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The Effects of Pericapsular nerve group (PENG) block on Postoperative Recovery in Elderly Patients with Hip fracture: a study protocol for randomized, parallel controlled, double-blind trial

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ABSTRACT

Introduction Hip fracture is a common and serious emergency in the elderly, it is associated with severe pain, significant postoperative morbidity and mortality. Featuring peripheral nerve block in Enhanced recovery after surgery (ERAS) pathway may have significantly effect on shortening length of hospital stay, decreasing complications and costs ,particular in improvement in dynamic pain and reducing the use of opioid . Pericapsular Nerve Group Block(PENG), suggested by Arango *et al*, may provide a effective blockade to the articular branches of the anterior hip joint,which innervate the most section of the hip capsule richly, with a potential motor-sparing effect.The purpose of this trail is to investigate whether PENG is effective to enhanced recovery in elderly patients with hip fracture.

Methods and analysis This study will be a single centre,randomized, parallel controlled, double-blind trail. 92 elderly patients scheduled for hip fracture surgery will be divided into two groups randomly to receive ultrasound-guided PENG block or ultrasound-guided femoral nerve(FN) block. The primary outcome will be compare the quality of recovery-15(QoR-15) score at 24h postoperatively between two groups.The secondary outcomes include the strength of quadriceps, the visual analogue scale(VAS) at rest and on movement, the total morphine consumption, the rescue analgesic, the first time of postoperative out-of-bed mobilization, the complications.

Ethics and dissemination This study has been approved by the Medical Science Research Ethics Committees of The First Affiliated Hospital of Guangzhou University of Chinese Medicine on 15 December 2020 (Reference K2020-110) . The results of this study will be published in peer-reviewed international journals.

Trial registration number ChiCTR2100042341.

Key words Quality of recovery; hip fracture; Pericapsular nerve group; elderly patients

Strengths and limitations of this study

- A major strength of this study is that to our knowledge, this is the first pragmatic, parallel group,randomized controlled, double-blind trial to investigate the effect of PENG block on pain control and recovery in elderly patients with hip fracture.

- Our findings may provide an new peripheral nerve analgesia for the elderly patients with hip fracture,which could relieve pain without motor dysfunction during rehabilitation, to accelerate recovery.
- The limitation of this study is that there isn't any optimal biomarker about the postoperative recovery. The patient-rated QoR-15 scale could be influence by delirium, which is a common complication in elderly with hip fracture, so we perform MMSE before QoR-15 at 24h postoperatively and compare with the preoperative result of MMSE to ensure the reliability of QoR-15.
- There is no gold standard for the pain assessment, and we choose both VAS and the morphine consumption to promote the reliability and validity of the results.

INTRODUCTION

The number of hip fractures in elder people is increasing steadily. In China, a study calculates, the annual incidence was 99.15 men and 177.13 women per 100,000 in 2016.[1] And in United States, the rates of age-adjusted hip fracture for 2015 were higher than projected, resulting in an estimated increase of more than 11,000.[2] The highest overall incidence is between 71 and 85 years old.[3]

The pain of hip fracture is serious, and VAS is more than 4 of 10 points,[4] which is moderate to severe pain. It is seriously increase length of hospital stay and postoperative mortality.[5] Early surgery is the definite treatment in most patients. It could control the pain, quicken the rehabilitation and decrease complications potentially.[6] However the elderly often suffer from compromised organ reserve capacity, poor perioperative health status and varying systemic diseases. So, with the high postoperative morbidity and mortality,[7] the safety of aging patients in perioperative period is full of challenges .

ERAS is a multimodal , multidisciplinary approach to the surgical patient in the perioperative period. There is good and increasing evidence that implementation of ERAS pathways can shorten length of hospital stay ,decrease complications and costs for the patients undergoing hip surgery.[8-10] And this multimodal pathway featuring peripheral nerve block may have significantly effect on fewer complications and perioperative outcomes after major orthopedic surgery. Comparing with tradional intravenous opioids during the initial postoperative period, peripheral nerve block can improve the dynamic pain control, quicken rehabilitation and reduce the use of opioids and the related adverse effects.[11-13]

With the development of the ultrasound guidance,peripheral nerve block is used frequently nowadays. Ultrasound guided femoral nerve(FN) block, fascia iliac block (FIB)and 3-in-1 FN block are popular peripheral nerve block techniques for hip fracture. However, as the obturator nerve(ON) and the accessory obturator nerve(AON) have often failed to exhibit adequate blockade from these blocks,the effect size is only moderate with decrease in the strength of quadriceps muscle.[14-16]

In order to improve the analgesia effect, according to the recent anatomical study by Short *et al*[17]about the identification of relevant landmarks to the innervation of the anterior hip capsule,Arango *et al*[18] created a new regional technique for hip fractures: ultrasound-guided pericapsular nerve group (PENG)block. They concluded this technique could provide a effective blockade to the article branch of FN, ON and AON with a potential motor-sparing effect.

However, the case series of PENG block is small. And, without appropriate control groups, the outcomes have been limited. It is still unclear that whether PENG block is effect on the pain relief and rehabilitation in elderly patients with hip fractures within a standard care program. Therefore, a randomized, parallel controlled, double-blind trial will be set up, comparing the QoR-15 score at 24h postoperatively between two groups, to investigate whether PENG is effective to the enhanced recovery in elderly patients with hip fracture.

METHODS AND ANALYSIS

Primary aims

The primary aim of this trail is to investigate whether PENG is effective to the enhanced recovery in elderly patients with hip fracture.

Secondary aims

The secondary aims are to investigate if PENG results in a motor-sparing effect,a reduction in the pain score at rest and on movement,a decrease in total morphine consumption and the rescue analgesic,an improvement in the first time of postoperative out-of-bed mobilization,and a decrease in complications .

Trail design

This is a pragmatic, parallel group,randomized controlled, double-blind trial.The study will be carried out at The First Affiliated Hospital of Guangzhou University of Chinese Medicine and has been registered with the Chinese Clinical Trial Registry (ChiCTR2100042341).The flow diagram for this trial is presented in Figure 1.

Eligibility criteria

Recruitment

Elderly patients (aged over 65 years old) with hip fracture who are selected for the hip surgery at The First Affiliated Hospital of Guangzhou University of Chinese Medicine will be recruited for this study.

Inclusion criteria

Patients will be included if they are cognitively intact, the American Society of Anesthesiologists physical status (ASA) I-Ⅲ and the body mass index(BMI) 18-30kg/m2.

