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Perioperative Patient-Controlled Regional Analgesia versus Patient-Controlled Intravenous Analgesia for Patients with Critical Limb Ischemia: A Study Protocol for a Randomized Controlled Trial

Si Chen[1], Zhonghuang Xu[1], Hongju Liu[1], Yuelun Zhang[2], Jiao Zhang[1], Yuexin Chen[3], Yuehong Zheng[3*], Yuguang Huang[1]

*Correspondence: yuehongzheng@yahoo.com

Si Chen And Zhonghuang Xu are joint first authors.

1Department of Anesthesiology, Peking Union Medical College Hospital, Chinese Academy of Medical Science & Peking Union Medical College, Beijing, 100730, China.

2 Department of Medical Research Center, Peking Union Medical College Hospital, Chinese Academy of Medical Science & Peking Union Medical College, Beijing, 100730, China.

3Department of Vascular surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Science & Peking Union Medical College, Beijing, 100730, China.

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Abstract:

Introduction: Both regional analgesia and intravenous analgesia are frequently used perioperatively for patients with critical limb ischemia (CLI). Nevertheless, the comparison of perioperative effect of regional and intravenous analgesia has not yet been thoroughly illustrated. This study will comprehensively compare patient-controlled regional analgesia (PCRA) and patient-controlled intravenous analgesia (PCIA) as two different perioperative analgesia approaches for patients with CLI. It investigates their effects on analgesia, reperfusion and the quality of recovery perioperatively, also aims to provide clinical evidence to those non-surgical patients with non-reconstructable arteries.

Methods: This trial is a randomized, single-center, open-label, parallel trial with target sample size of 78 in total. Eligible participants will be randomly allocated to the PCRA group (group R) or the PCIA group (group I) after admission. Participants in group R will receive ultrasound-guided subgluteal sciatic catheterization, followed by continuous patient-controlled regional analgesia infusion (0.2% ropivacaine 15ml as loading dose, 8ml/h as background with a patient-controlled bolus of 6ml). Participants in group I will receive patient-controlled intravenous analgesia (morphine is given in boluses of 1mg as needed, background infusion at 1mg/h). Data will be collected at baseline (T0), two hours before revascularization treatment (T1) and two hours before discharge (T2). The primary outcomes include the numerical rating scale (NRS) pain score at T1 and T2. The secondary outcomes include the perioperative transcutaneous oxygen pressure ($TcPO_2$), the tissue hemoglobin index (TOI), Hospital Anxiety and

Depression Scale (HADS) at T1 and T2; the Patient Global Impression of Change (PGIC) at T1 and T2; the perioperative cumulative morphine consumption, the length of postoperative hospital stay and adverse events (AEs).

Ethics and dissemination: This study received authorization from the Institutional Review Board of Peking Union Medical College Hospital on 21 March 2017 (approval no. ZS-1289X). Study findings will be disseminated through presentations at scientific conferences or publications in peer-reviewed journals.

Trial registration: Registered on 22 January 2020. Chinese Clinical Trial Registry, identifier ChiCTR2000029298.

Protocol version: V4CP.B1 (18, February, 2020)

Strengths and limitations of this study:

- Aiming to compare the perioperative efficacy of two different analgesia approaches, this study will assess their effects on analgesia, reperfusion, as well as the quality of recovery, rather than their effects on analgesia alone.
- Patient-controlled analgesia is used in this study so that the perioperative pain management for patients with CLI could be individual and continuous. The analgesia approaches cover the perioperative period thoroughly.
- Two different-principle-based measuring parameters are used to evaluate the reperfusion effect. $TcPO_2$ is by heating skin to a stable hyperemia equilibrium condition, TOI is by detecting the absorption and reflection of near-infrared light.

- As an open-labeled trial, all participants and some of the investigators are aware of group assignment, their expectation may introduce bias.

Keywords: critical limb ischemia, patient-controlled analgesia, perfusion, analgesia

Introduction

Critical limb ischemia (CLI) presents the end stage of peripheral arterial disease (PAD) [1]. CLI is clinically defined as ischemic rest pain, ulcers and gangrene in the presence of hemodynamic evidence of arterial insufficiency[2]. The mean annual incidence of CLI was 0.35% reported in a national investigation from the United States[3]. The prevalence is approximately 1% of the adult population, and up to 10% of patients with PAD may have CLI. In recent years, a consensus from Peripheral Academic Research Consortium has provided an objective hemodynamic definition for CLI[4]. In this study, this consensus definition will also be used to diagnose CLI.

The major goal of CLI treatment is to relieve ischemic pain, improve limb perfusion, heal wounds and prevent further tissue loss[5]. The Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II) emphasized the importance of the pain management for CLI patients and recommended a multidisciplinary approach to control pain[1]. Pain control is important not only to improve quality of life, but also reduce the possibility of phantom limb pain[6-7]. For patients with PAD, the general principles of perioperative pain management should be individual, continuous and cover the whole perioperative period thoroughly[8]. Over the past years, the patient-controlled analgesia has become the mainstay for providing postoperative pain relief[9]. Accordingly, we considered to establish patient-controlled analgesia preoperatively in our study. Existing studies suggested that intravenous morphine[10] and ultrasound-guided peripheral nerve block provided satisfactory analgesia effect on patients with CLI[11-14]. However, the analgesia effect of intravenous morphine and ultrasound-guided

regional block has not been compared before. Therefore, in this study, we plan to compare the perioperative analgesia effect of patient-controlled regional analgesia (PCRA) and patient-controlled intravenous analgesia (PCIA) for patients diagnosed with CLI.

Additionally, few of the previous studies have studied the effects on reperfusion besides analgesia. A previous prospective study showed that continuous peridural ropivacaine infusion provided satisfactory analgesia, dilated vessels, reconstructed collateral circulation and improved reperfusion remarkably in diabetic patients[15]. Regional analgesia can cause changes in vascular blood flow, but data regards to CLI patients' perioperative experiences is limited. Therefore, in this study, the reperfusion effect of the PCRA and PCIA methods will be further evaluated within participants with CLI. To compare the effect on reperfusion between the two analgesia approaches, we plan to use two different-principle-based measuring parameters, namely, the perioperative transcutaneous oxygen pressure ($TcPO_2$) and the tissue hemoglobin index (TOI). $TcPO_2$ is a transcutaneous, conventional clinical parameter measured heating a skin tissue in the range of 37℃ to 45℃ to reach a stable hyperemia equilibrium condition[16]. NIRS detects the absorption and reflection of near-infrared light and has the potential to provide continuous, real-time measurement of both blood volume and cellular respiration in skin tissue. Other perioperative data regarding the quality of recovery, such as the patients' emotional state, global impression of change, perioperative morphine consumption, length of postoperative hospital stay and adverse events (AEs) will be investigated as well.

We also hope this study offers a reference for the non-surgical patients. Although revascularization has been the most effective treatment for patients with CLI, some patients' arteries are impossible to revascularize and require other treatments such as drugs[17], transcutaneous electrical stimulation[18], peripheral blood mononuclear cells therapy[19] or lumbar sympathectomy[20] to relieve pain and/or increase peripheral perfusion to avoid amputation. For those patients with non-reconstructable arteries, long-term PCRA may be less invasive and adequate for both analgesia and perfusion. There are evidences showing that it is safe to discharge patient home with catheter[21]. In addition, it has been previously reported that continuous sciatic nerve block could be used at home for long-term pain control[22]. We expect this perioperative study can also be a future reference for those who lost their opportunity for revascularization, and whose quality of life may be significantly improved.

