response: Thanks for pointing this out. Participant retention and follow-up engagement is enhanced by communicate verbally and via common instant message app. In the case where primary outcome data is missing at T2, investigators will call the participants within two days of discharge to collect the missing data. We have added this description on page 15 and 16, in the section of “Data collection, monitoring and confidentiality”.

Comment 3: Data monitoring is not described in detail. Checklist #21a
Response: Thank you very much for the careful review. Since this is a single-center randomized controlled trial and the outcomes are relatively simple, no interim analysis will be performed during the

study. After completion of the study, all the data collected will be locked in the database then the data analyses will be conducted. This has been described on page 16, “Data collection, monitoring and confidentiality”.

Comment 4: There is no description about data and safety monitoring committee in this protocol, which decides the suspension and the termination of the trial if needed due to severe or unexpected adverse event. Checklist #21b
Response: We appreciate your careful review very much. Description of data and safety monitoring committee is added as a paragraph following the description of steering committee (page 20, “Data and Safety Monitoring Committee (DSMC)”).

Comment 5: The description about auditing is lacking. Checklist #23
Response: Thanks for pointing this out. There is no planned auditing for the study. We have added the description in the revised manuscript (page 16, in “Data collection, monitoring and confidentiality”).

Comment 6: There is no description about ancillary and post trial care in the protocol. Checklist #30
Response: Thank you for your careful review. Ancillary and post care will not be involved in this study. We have added the description in the revised manuscript (page 12, in “Interventions”).

References:
1. Rutherford R B, Baker J D, Ernst C, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. J vasc surg 1997;26(3):517-538.
2. McClellan KJ, Faulds D. Ropivacaine: An update of its use in regional anaesthesia. Drugs 2000; 60:1065–1093.
3. Craig D, Carli F. Bromage motor blockade score - a score that has lasted more than a lifetime. Can J Anaesth 2018;65(7):837-838.
4. Rutherford R B, Baker J D, Ernst C, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. J vasc surg 1997;26(3):517-538.

VERSION 2 – REVIEW

REVIEWER	Morihisa Hirota Tohoku Medical and Pharmaceutical University, Japan
REVIEW RETURNED	28-Jun-2020

GENERAL COMMENTS	No special comment.