Exclusion criteria

Patients will be excluded if they refuse to participate in the study,are allergies to analgesic drugs used in this study, dementia, multipal trauma, severe deafness and vision problems, communication difficulties, have an infection near the block site, are obesity (BMI>30kg/m2), have a significant clinically neurological,cardiovascular, renal and hepatic diseases(ASA Ⅳ-Ⅴ).

Informed consent

According the inclusion criteria and the exclusion criteria, patients will be assessed strictly by the dedicated researchers the day before the surgery. Once patients is eligible, the researchers will give the full explanations to the eligible patients and their families about this study (including the implications, the known adverse effects, any risks participated in taking part and constraints of the protocol), and answer the questions about this study which the participants are interested in, to make sure they are clear about the significance of this study and eliminate their doubts. If patients agree to enrol, the informed consent will be obtained. The participants and their proxies will be asked to give written informed consent and sign personally. Of course, the participants can choose to withdraw from the trial freely without any reasons, and we will ask the permission about the used of the data for the statistical analysis.

Preoperative management

In accordance with the national guideline,6 patients in both groups will be received a standard care to accelerate recovery. The pathway includes rapid assessment from the Emergency Department, adequate pain control, assessment of bone health and falls, multidisciplinary management, surgical procedures and mobilization strategies. The ASA status classification will be evaluated and preoperative cognitive assessment will be performed by using the Mini-Mental State Examination (MMSE).[19] The opioid will be avoided to use except for severe pain. Patients who participate in this study will avoid the use of premedication.

Intraoperative management

After entering the operating room, continuous electrocardiogram, noninvasive intermittent blood pressure and pulse oxygen saturation will be monitored. After an intravenous is performed with an 18-gauge vein needle, lactated ringer solution will be dripped. The patients will be given 4 L / min of oxygen through the mask. In order to reduce the pain and fear during the nerve blockade, 0.5 ug/ kg of fentanyl will be given intravenously. The blockade of Both groups will be performed by the same experienced anesthesiologist. Before the local anesthesia, the anesthesiologist will open the envelops to get the sequence and perform the blockade according the allocation information. The anesthesia for the surgery will be performed after the block and managed by another anesthesiologists.In accordance with the assessment of patients, the anesthetic mode will be at the discretion of the anesthesiologist.

Ultrasound guided pericapular nerve group block

With the participants are in a supine position, PENG block is performing as described by Arango *et al.*[18] The anterior inferior iliac spine, the femoral artery(FA), the pectineus muscle, the iliopubic eminence, the iliopsoas muscle and tendon could be observed using a curvilinear low-frequency ultrasound probe. The puncture site will be set 0.5-1.0 cm away from the lateral of the ultrasound probe. After 2 ml of 1% lidocaine is injected for the local anesthesia, a 22-gauge, 80-mm needle will be inserted carefully in an in-plane approach from lateral to inner. Following the tip of the needle reaches the musculofascial between the tendon of the psoas muscle anteriorly and the pubic ramus posteriorly , a total volume 20mL of 0.375%

ropivacaine will be slowly injected after negative aspiration every 5-mL.The ultrasound view of the fluid spread in the plane will be observed to ensure that the ropivacaine is injected right in the targeted location.

Ultrasound guided femoral nerve block

With the patients are in a supine position, FN block is performed as described by Marhofer *et al.* [20] A linear high-frequency probe will be used to visualize the FA and the FN. The puncture site will be set 0.5-1.0 cm away from the lateral of the ultrasound probe. After 2 ml of 1% lidocaine is injected for the local anesthesia, a 22-gauge, 80-mm needle will be inserted carefully in an in-plane approach from lateral to inner. Following the tip of the needle is close to the FN, a total volume 20mL of 0.375% ropivacaine will be slowly injected after negative aspiration every 5-mL. The ultrasound view of the fluid spread will be observed to ensure that the ropivacaine is injected around the FN.

Postoperative management and follow-up

After surgery , when participants are transferred to the ward, vital signs (heart rate, noninvasive blood pressure, SpO 2 and respiratory rate) will be monitored. In 48h postoperatively, a PCIA with morphine will be begun at the end of the operation and set to the bolus only mode(bolus 1.0 mg,lockout 6 minutes,maximal does 15mg/4 hours). All participants will receive 1 g paracetamol 6 hourly as a part of postoperative multimodal analgesia. In case of nausea and vomiting, 5mg of tropisetron injection will be intravenous.

Outcome measure

Before a series of clinical-scale evaluations and analgesia will be evaluated and recorded by the estimator, who is blinded to the group assignments, patients will be tested with the MMSE on the first and second postoperative days.

The primary outcome measurement of this study is the QoR-15 scale at 24h postoperatively. There are 15 items in the questionnaire about the quality of recovery. By being answered on an 11-point numerical rating scale, the score of each item ranges from 0 to 10. The full total scores of the QoR-15 are 150. The mean value and standard deviation will be used for descriptive analysis.

The secondary outcome are the strength of quadriceps , the VAS of the resting and the dynamic pain, the total morphine consumption, the rescue analgesic, the first time of postoperative out-of-bed mobilization, and complications. Patients will be asked to raise a straight leg of the affected limb to 15 degrees before and 3o minutes after the blockade to confirm if the quadriceps weakness is displayed. At the time before and 30 min after the block performance, 6h, 12h, 18h, 24h and 48h postoperatively, the pain scores at rest and on movement will be assessed respectively. After the patient have been resting in bed for 15 min, VAS at rest will be assessed. When VAS on movement is assessed, participants will be asked to flex hip. Being used an 11-point numerical rating scale, the VAS ranges from 0=no pain to 10=unbearable pain. The total morphine consumption in PCIA and the time of the bolus will be recorded. If the participants doesn't feel pain relief after injection of morphine from the PCIA, the participants will receive rescue anesthetic as required by the assessment, the time

and the dosage of analgesics in the first 48h will be recorded. A physiotherapist will evaluate the ability of the patients postoperatively, and record the first time patients get out of bed and do physiotherapy exercises. Postoperative complications, such as pneumonia, deep vein thrombosis, myocardial infarction, cerebrovascular accident and so on, will be recorded and treated. The complications of PENG, such as the nerve damage, the local anesthetic toxicity and the vascular puncture, will be recorded. A diagram of participant recruitment and secondary outcomes measurement is shown in Table 1.