Objective

The objectives of this randomized controlled trial are to compare the perioperative analgesia efficacy between PCRA and PCIA for patients with CLI. The perioperative effect on peripheral inflow perfusion, emotion, patient global impression of change (PGIC), morphine consumption, length of postoperative hospital stay and AEs of PCRA and PCIA will also be evaluated and compared.

Methods

Overall design

This trial is a randomized, single-center, open-label, parallel trial, and will be carried out in Peking Union Medical College Hospital (PUMCH). Institutional research ethics board approval was obtained from PUMCH Institutional Review Board (No. ZS-1289X, 21 March 2017). An overall flow diagram is provided in Fig.1. The timing of interventions and data collection is detailed in Fig 2. This protocol was designed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines[23], the checklist can be found in Appendix 1. The trial will be conducted at PUMCH in accordance with the Good Clinical Practice- International Conference on Harmonisation (GCP-ICH) guidelines. This trial was registered with the Chinese Clinical Trial Registry (ChiCTR2000029298).

Recruitment

Recruitment for this study will begin on 6 May 2020. Full written informed consents will be obtained from each participant by a qualified member of the research team prior to any trial-related procedures.

Inclusion criteria

Participants who meets the following criteria will be enrolled in this trial:

- 18~80 years of age
- Diagnosed with critical limb ischemia[2 4], admitted in hospital for elective surgery treatment, either open surgical or endovascular revascularization
- The lesions are mainly unilateral and in the supplied area of sciatic nerve

- Stage 6 in Rutherford symptom classification system[24]
- American Society of Anesthesiology (ASA) physical status II~III

Exclusion criteria

Participants who meets the following criteria will be excluded:

- Are taking opioids before admission
- Have known allergy to the drugs will be used in the study
- Have severe liver or kidney dysfunction
- Have contraindication for the catheterization (e.g. infection at injection site, coagulation disorders, refuse or be unable to cooperate the procedure)
- The dorsum of the affected foot is not intact
- Are unable to understand the scales or to describe to the investigators

Dropout criteria

Participants who meets the following criteria will be withdrawn from the study:

- Not willing to continue their participation
- Cannot follow the initial treatment plan due to any reason

Randomization, sequence concealment and blinding

All eligible participants will be randomly allocated to either group R or the group I in a ratio of 1:1 using the R software (R Foundation for Statistical Computing). The random allocation sequence will be computer-generated by an independent researcher

who has no contact with any participant and will not be involved in the following research. The participants' respective treatment group (group R or group I) will be sealed in an opaque envelope and will only be opened after the enrolment of the participants in the study. An investigator will be responsible for enrolling patients, obtaining consent form and requesting randomization.

This study is an open-label study whereby the participants, the personnel who carry out the intervention and the outcome assessor cannot be blinded because of the nature of the intervention. However, the researchers who are responsible for the statistical analysis will be blinded to the allocation.

Interventions

Analgesia approaches will be established after the baseline assessment (T0). The FORNIA CPE-101 electronic infusion pump will be used as the continuous patient-controlled analgesia device.

The PCRA group (group R)

Ultrasound-guided continuous subgluteal sciatic block will be applied on the participants enrolled in the group R. Patient will be placed partly lateral and partly prone, with the legs flexed in the hip and knee. Scanning begins in the depression between the greater trochanter of femur and the ischial tuberosity using the 8-3MHz curved probe of the ultrasound equipment (X-porte, SONOSITE, USA). The sciatic nerve can be identified in the cross-sectional view in between of the two bones, below the gluteus muscle. Then rotate the transducer 90° so that the sciatic nerve is imaged in

the longitudinal view. Insert needle in-plane from the cranial to caudal direction and underneath the fasica to enter the subgluteal space, then advance the needle until the tip is adjacent to the nerve. After confirming the needle placement by obtaining a motor response of the calf and foot using the peripheral nerve stimulator, inject 0.2% ropivacaine 15ml for loading dose, then insert the catheter 5cm beyond the needle tip in vicinity of the sciatic nerve. Finally, secure the catheter by tunneling and taping. The infusion strategy includes 0.2% ropivacaine at 8ml/h as background with a patient-controlled bolus of 6ml, lockout time 30min, 1-h limit 20ml.

The PCIA group (group I)

For the participants enrolled in the group I, patient-controlled intravenous analgesia will be connected after intravenous access is established. The infusion strategy is as follow. Intravenous morphine is given in boluses of 1mg as needed, background infusion 1mg/h, with a lockout time of 20min. The 1-h limit is 4mg morphine.

The intraoperative and postoperative patient management

The continuous patient-controlled analgesia will not be suspended during the revascularization treatment despite the type of anaesthesia method. After the revascularization, the device will be paused when patient report it is no longer needed, which usually takes several days. The device will be on standby for an additional 48 hours before removal. In case of inadequate analgesia is provided perioperatively, the infusion strategy dosage may be increased for patients in group I, extra-doses of intravenous morphine may be used and recorded for patients in group R.

Outcomes

Primary outcomes

The primary outcome of this trial is the numerical rating scale (NRS). NRS allows patients to describe the intensity of pain, which is 11-point scale ranging from 0 to 10, with 0 defined as no pain and 10 defined as the worst pain imaginable[25]. The measurement timepoint of the primary outcome will be two hours before revascularization treatment (T1) and two hours before discharge (T2).

Secondary outcomes

The secondary outcomes are as follows:

- The transcutaneous oxygen pressure ($TcPO_2$) at T1 and T2. $TcPO_2$ will be obtained with PeriFlux System 5000 (PERIMED, Sweden) transcutaneously using the $TcPO_2$ unit-PF 5040. Calibration will be completed before use. When measuring, patients will be in sitting position. The electrode of the PF 5040 will be placed on the dorsum of the affected foot, away from any skin lesion. Wait 10~15min for a stable reading.
- The tissue hemoglobin index (TOI) at T1 and T2. TOI will be obtained with the EGOS-600A near infrared spectroscopy (NIRS, ENGINMED, China). The transducer of NIRS will be placed at the same spot as PF5040 on a sitting position, after the completion of $TcPO_2$ measurement. Wait 30 sec for each interval to gain five readings. The values at each time point will be calculated as the mean of five consecutive values over 2min.
- Hospital Anxiety and Depression Scale (HADS) at T1 and T2. HADS is a self-

rating patient-reported outcome measure developed to assess depression and anxiety of patients with illness. The 24-item questionnaire is divided into two subscales: anxiety (HADS-A) and depression (HADS-D). The ratings are summed to yield a total score (0 to 42), or for each subscale (0 to 21) with special attention[26].

- Patient Global Impression of Change (PGIC) at T1 and T2. PGIC is a 7-point verbal scale commonly used to assess patient's perception of pain relief following treatment, which has been proved its significant relevance and correlations for peripheral neuropathic pain in daily practice[27].
- Cumulative morphine consumption perioperatively, the sum will be calculated before discharge.
- Length of postoperative hospital stay.
- AEs, such as hematoma, catheter displacement, nausea, vomiting, drowsiness, dizziness, urinary retention, pruritus, local anaesthesia intoxication, etc. The occurrence time, nature, duration and severity of AEs will all be collected in detail.

Trial safety

The establishment, configuration and dispensing of the patient-controlled analgesia devices will be completed by a dependable anesthesiologist. The continuous ultrasound-guided subgluteal sciatic block will be performed in an operating room, only after intravenous access and standard monitoring is established for the patient. Investigators will follow up the patient at least twice a day during the research. All the reported AEs and other unintended effects of trial conduct will be collected, assessed,

reported and managed according to the GCP-ICH guidelines. Any severe AE happens perioperatively will be reported to the adverse event registration system of the hospital.