Randomization and blinding

At the beginning of this study, a randomization sequence will be generated by SAS 9.0 statistical software and assign the participants to either the control group (the ultrasound-guided FN block group) or the intervention group(the ultrasound-guided PENG block group) on the basis of a 1:1 ratio. An independent statistician conceal the sequence (including allocation group, random numbers and intervention information) from the researcher, who assess the subjects, in the same look, opaque and sealed envelopes.

The effect of the block will be evaluated and recorded by the investigator who do not participate in the block performance. Neither the investigator nor the patients know about the grouping, and it will not be relieved until the end of the study.

Sample size estimation

Based on the results of our preliminary experiments, the QoR-15 scores (mean difference ± SD) of elderly patients for 24h were 98.97 ± 10.37 in the PENG group and 88.25 ± 8.32 in the FN block group. Myles *et al*[21] found that the minimal clinically important difference for QoR-15 scale is 8.0. Therefore, to detect the effect size (power = 0.8) with the type 1 error of 5% (α=0.05) , a dropout rate of 10% and a non-inferiority or superiority margin of 8, a sample size of 92 participants is required. As the result, 46 participants in each group are recruited in this study.

Reporting of adverse events

In the period of the study, the participants will be seen daily. All adverse events and other unintended effects of trial will be recorded. If any serious complications happen, researchers will be informed immediately, take measure based on symptom and make discussion with any treating medical practitioners about the seriousness and reason, the sequence will be revealed and researchers will evaluated the relations between the serious complications and the PENG block. All details of serious adverse events will be written down and reported to the ethics committee.

Ethics and declarations

The trial received ethical approval from The First Affiliated Hospital of Guangzhou University of Chinese Medicine Research Ethics Committee on 15 December 2020 (Reference K2020-110). This study has been registered at the Chinese Clinical Trial Registry (ChiCTR2100042341). The trial will be conducted in accordance with the Declaration of Helsinki 1996, principles of good clinical practice, and the Department of Health Research Governance Frame-work for Health and Social Care. The researchers will send reports about

the progress regularly and any changes of this trial to The First Affiliated Hospital of Guangzhou University of Chinese Medicine Research Ethics Committee.

Data management and monitoring

Demographic data and mental assessment data, QoR-15 data and information on pain scores, mobilization assessment data and complications will be collected and input into an electronic database. An independent researcher will guarantee the data quality during the process. All data of outcomes will be input into another independent data and double-checked to promote the data quality. The individual privacy information will be deleted to protect confidentiality. After data storage, only researchers can access to the final trial dataset directly. The progress and safety of this study will be monitored monthly by the data monitoring committee (DMC), which composed of two independent experts outside the study. The clinical experts can access the unblinded data. The data monitoring committee (DMC) can give suggestions about the safety, and even make the final decision to terminate the trial. The final trial data set will be managed by The First Affiliated Hospital of Guangzhou University of Chinese Medicine. Accessing to the data set needs to write requests to get the permission of the DMC, The First Affiliated Hospital of Guangzhou University of Chinese Medicine and all trial researchers.

Statistics analysis

All allocated subjects with available data will be analysed. According the variable type and distribution, data will be presented as mean and SD, frequency and proportion or median and IQR (25th-75th percentile). Base on the x2 test or Fisher's exact test, categorical variables will be evaluated. The parametric t-test, the Wilcoxon rank-sum test or the Kruskal-Wallis test will be used to analyse differences between two groups in continuous variables. And non-normal distributions will be assessed with the Mann-Whitney U test. To manage the missing data, mean completer and regression will be used. A p value of <0.05 will be considered statistically significant and results will be presented with 95% CIs. Analysis of date will be performed with the SPSS software V.21.0 (developed by IBM Corp, Armonk, New York, USA).

Discussion

Hip fracture is often associated with serious pain. Lack of sufficient pain treatment leads to not only the deceleration of the recovery after surgery, but also the high risk of cardiovascular adverse events and long-term chronic pain. So for rehabilitation, an adequate pain treatment should be carry into effect in the perioperative period.

Opioid use could be appropriate for the requirement of pain relief after surgery. So it is still the mainstay of potent analgesia to hip fracture worldwide in the past 20 years.[22-24] Amalie H. Simoni *et al*[25] pointed out about 26.8% of patients redeemed one or more opioid prescription before surgery and 61.8% received opioid therapy postoperatively. But, unfortunately, the opioid-relatied adverse events are more common to be found in elderly. It occurs in 80 percents of patients. These adverse events, including cognitive impairment, increase of fall risk and mortality, are delay rehabilitation after surgery seriously. And opioids just offer a good pain relief at rest, but are helpless in pain on movement.

Therefore, to reduce the related adverse events and improve patients' experience, neuraxial techniques have been recommended. Consistent evidence was found to suggest that

regional analgesia techniques can reduce the pain with providing the reasonable, rapid-onset and site-specific analgesia, which is more effective than traditional systemic analgesia. In addition, there is evidence that peripheral nerve block may decrease the incidence of delirium, shorten the hospital stay, reduce morbidity and mortality.[26] Follow the development of the ultrasound guidance, the success rate of peripheral nerve block is improved.[27] So nerve block may have an excellent effect on fast-track recovery.

Nowadays the FN block, FIB and 3-in-1 FN block are popular peripheral nerve block techniques. Unfortunately, none of these nerve block techniques are ideal to hip fracture at present. According many anatomical studies suggested, the articular branches of FN,ON and AON innervate the anterior hip joint, which plays a great role in the innervation of hip capsule.[17 28 29] So they should be the main goal in the regional analgesia. The three main nerves can be anesthetized by 3-in-1 FN block and FIB. However the rates of the obturator block with 3-in-1 FN block are 77-80%, while the rates with FIB are 88%.[30] Both of FIB and 3-in-1 FN block may result in failed to anesthetize ON, and the FN block also can not anesthetize ON. In addition, these three nerve block techniques may produce quadriceps weakness, which could slow mobilization and increase the incidence of falls. Therefore a new regional analgesia ,which can provide a complete analgesia without significant motor dysfunction, should be put forward.

The PENG block, developed by Arango *et al*[18], gives a new idea of peripheral nerve block for patients with hip fracture. With performing the PENG block in 5 patients, they found Numeric Rating Scale (NRS) for rest pain in 4 cases decreased from 4 points or above to 0 point, the reduction of NRS for dynamic pain in 5cases was more than 4 points, and the median reduction of pain was 7 points. Over 100 PENG blocks have been performed by Yu *et al*[31] for hip fracture and surgery, and these blocks were effective highly. Ince *et al* [32] combined PENG and lumbar erector spinae plane to provide postoperative pain treatment in a 4-year-old child undergone surgery for congenital hip dyplasia, and the FLACC score in 24 hours was less than 1 point without any need for additional analgesics.

These case series and letters give the evidence about the effectiveness of PENG for hip surgery. What impressed us most is this approach provides significant dynamic pain control with a motor-sparing effect. This may give a high quality to the early mobilization as expected. So PENG seems to meet the condition for a ideal peripheral nerve block to geriatric patients with hip fracture.

To test whether PENG is effective to enhanced recovery in elderly patients with hip fracture, a variety of measurement tool should be chosen. At present, there are many clinical observational index to evaluate the effectiveness and safety of anesthesia in postoperative recovery, but most of them are focused on the physiological endpoints, such as the incidence of complications, the length of hospital stay, the mortality and so on. Though these indexes are objective and important to be measured, the evaluations from patients' view are more humanized and also important to be assessed. So a patient-rated QoR-15 was set out by Peter *et al* [33]. It includes five dimensions: pain,physical comfort, physical independence, psychological support and emotional state. The score was demonstrated with the well reliability, validity, clinical acceptability, feasibility and responsiveness, and is able to differentiate between the known factors of recovery after surgery, including ambulatory

surgery. Peter *et al*[33] suggested there was no relation between the QoR-15 and patient age, which indicates QoR-15 could be used in aged patients. And now it has been one of common used measure in orthopedic surgery. So in this study, we choose QoR-15 as the instrument of ERAS.

Conclusion

In conclusion,to our knowledge, this is the first study using a randomized, parallel controlled, double-blind trial to compare the QoR-15 scores between ultrasound-guided FN block and ultrasound-guided PENG block, and to explore the effectiveness and safety of PENG block in elderly patients with hip fracture. Our findings may provide an new peripheral nerve analgesia for hip fracture, which could relieve pain without motor dysfunction, to accelerate recovery. This will offer clinical evidence for the optimal analgesia method in elderly patients with hip fracture.

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Author contributions WL,JTW,QHL conceived of the study, designed the study protocol and drafted the manuscript. WL and QHL wrote the manuscript. WHM is in charge of coordination and direct implementation.JHL and HYW helped to develop the study measures and analyses.WL, JHL, HYW and YHL performed the trial. YHO input the data and guarantee the data quality. HYW and YHL provided statistical knowledge for study initiation. All authors contributed to have read and approved the final manuscript.

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REFERENCES

1 Chenggui Zhang, Jingnan Feng, Shengfeng Wang, *et al.* Incidence of and trends in hip fracture among adults in urban China: a nationwide retrospective cohort study. *PLOS Medicine* 2020;17:e1003180.

2 Michael LE, Wright NC, Curtis JR, *et al*. Hip fracture trends in the United States, 2002 to 2015. *Osteoporosis International* 2017;29: 717–22.

3 Bing Yin, Jialiang Guo, Tianhua Dong, *et al*. Clinical features and proportion analysis of adult hip fractures at 11 hospitals in Southwest China from 2010 to 2011. *Zhonghua Wai Ke Za Zhi* 2015;53:349-52.

4 Gerbershagen HJ, Aduckathil S, van Wijck AJM, *et al*. Pain intensity on the first day after surgery: a prospective cohort study comparing 179 surgical procedures. *Anesthesiology* 2013;118:934–44.

5 Morrison RS, Magaziner J, McLaughlin MA, *et al*. The impact of post-operative pain on outcomes following hip fracture. *Pain* 2003;103:303–11.

6 National Clinical Guideline Centre: The management of hip fracture in adults. *London: National Clinical Guideline Centre* 2017: Available from www.ncgc.ac.uk.

7 Fox KMMJ, Hawkes WG, Yu-Yahiro J, *et al*. Loss of bone density and lean body mass after hip fracture. *Osteoporosis International* 2000;11:31–35.

8 Ljungqvist O, Scott M, Fearon KC. Enhanced recovery after surgery: a review. *JAMA Surgery* 2017;152: 292-98.

9 Macfie D, Zadeh RA, Andrews M, *et al*. Perioperative multimodal optimisation in patients undergoing surgery for fractured neck of femur. *The Surgeon* 2012;10:90–94.

10 Rasmussen S, Kristensen BB, Foldager S, *et al*. Accelerated recovery program after hip fracture surgery. *Ugeskr Laeger* 2002;165:29-33.

11 James R, John A, David E, *et al*. A pre-emptive multimodal pathway featuring peripheral nerve block improves perioperative outcomes after major orthopedic surgery.*Reg Anesth Pain Med* 2008;33:510-17.

12 Ellis TA, Hammoud H, Dela Merced P, *et al*. Multimodal clinical pathway with adductor canal block decreases hospital length of stay, improves pain control, and reduces opioid consumption in total knee arthroplasty patients: a retrospective review.*The Journal of Arthroplasty* 2018;33:2440-48.

13 Fabi DW. Multimodal analgesia in the hip fracture patient. *J Orthop Trauma* 2016;30:S6-S11.

14 Unneby A, Svensson O, Gustafson Y, *et al*.Femoral nerve block in a representative sample of elderly people with hip fracture: a randomized controlled trial. *Injury* 2017;48:1542–49.

15 Dickman E, Ayvazyan S, Pearl M, *et al*. Ultrasound-guided fascia iliaca compartment block for hip fractures in the emergency department.*J Emerg Med* 2012;43:692–97.

16 Beaudoin FL, Haran JP, Liebmann O. A comparison of ultrasound-guided three-in-one femoral nerve block versus parenteral opioids alone for analgesia in emergency department patients with hip fractures: a randomized controlled trial. *Acad Emerg Med* 2013;20:584–91.

17 Short AJ, Barnett JJG, Gofeld M, *et al*. Anatomic study of innervation of the anterior hip capsule：implication for image-guided intervention. *Reg Anesth Pain Med* 2018;43:186-92.

18 Girón-Arango L, Peng PWH, Chin KJ, *et al*. Pericapsular nerve group (PENG) block for hip fracture. *Reg Anesth Pain Med* 2018;43:859–63.