Patient and public involvement

Patients and public were not involved in the development of the research question or in the design of the study. Patients will receive oral and written information about this trial. However, they will not be involved in the recruitment and conduct of the study. The burden of the intervention will be assessed by patients themselves. On completion of the study, dissemination of the general study results or the anonymized individual patient data will be made on demand.

Sample size

The primary outcome of this trial is the NRS score after analgesia. Sample size was calculated based on our pilot study which had included ten patients in total (five for each group). The result of the pilot study showed that the NRS scores in group R and group I was1.63 and 3.31, and the standard deviation was 1.85 and 2.12 respectively. We used the statistical power of 80% and two-sided α of 0.05. The target sample size for each group is at least 22 participants. Taking into account a dropout rate of 20%, a sample size of 52 (26 for each group) was finally determined.

Data collection, monitoring and confidentiality

Each patient's ID and demographic information (including age, gender, height, weight) will be collected. We will document all the AEs related to PCRA or PCIA, including hematoma, catheter displacement, local anaesthesia intoxication, nausea, dizziness, urinary retention, pruritus, etc. All the calibration and measurements of $TcPO_2$ and TOI will be performed and recorded by one special technician using the same apparatuses. Collected data will be recorded on paper case report forms (CRFs), then entered into electronic case report forms (eCRFs) and uploaded to a central server. The CRFs and eCRFs will be kept for at least five years after publication in case of any inquiry. A qualified clinical trial expert will be invited in the middle and at the end of the investigation to ensure that the protocol and GCP-ICH are being followed. No interim analysis will be performed during the study. Personal information about the enrolled participants will be safely and confidentially kept. The eCRFs and all the data collected will be stored anonymously in the password-protected central server and restricted to relevant members of the research team. Paper copies of the CRFs will be stored in a locked cabinet in the relevant research office.

Statistical analyses

Continuous variables will firstly be checked for normality using the visual inspection of the histogram. Normally distributed continuous variables will be expressed as the mean ± SD, and non-normally distributed continuous variables will be expressed as the median and interquartile range (IQR). The categorical variables will be summarized as frequencies and percentages. The primary outcome, difference of NRS between groups,

which is generally normally distributed from experience, will be analyzed using student's *t* test, and the mean difference with corresponding one-sided 95% confidence interval (CI) will be calculated. For the secondary outcomes including $TcPO_2$, TOI, HADs and PGIC, student's *t* test will be used to compare the group difference. Data with a skewed distribution, such as cumulative morphine consumption and length of postoperative hospital stay, will be analyzed using the Mann-Whitney U test. As categorical variables, AEs will be compared using chi-squared test. The main analysis will be performed after the study has been completed. Data analysis will be performed according to the intention to treat principle. The results of this study will be reported according to the Consolidated Standards of Reporting Trials (CONSORT) statement[28]. Statistical analyses will be conducted using SPSS 19.0 (Version 22; SPSS Inc., Chicago, IL, USA). A two-sided $p<0.05$ is considered significant.

Trial status and time scale

The study was funded and ethically approved in 2017. A pilot study was conducted subsequently. We had finished the pilot study by 8 July 2018, then the study was delayed because of the maternity leave of Si Chen until January 2020. The trial was registered on 22 January 2020 and will begin to recruit participants on 6 May 2020.

Abbreviations

PAD, peripheral artery disease; CLI, critical limb ischemia; PCRA, patient-controlled regional analgesia; PCIA, patient-controlled intravenous analgesia; $TcPO_2$,

transcutaneous oxygen pressure; TOI, tissue hemoglobin index; AE, adverse events; PUMCH, Peking Union Medical College Hospital; SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials; GCPs, Good Clinical Practice; ICH, International Conference on Harmonisation; ASA, American Society of Anesthesiology; NIRS, near infrared spectroscopy; NRS, numerical rating scale; HAD, Hospital Anxiety and Depression Scale; PGIC, Patient Global Impression of Change; VAS, visual analogue scale; CRFs, case report forms, CONSORT, Consolidated Standards of Reporting Trials; rSO_2, region tissue oxygenation saturation.

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Steering Committee

The Steering Committee carries the ultimate responsibility for the trial and has access to the final dataset. Specific tasks of the Steering Committee are: final approval of the study protocol, approval of the amendments to the study protocol, approval of manuscripts and publications of the trial. The members of the Steering Committee in this trial include: Si Chen, anaesthesiologist; Yuehong Zheng, vascular surgery surgeon; Yuelun Zhang, statistician.

Author contributions

SC and ZHX are joint first authors. SC obtained funding and the ethical approval, registered and drafted the manuscript. ZHX and YHZ conceived the study and participated in the design of the study. YGH, HJL and YXC participated in the study coordination. YLZ contributed to the statistical analysis plan. JZ acquired and analyzed the data of the work. YHZ is the corresponding author. He critically edited the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This research project was approved by the Peking Union Medical College Hospital Institutional Review Board (ZS-1289X) on 21 March 2017. Important protocol amendments will be communicated to relevant parties (eg, investigators, IRB, trial participants, trial registries, journals) by Dr. Yuehong Zheng, trial principal investigator, as soon as changes are made. Written informed consent (details see Appendix 2) will be obtained from all participants.

Dissemination plan

The result of this study will be presented in national and international meetings and will be submitted for publication to relevant vascular surgery, analgesia or anaesthesia peer-reviewed journals.

Consent for publication

All authors approved the final manuscript and agreed the submission.

Competing interests

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: no financial relationships with any organization that might have an interest in the submitted work in the previous three years, no other relationships of activities that could appear to have influenced the submitted work. There is no conflict of interests.

Data sharing

No additional data are available.

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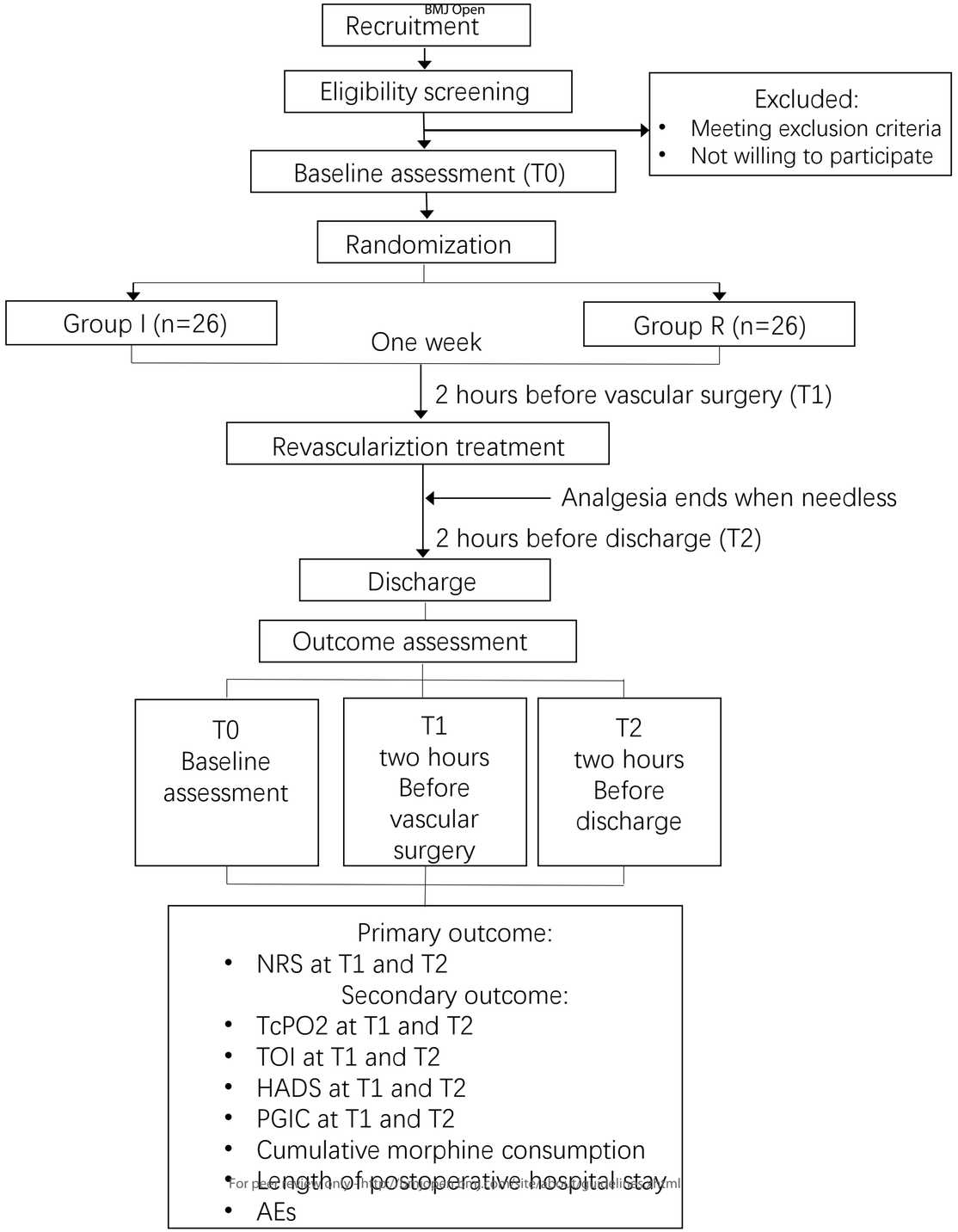