19 Girard TD, Thompson JL, Pandharipande PP, *et al*. Clinical phenotypes of delirium during critical illness and severity of subsequent long- term cognitive impairment: a prospective cohort study. *Lancet Respir Med* 2018;6:213–22.

20 Marhofer P, Schrogendorfer K, Koinig H, *et al*. Ultrasonographic guidance improves sensory block and onset time of three-in-one blocks. *Anesth Analg* 1997; 85: 854 – 57.

21 Myles PS, Myles DB, Galagher W, *et al*. Minimal clinically important difference for three quality of recovery scales. *Anesthesiology* 2016;125:39–45.

22 Gomes T, Tadrous M, Mamdani MM, *et al*. The burden of opioid-related mortality in the United States. *JAMA Network Open*

2018;1:e180217.

23 Wetzel M, Hockenberry J, Raval MV. Interventions for postsurgical opioid prescribing: a systematic review. *JAMA Surg* 2018;153:948-54.

24 Birke H, Ekholm O, Sjøgren P,*et al*. Long-term opioid therapy in Denmark: a disappointing journey. *Eur J Pain* 2017;21:1516–27.

25 Simoni AH, Nikolajsen L, Olesen AE, *et al*. Opioid use after hip fracture surgery: a Danish nationwide cohort study from 2005 to 2015. *Eur J Pain* 2019;23:1309-17.

26 Scurrah A, Shiner CT, Stevens JA, *et al*. Regional nerve blockade for early analgesic management of elderly patients with hip fracture - a narrative review. *Anaesthesia* 2017;73:769–83.

27 Reid N, Stella J, Ryan M, *et al*. Use of ultrasound to facilitate accurate femoral nerve block in the emergency department. *Emerg Med Australas* 2009;21:124–30.

28 Birnbaum K , Prescher A , Hessler S , *et al*. The sensory innervation of the hip joint - an anatomical study. *Surg Radiol Anat* 1997;19:371-75.

29 Gerhardt M, Johnson K, Atkinson R, *et al*. Characterisation and classification of the neural anatomy in the human hip joint. *Hip Int* 2012;22:75–81

30 Ali AM, Tahoun HM, Ahmed AA, *et al*. Comparative study between the analgesic efficacies of nerve stimulator-guided 3-in-1 block, ultrasonographic-guided 3-in-1 block and posterior approach lumbar plexus block following total hip arthroplasty. *Egyptian J Anaesth* 2003;19:39–43.

31 Yu HC, Moser JJ, Chu AY, *et al*. Inadvertent quadriceps weakness following the pericapsular nerve group (PENG) block. *Reg Anesth Pain Med* 2019;44:611–13.

32 Ince I, Kilicaslan A, Kutlu E, *et al*. Combined pericapsular nerve block(PENG) and lumbar erector spinae plane(ESP) blockfor congenital hip dislocation surgery. *J Clin Anesth* 2020;61:109671. doi: 10.1016/j.jclinane.2019.109671. Epub 2019 Nov 27.

33 Stark PA, Myles PS, Burke JA, *et al*. Development and psychometric evaluation of a postoperative quality of recovery score: the QoR-15. *Anesthesiology* 2013;118:1332-40.

The time	30min	Postoperatvie	Postoperatvie	Postoperatvie	Postoperatvie	Postoperatvie
before surgery	After block	6h	12h	18h	24h	48h
×	×	×	×	×	×	×
×	×	×	×	×	×	×
×	×	×	×	×	×	×
×	×	×	×	×	×	×
×	×	×	×	×	×	×
×	×	×	×	×	×	×
×	×	×	×	×	×	×

Items
Inclusion criteria
Exclusion criteria
Informed consent
Randomization and allocation
The rest pain score
The dynamic pain score
The strength of quadriceps
The consumption morphine
The rescue analgesic use
The effective bolus time
The useless bolus time
The first out-of-bed time
The postoperative complications
others

Table 1 Trial process chart

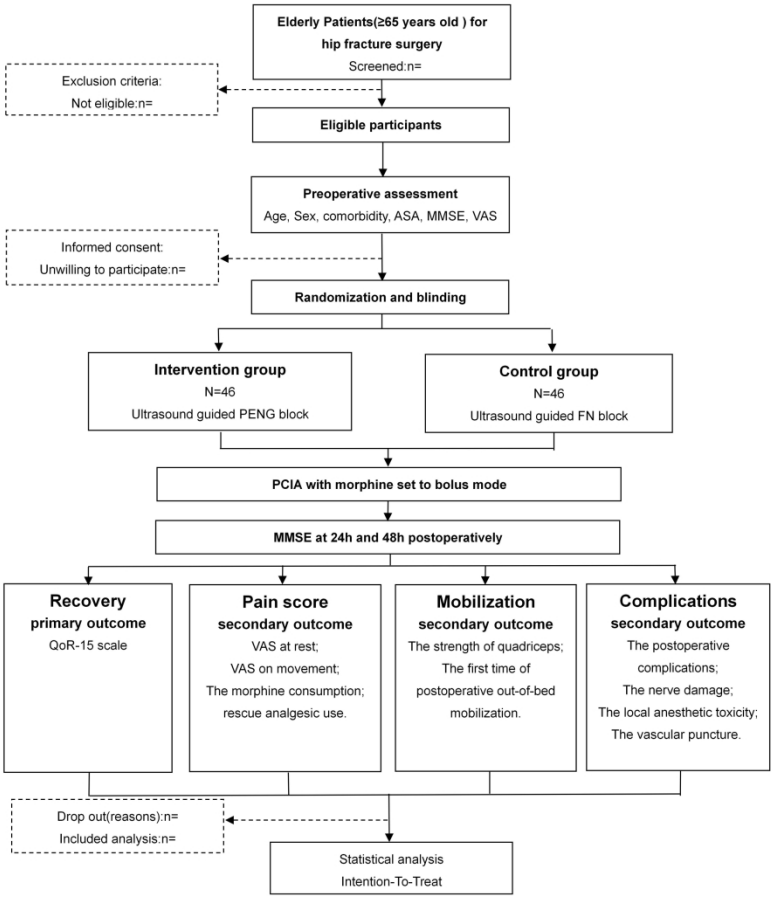

Figure 1 The flow diagram for this trial. ASA: American Society of Anesthesiologists class; MMSE: Mini- Mental State Examination; VAS: Visual analogue scale; PENG: Pericapsular nerve group; FN: Femoral nerve; PCIA: Patient controlled intravenous analgesia; QoR-15: quality of recovery-15.

Figure 1

209x296mm (300 x 300 DPI)

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.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	P1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	P1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	P1
Protocol version	#3	Date and version identifier	P1
Funding	#4	Sources and types of financial, material, and other support	N/A

Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	P1,P9
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	N/A
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	P6
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)	P6- P7
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	P2-P3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	P2
Objectives	#7	Specific objectives or hypotheses	P3
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)	P3 P6

Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	P3
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)	P3
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	P4- P5
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)	P5
Interventions: adherence	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	P5
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	P4
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	P5

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)	P4- P5 Figure 1
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	P6
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	P3
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	P6
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	P6
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	P6
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	P4, P6

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	P6
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, if not in the protocol	P5, P6-P7
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	P4
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	P6- P7
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	P7
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	P7
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)	P7

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	P6- P7
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	P6- P7
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	P6
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	P6
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	P6
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)	P6
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	P3- P4

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	P6
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	P9
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	P7
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	P6
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, reporting in results databases, or other data sharing arrangements), including any publication restrictions	P9
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	P6- P7
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	P3

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

BMJ Open

The effects of pericapsular nerve group (PENG) block on postoperative recovery in elderly patients with hip fracture: study protocol for a randomized, parallel controlled, double-blind trial

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The effects of pericapsular nerve group (PENG) block on postoperative recovery in elderly patients with hip fracture: study protocol for a randomized, parallel controlled, double-blind trial

Wei Luo,[1] Jianhui Liang,[1] Jieting Wu,[2] Quehua Luo,[3] Huiyi Wu,[1] Yanhua Ou,[1] Yuhui Li,[1] Wuhua Ma.[1]

ABSTRACT

Introduction Hip fracture is a common and serious emergency in the elderly, it is associated with severe pain, significant postoperative morbidity and mortality. The use of nerve block can relief pain effectively and reduce opioid requirements, which may accelerate patient recovery. The pericapsular nerve group (PENG) block has been found to provide an effective blockade to the hip joint and also have a potential motor-sparing effect, so we hypothesized that PENG block may be an effective tool to enhance recovery in elderly patients after hip fracture surgery.

Methods and analysis This study is a single centered, randomized, parallel controlled, double-blind trial. A total of 92 elderly patients scheduled for hip fracture surgery will be divided into two groups at random to receive either ultrasound-guided femoral nerve block or ultrasound-guided PENG block. The primary outcome will be to compare the Quality of Recovery-15 scores at 24h postoperatively between the two groups. The secondary outcomes will include measuring and comparing the strength of the quadriceps, the visual analogue scale at rest and on movement, the total morphine consumption, the rescue analgesic, the first time of postoperative out-of-bed mobilization, including complications.

Ethics and dissemination This study was approved by the Institutional Review Board of the Ethics Committee of The First Affiliated Hospital of Guangzhou University of Chinese Medicine on 15 December 2020 (Reference K2020-110). The results of this study will be published in peer-reviewed international journals.

Trial registration number ChiCTR2100042341.

Key words Quality of recovery, Hip fracture, Pericapsular nerve group block, Elderly patients

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Strengths and limitations of this study

- This study was done to investigate the effects of pericapsular nerve group block on the quality of recovery in elderly patients after hip fracture surgery.
- The primary outcome is Quality of Recovery-15, which can assess multiple domains of recovery.
- Both objective and subjective quality of recovery in the postoperative 24h are included.
- A limitation of this study is that Quality of Recovery-15 score could be influenced by delirium, which is a common complication in elderly patients with hip fracture.
- Though objective and subjective outcomes are recorded, but measurements are incomplete, for example, some level of neuroinflammatory markers could be the evaluation of recovery.

INTRODUCTION

Hip fracture is one of the most serious medical emergency in the elderly patients, associated with high postoperative morbidity and mortality.[1] To quicken rehabilitation and decrease complications, early surgery for hip fractures is the definite treatment in most patients.[2] However, the pain after hip fracture surgery is serious.[3] Such pain can significantly increase both postoperative complications and mortality, which seriously delay the recovery after surgery.[4]

Nerve blocks are the popular analgesic techniques for elderly patients.[5] Compared with traditional intravenous opioids during the initial postoperative period, a multimodal pathway featuring a peripheral nerve block can improve control of dynamic pain, quicken mobilization and reduce the opioid related adverse effects, which may result in fewer complications and improved perioperative outcomes after major orthopedic surgery.[6-8]

In recent the popular peripheral nerve block techniques for dealing with hip fracture are ultrasound-guided femoral nerve (FN) block, fascia iliac compartment (FIC) block, and 3-in-1 FN block. However, the obturator nerve (ON) and the accessory obturator nerve (AON) have often failed to exhibit adequate blockade from these blocks, the effectiveness of these block is only moderate accompanied by decreasing the strength of quadriceps.[9-11]

In 2018 Arango *et al* found out a new regional technique for hip fractures: ultrasound-guided pericapsular nerve group (PENG) block.[12] They concluded that this technique could provide an effective blockade to the articular branches of FN, ON, and AON, with a potential motor-sparing effect. Most of the case reports indicated the PENG block could provide sufficient analgesia with no to minimal opioid requirements at postoperative 24h.[13] A study showed that the patients receiving PENG block experienced better postoperative pain relief coupled with quadriceps strength improvement than those receiving FN block in the post-anesthesia care unit.[14] With this outcome, PENG block may provide a high quality of recovery for the hip fractures.

However, this study also suggested that there was no difference detected in pain scores by postoperative Day-1 between patients receiving PENG block versus those receiving FN block.[14] Within a standard care program, whether PENG block would affect the quality of rehabilitation in elderly patients with hip fractures is still unclear. Therefore, this randomized, parallel controlled, double-blind trial will compare the Quality of Recovery-15 (QoR-15) scores at 24h postoperatively between two groups to investigate whether PENG block enhances recovery in elderly patients after hip fracture surgery.

METHODS AND ANALYSIS

Primary aims

The primary aim of this trial is to investigate whether PENG block effectively enhances recovery in elderly patients after hip fracture surgery.

Secondary aims

The secondary aims are to investigate whether PENG block results in a motor-sparing effect, a reduction in pain score at rest and on movement, a decrease in total morphine consumption and the rescue analgesic, an improvement in the first time of postoperative out-of-bed mobilization, and a decrease in complications.