	STUDY PERIOD				
	Enrolment	Allocation	Post-allocation		Close-out
TIMEPOINT		T0	T1		T2
ENROLMENT:					
Eligibility screen	×				
Informed consent	×				
Randomization		×			
INTERVENTIONS:					
Group I		←	—	→	
Group R		←	—	→	
ASSESSMENTS:					
Demographic data	×				
NRS		×	×		×
TcPO2		×	×		×
TOI		×	×		×
HADS		×	×		×
PGIC			×		×
Cumulative morphine consumption					×
Length of postoperative hospital stay					×
Adverse events					×

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

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Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

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Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2, 3
Protocol version	#3	Date and version identifier	3
Funding	#4	Sources and types of financial, material, and other support	17
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 17

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	17
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	17
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Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
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Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9
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Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15
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受试者知情同意书

研究项目名称：不同镇痛方式用于重症下肢缺血患者的围术期作用效果研究

研究负责人：陈思

联系电话：13466364034

研究单位：中国医学科学院北京协和医院

1. 研究背景、目的：重症下肢缺血以静息痛、溃疡、坏疽为主要特征。疼痛刺激不仅降低患者的生活质量，还可诱发心脑血管事件、进一步加重神经病理性改变。良好的疼痛管理可帮助患者减轻临床症状、延缓病情发展、改善生活质量、延长生存周期。本研究目的在于比较病人自控周围神经连续阻滞技术（方法 1）与病人自控静脉镇痛技术（方法 2）在患者围术期的镇痛效果以及其对下肢血流灌注的改善作用。其中，方法 1 属疼痛介入治疗，通过坐骨神经周围置管完成，优势在于能够扩张下肢血管、减少患者阿片类药物使用量、镇痛效果明确；不足在于属有创操作，导管置于体内，有渗漏、移位、感染等风险。方法 2 通过静脉持续使用阿片类药物完成，优势在于镇痛效果明确，不足在于有嗜睡、头晕、恶心、呕吐、瘙痒、阿片类药物过量、耐受等风险。

2. 研究内容、方法及程序：入院后将随机为患者选取一种镇痛方式，在镇痛前后分别进行以下内容：
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   b) 研究所附加的诊疗项目：填写调查问卷、测量皮肤温度及患肢血流速度（无创伤）。

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   b) 收益：获得更为确切、舒适的疼痛诊疗体验和更密切的镇痛随访，对于未来此类患者的治疗选择将更加有益。

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Perioperative Patient-Controlled Regional Analgesia versus Patient-Controlled Intravenous Analgesia for Patients with Critical Limb Ischemia: A Study Protocol for a Randomized Controlled Trial

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Perioperative Patient-Controlled Regional Analgesia versus Patient-Controlled Intravenous Analgesia for Patients with Critical Limb Ischemia: A Study Protocol for a Randomized Controlled Trial

Si Chen[1], Zhonghuang Xu[1], Hongju Liu[1], Yuelun Zhang[2], Jiao Zhang[1], Yuexin Chen[3], Yuehong Zheng[3*], Yuguang Huang[1]

*Correspondence: yuehongzheng@yahoo.com

Si Chen And Zhonghuang Xu are joint first authors.

1 Department of Anesthesiology, Peking Union Medical College Hospital, Chinese Academy of Medical Science & Peking Union Medical College, Beijing, 100730, China.

2 Medical Research Center, Peking Union Medical College Hospital, Chinese Academy of Medical Science & Peking Union Medical College, Beijing, 100730, China.

3 Department of Vascular surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Science & Peking Union Medical College, Beijing, 100730, China.

Word count: 3605

Abstract:

Introduction: Both regional analgesia and intravenous analgesia are frequently used perioperatively for patients with critical limb ischemia (CLI). Nevertheless, the comparison of perioperative effect of regional and intravenous analgesia has not yet been thoroughly illustrated. This study will comprehensively compare patient-controlled regional analgesia (PCRA) and patient-controlled intravenous analgesia (PCIA) as two different perioperative analgesia approaches for patients with CLI. It investigates their effects on analgesia, reperfusion and the quality of recovery perioperatively, also aims to provide clinical evidence to those non-surgical patients with non-reconstructable arteries.

Methods and analysis: This trial is a randomized, single-centre, open-label, parallel trial with target sample size of 78 in total. Eligible participants will be randomly allocated to the PCRA group (group R) or the PCIA group (group I) after admission. Participants in group R will receive ultrasound-guided subgluteal sciatic catheterization, followed by continuous patient-controlled regional analgesia infusion (0.2% ropivacaine 15ml as loading dose, 8ml/h as background with a patient-controlled bolus of 6ml). Participants in group I will receive patient-controlled intravenous analgesia (morphine is given in boluses of 1mg as needed, background infusion at 1mg/h). Data will be collected at baseline (T0), two hours before revascularization treatment (T1) and two hours before discharge (T2). The primary outcomes include the numerical rating scale (NRS) pain score at T1 and T2. The secondary outcomes include the perioperative

transcutaneous oxygen pressure ($TcPO_2$), the tissue hemoglobin index (TOI), Hospital Anxiety and Depression Scale (HADS) at T1 and T2; the Patient Global Impression of Change (PGIC) and patient satisfaction at T1 and T2; the perioperative cumulative morphine consumption, the length of postoperative hospital stay and adverse events (AEs).

Ethics and dissemination: This study received authorization from the Institutional Review Board of Peking Union Medical College Hospital on 21 March 2017 (approval no. ZS-1289X). Study findings will be disseminated through presentations at scientific conferences or publications in peer-reviewed journals.

Trial registration: Registered on 22 January 2020. Chinese Clinical Trial Registry, identifier ChiCTR2000029298.

Protocol version: V4CP.B2 (15, June, 2020)

Strengths and limitations of this study:

- Aiming to compare the perioperative efficacy of two different analgesia approaches, this study will assess their effects on analgesia, reperfusion, as well as the quality of recovery, rather than their effects on analgesia alone.
- Patient-controlled analgesia is used in this study so that the perioperative pain management for patients with CLI could be individual and continuous. The analgesia approaches cover the perioperative period thoroughly.

- Two different-principle-based measuring parameters are used to evaluate the reperfusion effect. $TcPO_2$ is by heating skin to a stable hyperemia equilibrium condition, TOI is by detecting the absorption and reflection of near-infrared light.
- As an open-labeled trial, all participants and some of the investigators are aware of group assignment, their expectation may introduce bias.

Keywords: critical limb ischemia, patient-controlled analgesia, perfusion, analgesia

Introduction

Critical limb ischemia (CLI) presents the end stage of peripheral arterial disease (PAD) [1]. CLI is clinically defined as ischemic rest pain, ulcers and gangrene in the presence of hemodynamic evidence of arterial insufficiency[2]. The mean annual incidence of CLI was 0.35% reported in a national investigation from the United States[3]. The prevalence is approximately 1% of the adult population, and up to 10% of patients with PAD may have CLI. In recent years, a consensus from Peripheral Academic Research Consortium has provided an objective hemodynamic definition for CLI[4]. In this study, this consensus definition will also be used to diagnose CLI.

The major goal of CLI treatment is to relieve ischemic pain, improve limb perfusion, heal wounds and prevent further tissue loss[5]. The Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II) emphasized the importance of the pain management for CLI patients and recommended a multidisciplinary approach to control pain[1]. Pain control is important not only to improve quality of life, but also reduce the possibility of phantom limb pain[6-7]. For patients with PAD, the general principles of perioperative pain management should be individual, continuous and cover the whole perioperative period thoroughly[8]. Over the past years, the patient-controlled analgesia has become the mainstay for providing postoperative pain relief[9]. Accordingly, we considered to establish patient-controlled analgesia preoperatively in our study. Existing studies suggested that intravenous morphine[10] and ultrasound-guided peripheral nerve block provided satisfactory analgesia effect on patients with

CLI[11-14]. However, the analgesia effect of intravenous morphine and ultrasound-guided regional block has not been compared before. Therefore, in this study, we plan to compare the perioperative analgesia effect of patient-controlled regional analgesia (PCRA) and patient-controlled intravenous analgesia (PCIA) for patients diagnosed with CLI.

Additionally, few of the previous studies have studied the effects on reperfusion besides analgesia. A previous prospective study showed that continuous peridural ropivacaine infusion provided satisfactory analgesia, dilated vessels, reconstructed collateral circulation and improved reperfusion remarkably in diabetic patients[15]. Regional analgesia can cause changes in vascular blood flow, but data regards to CLI patients' perioperative experiences is limited. Therefore, in this study, the reperfusion effect of the PCRA and PCIA methods will be further evaluated within participants with CLI. To compare the effect on reperfusion between the two analgesia approaches, we plan to use two different-principle-based measuring parameters, namely, the perioperative transcutaneous oxygen pressure ($TcPO_2$) and the tissue hemoglobin index (TOI). $TcPO_2$ is a transcutaneous, conventional clinical parameter measured heating a skin tissue in the range of 37℃ to 45℃ to reach a stable hyperemia equilibrium condition[16]. NIRS detects the absorption and reflection of near-infrared light and has the potential to provide continuous, real-time measurement of both blood volume and cellular respiration in skin tissue. Other perioperative data regarding the quality of recovery, such as the patients' emotional state, global impression of change, patient satisfaction,

perioperative morphine consumption, length of postoperative hospital stay and adverse events (AEs) will be investigated as well.

Objective

The objectives of this randomized controlled trial are to compare the perioperative analgesia efficacy between PCRA and PCIA for patients with CLI. The perioperative effect on peripheral inflow perfusion, emotion, patient global impression of change (PGIC), patient satisfaction, morphine consumption, length of postoperative hospital stay and AEs of PCRA and PCIA will also be evaluated and compared.

Methods and analysis

Overall design

This trial is a randomized, single-centre, open-label, parallel trial, and will be carried out in Peking Union Medical College Hospital (PUMCH). Institutional research ethics board approval was obtained from PUMCH Institutional Review Board (No. ZS-1289X, 21 March 2017). An overall flow diagram is provided in Fig.1. The timing of interventions and data collection is detailed in Fig 2. This protocol was designed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines[17], the checklist can be found in Appendix 1. The trial will be conducted at PUMCH in accordance with the Good Clinical Practice- International

Conference on Harmonisation (GCP-ICH) guidelines. This trial was registered with the Chinese Clinical Trial Registry (ChiCTR2000029298).

Recruitment

Recruitment for this study will begin on 27 July 2020. Full written informed consents will be obtained from each participant by a qualified member of the research team prior to any trial-related procedures.

Inclusion criteria

Participants who meets the following criteria will be enrolled in this trial:

- 18~80 years of age
- Diagnosed with critical limb ischemia[2 4], admitted in hospital for elective surgery treatment, either open surgical or endovascular revascularization
- The lesions are mainly unilateral and in the supplied area of sciatic nerve
- Stage 6 in Rutherford symptom classification system[18]
- American Society of Anesthesiology (ASA) physical status II~III

Exclusion criteria

Participants who meets the following criteria will be excluded:

- Are taking opioids before admission
- Have known allergy to the drugs will be used in the study

- Have severe liver or kidney dysfunction
- Have contraindication for the catheterization (e.g. infection at injection site, coagulation disorders, refuse or be unable to cooperate the procedure)
- The dorsum of the affected foot is not intact
- Are unable to understand the scales or to describe to the investigators

Dropout criteria

Participants who meets the following criteria will be withdrawn from the study:

- Not willing to continue their participation or cannot follow the initial treatment plan
- From whom none of the primary outcome data can be obtained due to any reason

Randomization, sequence concealment and blinding

All eligible participants will be randomly allocated to either group R or the group I in a ratio of 1:1 using the R software (R Foundation for Statistical Computing). The random allocation sequence will be computer-generated by an independent researcher who has no contact with any participant and will not be involved in the following research. The participants' respective treatment group (group R or group I) will be sealed in an opaque envelope and will only be opened after the enrolment of the participants in the study. An investigator will be responsible for enrolling patients, obtaining consent form and requesting randomization.

This study is an open-label study whereby the participants, the personnel who carry out the intervention and the outcome assessor cannot be blinded because of the nature of the intervention. However, the researchers who are responsible for the statistical analysis will be blinded to the allocation.

Interventions

Analgesia approaches will be established after the baseline assessment (T0) and randomization, normally three to five days before the revascularization treatment. The FORNIA CPE-101 electronic infusion pump will be used as the continuous patient-controlled analgesia device. Relevant concomitant intervention is not involved in this study. Analgesics outside the intervention plan are prohibited during the trial. Remedial analgesia therapy will be carried out according to clinical needs for participants who are dropped out from the trial.

The PCRA group (group R)

Ultrasound-guided continuous subgluteal sciatic block will be applied on the participants enrolled in the group R. Patient will be placed partly lateral and partly prone, with the legs flexed in the hip and knee. Scanning begins in the depression between the greater trochanter of femur and the ischial tuberosity using the 8-3MHz curved probe of the ultrasound equipment (X-porte, SONOSITE, USA). The sciatic nerve can be identified in the cross-sectional view in between of the two bones, below the gluteus muscle. Then rotate the transducer 90° so that the sciatic nerve is imaged in

the longitudinal view. Insert needle in-plane from the cranial to caudal direction and underneath the fasica to enter the subgluteal space, then advance the needle until the tip is adjacent to the nerve. After confirming the needle placement by obtaining a motor response of the calf and foot using the peripheral nerve stimulator, inject 0.2% ropivacaine 15ml for loading dose, then insert the catheter 5cm beyond the needle tip in vicinity of the sciatic nerve. Finally, secure the catheter by tunneling and taping. The infusion strategy includes 0.2% ropivacaine at 8ml/h as background with a patient-controlled bolus of 6ml, lockout time 30min, 1-h limit 20ml.