Trial design

This is a pragmatic, parallel group, randomized controlled, double-blind trial. The study will be conducted at The First Affiliated Hospital of Guangzhou University of Chinese Medicine and has been registered with the Chinese Clinical Trial Registry (ChiCTR2100042341). The methods and results of this study will be reported according to the Standard Protocol Items: Recommendations for Interventional Trials and 2013 statement.[15] The flow diagram for this trial is presented in figure 1.

Eligibility criteria

Recruitment

Elderly patients (over 65 years old) with hip fracture who are selected for hip surgery at The First Affiliated Hospital of Guangzhou University of Chinese Medicine will be recruited for this study. Inclusion was initiated in March 2021. The expected study completion date is March 2023.

Inclusion criteria

Patients will be included if they are cognitively intact, have an American Society of Anesthesiologists physical status (ASA) between I-Ⅲ, and have a body mass index (BMI) between 18-30kg/m^2.

Exclusion criteria

Patients will be excluded if they refuse to participate in the study, have an allergy or contraindication to the drug or anesthetic technique in this study, have dementia, multiple traumas, severe deafness and vision problems, communication difficulties, an infection near the block site, are obese (BMI > 30 kg/m^2), or have clinically significant neurological, cardiovascular, renal, or hepatic disease (ASA Ⅳ-Ⅴ).

Informed consent

According to the inclusion and exclusion criteria， patients will be assessed by members of the research team the day before the surgery. Once patients are eligible, researchers will fully explain the study, including the implications, known adverse effects, any risks in taking part, and constraints of the protocol, to the eligible patients and their families and answer any questions. If patients agree to enroll, written informed consent will be obtained from the participants and their proxies. Participants can choose to withdraw from the trial at any time and for any reason. Permission will be obtained from each patient regarding the use of their data for statistical analysis.

Preoperative management

In accordance with national guideline,[2] patients in both groups will be receiving standard care to accelerate recovery. The pathway includes rapid assessment from the Emergency Department, adequate pain control, assessment of bone health and falls, multidisciplinary management, surgical procedures, and mobilization strategies. The ASA status classification will be evaluated, and preoperative cognitive assessment will be

performed by using the Mini-Mental State Examination (MMSE).[16] Opioid use will be avoided except for severe pain. Patients who participate in this study will also avoid the use of premedication.

Intraoperative management

After entering the operating room, continuous electrocardiogram, noninvasive intermittent blood pressure, and pulse oxygen saturation will be monitored. The patients will be given 4 L/min of oxygen through a mask. In order to reduce any pain or anxiety during the nerve blockade, 0.5 μg/kg of fentanyl will be given intravenously.
The blockade for both groups will be performed by the same experienced anesthesiologist. Before local anesthesia, the anesthesiologist will obtain the sequence from a sealed envelope and perform the blockade according to the allocated information. The anesthesia for the surgery will be performed after the block and will be managed by a second anesthesiologist. For both groups, spinal anesthesia will be chosen as the main anesthetic technique and will be provided with 0.5% bupivacaine 1.2 mL to 1.8 mL (6 mg to 9 mg) at the L3-L4 interspace, and the sensory block will be controlled at T8-T10.

Ultrasound-guided pericapsular nerve group block

With patients in a supine position, PENG block will be performed as described by Arango *et al.*[12] The anterior inferior iliac spine, the femoral artery, the pectineus muscle, the iliopubic eminence, the iliopsoas muscle, and tendon will be observed using a curvilinear low-frequency ultrasound probe. The puncture site will be set 0.5-1.0 cm away from the lateral of the ultrasound probe. After 2 ml of 1% lidocaine is injected for local anesthesia, a 22-gauge, 80-mm needle will be inserted carefully in an in-plane approach from lateral to inner. After the tip of the needle is placed the musculofascial plane between the tendon of the psoas muscle anteriorly and the pubic ramus posteriorly, which is between the iliopubic eminence and anterior inferior iliac spine,[17 18] 1mL of 0.9% saline solution will be injected to ensure that the solution will be spread in the plane beneath the iliopsoas muscle. After negative aspiration, a total volume of 20 mL of 0.375% ropivacaine will be slowly injected every 5 mL. The spread of the ropivacaine is in the musculofascial plane towards the iliopubic eminence with the iliopsoas tendon lifted up.[17] The ultrasound view of the fluid spread in the plane will be observed to ensure that the ropivacaine is injected right in the targeted location.

Ultrasound-guided femoral nerve block

With the patients in a supine position, FN block will be performed as described by Marhofer *et al.*[19] A linear high-frequency probe will be used to visualize the femoral artery and the FN. The puncture site will be set 0.5-1.0 cm away from the lateral of the ultrasound probe. After 2 ml of 1% lidocaine is injected for local anesthesia, a 22-gauge, 80-mm needle will be inserted carefully in an in-plane approach from lateral to inner. After the tip of the needle is placed next to the FN, a total volume of 20 mL of 0.375% ropivacaine will be slowly injected after negative aspiration every 5 mL. The ultrasound view of the fluid spread will be observed to ensure that the ropivacaine is injected around the FN.

Postoperative management and follow-up

After surgery, when participants are transferred to the ward, vital signs (heart rate, noninvasive blood pressure, pulse oxygen saturation, and respiratory rate) will be monitored. Over the course of postoperative 48h, a PCIA with morphine will be started when the operation concludes and set to the bolus only mode (bolus 1.0 mg, lockout 6 min, maximum dosage 15mg/4h). All participants will receive 1 g paracetamol every 6h as a part of

postoperative multimodal analgesia. In case of nausea or vomiting, 5mg of tropisetron will be intravenously injected.

Outcome measurement

Before a series of clinical-scale evaluations and analgesia are evaluated and recorded by an estimator, who is blinded to the group assignments, patients will first be tested with the MMSE on postoperative Day-1 and Day-2.

The primary outcome measurement of this study will be the QoR-15 scores answered by patients at 24h postoperatively.[20 21] The questionnaire contains 15 items concerning the patient's quality of recovery. Each item is scored on an 11-point scale ranging from 0 to 10, with a total possible score of up to 150 points. The mean value and standard deviation (SD) will be used for descriptive analysis.