The PCIA group (group I)

For the participants enrolled in the group I, patient-controlled intravenous analgesia will be connected after intravenous access is established. The infusion strategy is as follow. Intravenous morphine is given in boluses of 1mg as needed, background infusion 1mg/h, with a lockout time of 20min. The 1-h limit is 4mg morphine.

The intraoperative and postoperative patient management

The continuous patient-controlled analgesia will not be suspended during the revascularization treatment despite the type of anaesthesia method. After the revascularization, the device will be paused when patient report it is no longer needed, which usually takes several days. The device will be on standby for an additional 48 hours before removal. In case of inadequate analgesia is provided perioperatively, the infusion strategy dosage may be increased for patients in group I, extra-doses of

intravenous morphine may be used and recorded for patients in group R. Ancillary and post care will not be involved in this study.

Outcomes

Primary outcomes

The primary outcome of this trial is the numerical rating scale (NRS). NRS allows patients to describe the intensity of pain, which is 11-point scale ranging from 0 to 10, with 0 defined as no pain and 10 defined as the worst pain imaginable[19]. The measurement timepoint of the primary outcome will be two hours before revascularization treatment (T1) and two hours before discharge (T2).

Secondary outcomes

The secondary outcomes are as follows:

- The transcutaneous oxygen pressure ($TcPO_2$) at T1 and T2. $TcPO_2$ will be obtained with PeriFlux System 5000 (PERIMED, Sweden) transcutaneously using the $TcPO_2$ unit-PF 5040. Calibration will be completed before use. When measuring, patients will be in sitting position. The electrode of the PF 5040 will be placed on the dorsum of the affected foot, away from any skin lesion. Wait 10~15min for a stable reading.
- The tissue hemoglobin index (TOI) at T1 and T2. TOI will be obtained with the EGOS-600A near infrared spectroscopy (NIRS, ENGINMED, China). The transducer of NIRS will be placed at the same spot as PF5040 on a sitting position,

after the completion of $TcPO_2$ measurement. Wait 30 sec for each interval to gain five readings. The values at each time point will be calculated as the mean of five consecutive values over 2min.

- Hospital Anxiety and Depression Scale (HADS) at T1 and T2. HADS is a self-rating patient-reported outcome measure developed to assess depression and anxiety of patients with illness. The 24-item questionnaire is divided into two subscales: anxiety (HADS-A) and depression (HADS-D). The ratings are summed to yield a total score (0 to 42), or for each subscale (0 to 21) with special attention[20].
- Patient Global Impression of Change (PGIC) at T1 and T2. PGIC is a 7-point verbal scale commonly used to assess patient's perception of pain relief following treatment, which has been proved its significant relevance and correlations for peripheral neuropathic pain in daily practice[21].
- Patient satisfaction at T1 and T2. This item 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.
- Cumulative morphine consumption perioperatively, the sum will be calculated before discharge.
- Length of postoperative hospital stay.
- AEs, such as hematoma, catheter displacement, nausea, vomiting, drowsiness, dizziness, urinary retention, pruritus, local anaesthesia intoxication, fall, etc. The

occurrence time, nature, duration and severity of AEs will all be collected in detail.

Trial safety

The establishment, configuration and dispensing of the patient-controlled analgesia devices will be completed by a dependable anesthesiologist. The continuous ultrasound-guided subgluteal sciatic block will be performed in an operating room, only after intravenous access and standard monitoring is established for the patient. Investigators will follow up the patient at least twice a day during the research. Motor block will be assessed everyday using Bromage motor blockage score[22] in group R to prevent falling. All the reported AEs and other unintended effects of trial conduct will be collected, assessed, reported and managed according to the GCP-ICH guidelines. Any severe AE happens perioperatively will be reported to the adverse event registration system of the hospital.

Patient and public involvement

Patients and public were not involved in the development of the research question or in the design of the study. Patients will receive oral and written information about this trial. However, they will not be involved in the recruitment and conduct of the study. The burden of the intervention will be assessed by patients themselves. On completion of the study, dissemination of the general study results or the anonymized individual patient data will be made on demand.

Sample size

The primary outcome of this trial is the NRS score after analgesia. Sample size was calculated based on our pilot study which had included ten patients in total (five for each group). The result of the pilot study showed that the NRS scores in group R and group I was1.63 and 3.31, and the standard deviation was 1.85 and 2.12 respectively. We used the statistical power of 80% and two-sided α of 0.05. The target sample size for each group is at least 22 participants. Taking into account a dropout rate of 20%, a sample size of 52 (26 for each group) was finally determined.

Data collection, monitoring and confidentiality

Each patient's ID and demographic information (including age, gender, height, weight) will be collected. We will document all the AEs related to PCRA or PCIA, including hematoma, catheter displacement, local anaesthesia intoxication, nausea, dizziness, urinary retention, pruritus, fall, etc. All the calibration and measurements of $TcPO_2$ and TOI will be performed and recorded by one special technician using the same apparatuses. 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. Collected data will be recorded on paper case report forms (CRFs), then entered into electronic case report forms (eCRFs) and

uploaded to a central server. The CRFs and eCRFs will be kept for at least five years after publication in case of any inquiry. A qualified clinical trial expert will be invited in the middle and at the end of the investigation to ensure that the protocol and GCP-ICH are being followed. No interim analysis will be performed during the study. There is no planned auditing for the study. Personal information about the enrolled participants will be safely and confidentially kept. After completion of the study, the eCRFs and all the data collected will be stored anonymously in the password-protected central server and restricted to relevant members of the research team. Paper copies of the CRFs will be stored in a locked cabinet in the relevant research office.

Statistical analyses

Continuous variables will firstly be checked for normality using the visual inspection of the histogram. Normally distributed continuous variables will be expressed as the mean ± SD, and non-normally distributed continuous variables will be expressed as the median and interquartile range (IQR). The categorical variables will be summarized as frequencies and percentages. Variables such as anaesthesia method and surgery type will be checked in the description of baseline characteristics, unbalanced variables will be adjusted using a multivariable method. The primary outcome, difference of NRS between groups, which is generally normally distributed from experience, will be analyzed using student's *t* test, and the mean difference with corresponding one-sided 95% confidence interval (CI) will be calculated. For the secondary outcomes including

$TcPO_2$, TOI, HADs and PGIC, student's *t* test will be used to compare the group difference. Data with a skewed distribution, such as cumulative morphine consumption and length of postoperative hospital stay, will be analyzed using the Mann-Whitney U test. As categorical variables, AEs will be compared using chi-squared test. A post-hoc subgroup analysis by the type of revascularization treatment (whether endovascular or open surgical) will be conducted. The main analysis will be performed after the study has been completed. Data analysis will be performed according to the intention to treat principle. The results of this study will be reported according to the Consolidated Standards of Reporting Trials (CONSORT) statement[23]. Statistical analyses will be conducted using SPSS 19.0 (Version 22; SPSS Inc., Chicago, IL, USA). A two-sided $p<0.05$ is considered significant.

Ethics and dissemination

Ethics approval and consent to participate

This research project was approved by the Peking Union Medical College Hospital Institutional Review Board (ZS-1289X) on 21 March 2017. Important protocol amendments will be communicated with relevant parties (eg, investigators, IRB, trial participants, trial registries, journals) by Dr. Yuehong Zheng, trial principal investigator, as soon as changes are made. Written informed consent (details see Appendix 2) will be obtained from all participants.

Trial Organization

Steering Committee

The Steering Committee carries the ultimate responsibility for the trial and has access to the final dataset. Specific tasks of the Steering Committee are: final approval of the study protocol, approval of the amendments to the study protocol, approval of manuscripts and publications of the trial. The Steering Committee is chaired by Yuehong Zheng, vascular surgery surgeon. Other members include Si Chen, anaesthesiologist and Yuelun Zhang, statistician.

Data and Safety Monitoring Committee (DSMC)

The DSMC is established to assess the progress of the study, the safety of data and the critical efficacy end points independently from the sponsor and competing interests. Wellbeing of the participants will be monitored by the DSMC, who makes decision on the suspension or termination of the trial to protect the participants under circumstances of severe or unexpected AEs. The DSMC is chaired by Yuguang Huang, Anaesthesiologist. Other members include Hongju Liu, anaesthesiologist and Yuexin Chen, vascular surgery surgeon.

Trial status and time scale

The study was funded and ethically approved in 2017. A pilot study was conducted subsequently. We had finished the pilot study by 8 July 2018, then the study was

delayed because of the maternity leave of Si Chen until January 2020. The trial was registered on 22 January 2020 and will begin to recruit participants on 27 July 2020.

Dissemination plan

The result of this study will be presented in national and international meetings and will be submitted for publication to relevant vascular surgery, analgesia or anaesthesia peer-reviewed journals. Authorship eligibility will follow the Good Publication Practice (GPP) guideline 3.

Discussion

The purpose of this study is to compare the analgesia effect of PCRA and PCIA. The effects on reperfusion and quality of recovery are meanwhile investigated in patients diagnosed with CLI.

In this study, a low concentration ropivacaine of 0.2% will be used for patients in group R, and a low to median dosage of intravenous morphine will be used for patients of group I. Morphine is a strong opioid which is well known for its supreme analgesia and adverse effects such as nausea, vomiting, drowsiness, itching etc. Ropivacaine is a long-acting regional anesthetic that blocks nerve fibers involved in pain transmission to a greater degree than those controlling motor functions[24].

Regional analgesia can cause changes in vascular blood flow, but data regards to CLI patients' perioperative experiences is limited. In this study, we plan to perform two

different measuring methods to observe the effects on reperfusion of PCRA and PCIA. In previous researches, the parameter TOI was also known as the region tissue oxygenation saturation (rSO_2). A recent study has revealed a significant correlation between $TcPO_2$ and rSO_2 measured by NIRS to evaluate limb ischemia in patients with peripheral arterial disease[25]. We expect the outcomes of this study provide clinical evidence for the efficacy of the two different analgesia approaches perioperatively.

We also hope this study offers a reference for the non-surgical patients. Although revascularization has been the most effective treatment for patients with CLI, some patients' arteries are impossible to revascularize and require other treatments such as drugs[26], transcutaneous electrical stimulation[27], peripheral blood mononuclear cells therapy[28] or lumbar sympathectomy[29] to relieve pain and/or increase peripheral perfusion to avoid amputation. For those patients with non-reconstructable arteries, long-term PCRA may be less invasive and adequate for both analgesia and perfusion. There are evidences showing that it is safe to discharge patient home with catheter[30]. In addition, it has been previously reported that continuous sciatic nerve block could be used at home for long-term pain control[31]. We expect this perioperative study can also be a future reference for those who lost their opportunity for revascularization to improve their quality of life.

Abbreviations

PAD, peripheral artery disease; CLI, critical limb ischemia; PCRA, patient-controlled regional analgesia; PCIA, patient-controlled intravenous analgesia; $TcPO_2$, transcutaneous oxygen pressure; TOI, tissue hemoglobin index; AE, adverse events; PUMCH, Peking Union Medical College Hospital; SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials; GCPs, Good Clinical Practice; ICH, International Conference on Harmonisation; ASA, American Society of Anesthesiology; NIRS, near infrared spectroscopy; NRS, numerical rating scale; HAD, Hospital Anxiety and Depression Scale; PGIC, Patient Global Impression of Change; VAS, visual analogue scale; CRFs, case report forms, CONSORT, Consolidated Standards of Reporting Trials; rSO_2, region tissue oxygenation saturation; DSMC, Data and Safety Monitoring Committee; GPP, Good Publication Practice.

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and management; data collection, analysis and interpretation; report writing; or publication.

Authors' contributions

SC and ZHX are joint first authors. SC obtained funding and the ethical approval, registered and drafted the manuscript. ZHX and YHZ conceived the study and participated in the design of the study. YGH, HJL and YXC participated in the study coordination. YLZ contributed to the statistical analysis plan. JZ acquired and analyzed the data of the work. YHZ is the corresponding author. He critically edited the manuscript. All authors read and approved the final manuscript and agreed the submission.

Competing interests

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: no financial relationships with any organization that might have an interest in the submitted work in the previous three years, no other relationships of activities that could appear to have influenced the submitted work. There is no conflict of interests.

Data sharing

No additional data are available.

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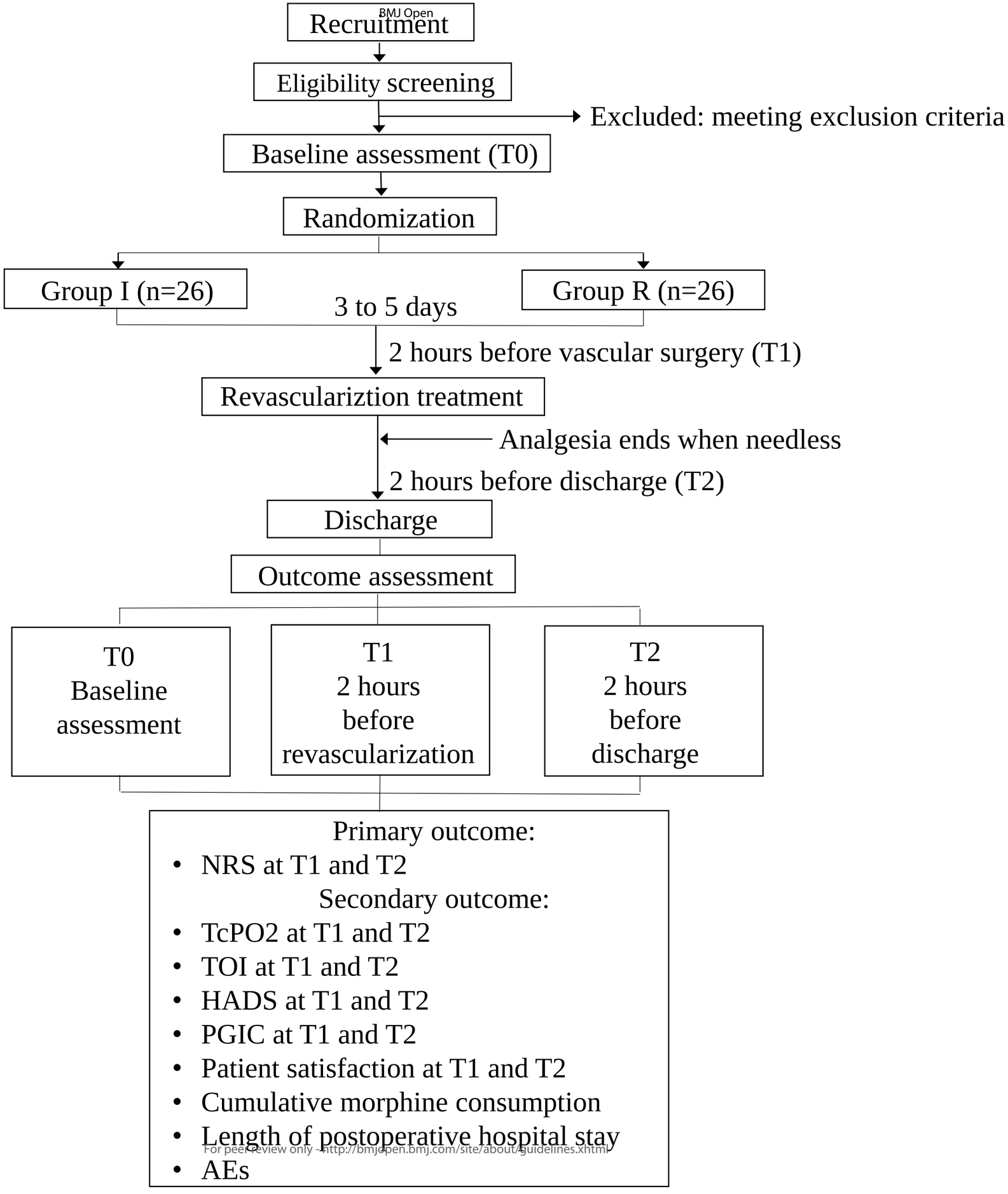
Figure Legends

Fig 1. Study process diagram

Fig 2. Schedule of the enrollment, interventions and assessments



	STUDY PERIOD				
	Enrolment	Allocation	Post-allocation		Close-out
TIMEPOINT		T0	T1		T2
ENROLMENT:					
Eligibility screen	×				
Informed consent	×				
Randomization		×			
INTERVENTIONS:					
Group I		←	—	→	
Group R		←	—	→	
ASSESSMENTS:					
Demographic data	×				
NRS		×	×		×
TcPO2		×	×		×
TOI		×	×		×
HADS		×	×		×
PGIC			×		×
Patient satisfaction			×		×
Cumulative morphine consumption					×
Length of postoperative hospital stay					×
Adverse events					×

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	3, 8
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	#3	Date and version identifier	3
Funding	#4	Sources and types of financial, material, and other support	21
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 22

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	21
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	21
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	21
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5, 6, 7
Objectives	#7	Specific objectives or hypotheses	7
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	7, 8
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will	7, 8

		be collected. Reference to where list of study sites can be obtained	
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8, 9
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	10, 11
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	10
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12, 13
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	12, Fig1, Fig2
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	15

Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9, 10
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9, 10
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9, 10
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9, 10
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found,	15, 16

		if not in the protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	15
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15, 16
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16,17
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	17
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9, 17
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	18
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	16
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial	14, 18

		conduct	
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	16
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	17
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	17
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8, 9, 17
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15, 16
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	12
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication,	19

		reporting in results databases, or other data sharing arrangements), including any publication restrictions	
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	19
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	17, Appendix 2
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

受试者知情同意书

研究项目名称：不同镇痛方式用于重症下肢缺血患者的围术期作用效果研究
研究负责人：陈思
联系电话：13466364034
研究单位：中国医学科学院北京协和医院

1. 研究背景、目的：重症下肢缺血以静息痛、溃疡、坏疽为主要特征。疼痛刺激不仅降低患者的生活质量，还可诱发心脑血管事件、进一步加重神经病理性改变。良好的疼痛管理可帮助患者减轻临床症状、延缓病情发展、改善生活质量、延长生存周期。本研究目的在于比较病人自控周围神经连续阻滞技术（方法 1）与病人自控静脉镇痛技术（方法 2）在患者围术期的镇痛效果以及其对下肢血流灌注的改善作用。其中，方法 1 属疼痛介入治疗，通过坐骨神经周围置管完成，优势在于能够扩张下肢血管、减少患者阿片类药物使用量、镇痛效果明确；不足在于属有创操作，导管置于体内，有渗漏、移位、感染等风险。方法 2 通过静脉持续使用阿片类药物完成，优势在于镇痛效果明确，不足在于有嗜睡、头晕、恶心、呕吐、瘙痒、阿片类药物过量、耐受等风险。本研究于 2017 年 3 月 21 日通过北京协和医院伦理委员会审查（编号 ZS-1289X）。
2. 受试者纳入标准：
   a) 18~80 岁；
   b) 诊断为重症下肢缺血，入院行血管开通治疗；
   c) 单侧为主，疼痛部位主要在坐骨神经支配区域；
   d) Rutherford 症状分级 6 级；
   e) ASA（美国麻醉医师协会）分级 II~III 级。

   受试者排除标准：
   a) 入院前使用阿片类药物止痛；
   b) 对研究中可能使用的药物有明确的过敏史；
   c) 严重肝肾功能不全；
   d) 神经周围置管禁忌（如穿刺部位感染、凝血功能异常、无法配合体位或拒绝穿刺）；
   e) 患侧足背皮肤不完整；
   f) 无法理解调查量表或无法表述自己的感受。
3. 研究内容、方法及程序：入院后将随机为患者选取一种镇痛方式，在镇痛前后分别进行以下内容：
   a) 常规疼痛诊疗：治疗疼痛、协助医生评估镇痛效果；
   b) 研究所附加的诊疗项目：填写调查问卷、测量皮肤温度及患肢血流速度（无创伤）。
4. 参加研究的可能风险（或不适、不便）和收益（个人或社会群体受益）：
   a) 可能风险（或不适、不便）：携带病人自控镇痛装置可能存在轻微不便，
   b) 收益：获得更为确切、舒适的疼痛诊疗体验和更密切的镇痛随访，对于未来此类患者的治疗选择将更加有益。
5. 有关内容的咨询：您有权就有关研究内容进行咨询，咨询电话（主要研究者）：010-69152020 或 13466364034，电子邮箱：yuehongzheng@yahoo.com；您有权就有关您的权利或相关风险等问题进行咨询，咨询电话（伦理审查委员会电话）：010-69154494，电子邮箱：pumchkyc@126.com。
6. 退出研究的权利：您参加此项研究是完全自愿的。无需任何原因，您不愿意参加或不愿

继续参加此研究，并不会对您的权益有任何影响。此外，您有权在任何时间退出此研究。（如果您没有按医生指示，或医生为您的健康和益处着想，医生或研究者也可能要求您退出。）

7. 研究的费用及赔偿问题：常规疼痛诊疗产生的费用由您及患者自行缴纳的医疗保险承担及赔付；研究所附加的诊疗项目产生的费用由课题组经费承担，如果您由于参加此研究所附加的项目而使健康受到损害，将由北京协和医院麻醉科及血管外科负责提供补偿费用。

8. 保密制度：您参加此研究所获得的医疗信息将得到保密。研究结果在学术刊物上发表时也不会泄露任何可识别您个人身份的信息。北京协和医院将保存您在这项研究中的全部记录以及有关的医院和办公室记录，未经授权任何人不得获取这些信息。

9. 本知情同意书一式两份，受试者和研究者各一份，双方签字后有效。

受试者的知情同意：

我已详细阅读并充分了解以上内容，并对以上内容，特别是我参与此研究的权利、风险和受益进行了认真考虑。我自愿参加这项研究，愿意与研究人员合作。同时声明我可以在任何时候因任何原因退出此研究，而不会丧失任何合法权利。

受试者姓名：_____受试者签字：_____日期：_____年_____月_____日

研究者姓名：_____研究者签字：_____日期：_____年_____月_____日