The secondary outcomes will include the strength of the quadriceps, the visual analogue scale (VAS) of both resting and dynamic pain, the total morphine consumption, the rescue analgesic, the first time of postoperative out-of-bed mobilization, and any complications. To test the strength of quadriceps, patients will be asked to extend the knee of the affected limb while supporting the knee under the popliteal fossa 30 min after the blockade, and at 6h, 12h, 18h, 24h and 48h postoperatively. The quadriceps strength will be graded to a 6-point scale: 5, normal strength; 4, extension against gravity and light resistance; 3, extension against gravity; 2, extension against gravity eliminated; 1, muscle twitch; 0, paralysis.[22] At the time before and 30 min after the blockade, and at 6h, 12h, 18h, 24h and 48h postoperatively, the pain scores at rest and on movement will be assessed, respectively. After patients have been resting in bed for 15 min, VAS at rest will be assessed. When VAS on movement is assessed, participants will be asked to perform the operative hip flexion to 45 degrees. Using an 11-point numerical rating scale, the VAS ranges from 0=no pain to 10=unbearable pain. The total morphine consumption in PCIA and the time of the bolus will be recorded. If the participants do not feel pain relief after injection of morphine from the PCIA, they will receive rescue anesthetic as required by the assessment. The time and the dosage of analgesics in the first 48h will be recorded. A physiotherapist will evaluate the patients' postoperative ability; including the time taken for a patient to get out of bed, and perform physiotherapy exercises. Any postoperative complications such as pneumonia, deep vein thrombosis, myocardial infarction, cerebrovascular accident, and so on will be recorded and treated. Additionally, any PENG block complications such as nerve damage, local anesthetic toxicity, and vascular puncture will be recorded. A diagram of participant recruitment and secondary outcomes measurement is shown in table 1.

Randomization and blinding

At the beginning of this study, a randomization sequence will be generated by SAS 9.0 statistical software and assign the participants to either the control group (ultrasound-guided FN block group) or the intervention group (ultrasound-guided PENG block group) at a 1:1 ratio. An independent statistician will conceal the sequence (including allocated group, random numbers, and intervention information) from the researcher, who will assess the subjects, in identical opaque and sealed envelopes.

The effect of the block will be evaluated and recorded by an investigator who is blinded in the block performance analysis.

Sample size estimation

Based on the results of preliminary experiments, the QoR-15 scores (mean difference ± SD) of elderly patients for 24h were 88.25 ± 8.32 in the FN block group and 98.97 ± 10.37 in the PENG block group. Myles *et al*[23] found that the minimal clinically important difference for the QoR-15 is 8.0. Therefore, to detect the effect size (power = 0.8)

with the type 1 error of 5% (α=0.05), a dropout rate of 10% and a non-inferiority or superiority margin of 8, a sample size of 92 participants is required. As a result, 46 participants per group will be recruited for this study.

Reporting of adverse events

Participants will be seen daily for the duration of the study. All adverse events and other unintended effects of the trial will be recorded. If any serious complications occur, researchers will be informed immediately, medical practitioners will then take proper measures to ensure the safety of patients. After the treatment, the allocated group of the patient will be revealed, and the evaluation about the correlation between adverse events and intervention will be discussed comprehensively. All details of any serious adverse events will be recorded and reported to the ethics committee.

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

Ethics and declarations

This trial received ethical approval from the Institutional Review Board of the Ethics Committee of The First Affiliated Hospital of Guangzhou University of Chinese Medicine on 15 December 2020 (Reference K2020-110). This study has been registered at the Chinese Clinical Trial Registry (ChiCTR2100042341). The trial will be conducted in accordance with the Declaration of Helsinki 1996, principles of good clinical practice, and the Department of Health Research Governance Framework for Health and Social Care. The researchers will send regular reports about the progress and any changes to this trial to the Institutional Review Board of the Ethics Committee of The First Affiliated Hospital of Guangzhou University of Chinese Medicine. The results of this study will be published in peer-reviewed international journals.

Data management and monitoring

Demographic data and mental assessment data, QoR-15 data and information on pain scores, mobilization assessment data, and information about complications will be collected and input into an electronic database. An independent researcher will guarantee the data quality during the process. All data of outcomes will be input into another independent database and will be double-checked to promote data quality. Any individual privacy information will be deleted to protect confidentiality. After data storage, only researchers will have direct access to the final trial dataset. The progress and safety of this study will be monitored monthly by the data monitoring committee (DMC), which is composed of two independent experts outside the study. The clinical experts will be able to access the unblinded data. The DMC will be able to give suggestions regarding safety, and will also have authority to terminate the trial. The final trial dataset will be managed by The First Affiliated Hospital of Guangzhou University of Chinese Medicine. Accessing the dataset will require the written permission of the corresponding author.

Statistical analysis

All allocated subjects with available data will be analysed. According to the variable type and distribution, data will be presented as mean and SD, frequency and proportion, or median and interquartile range (25th-75th percentile). Based on the $\chi 2$ test or Fisher's exact test, categorical variables will be evaluated. The parametric t-test, the Wilcoxon rank-sum test, or the Kruskal-Wallis test will be used to analyse differences between the two groups in continuous variables. Non-normal distributions will be assessed with the Mann-Whitney U test. To manage

missing data, mean completer and regression will be used. A p value of <0.05 will be considered statistically significant, and results will be presented with 95% CIs. Analysis of data will be performed with SPSS software V.21.0 (developed by IBM Corp, Armonk, New York, USA).

Discussion

Hip fracture is often associated with serious pain. Lack of sufficient pain treatment can lead to not only the deceleration of recovery after surgery, but also high risk of cardiovascular adverse events and long-term chronic pain.[4] Because of this, adequate pain treatment is needed in the perioperative period for more effective recovery.

Opioid use could be appropriate for the requirement of pain relief after surgery, so it has been the mainstay of potent analgesia for hip fractures worldwide in the past 20 years.[24-26] Simoni *et al*[27] found that 26.8% of patients redeemed one or more opioid prescriptions before surgery, and 61.8% received opioid therapy postoperatively. However, opioid-related adverse events are more common among the elderly, occurring in 80% of patients. These adverse events, including cognitive impairment and increased fall risk (and in some cases, mortality) seriously delay rehabilitation after surgery. In addition, opioids offer pain relief at rest but are ineffective at addressing pain on movement.

Therefore, to reduce related adverse events and improve patients' experience, neuraxial techniques have been recommended. Consistent evidence has suggested that regional analgesia techniques can reduce pain by providing reasonable, rapid-onset and site-specific analgesia, which is more effective than traditional systemic analgesia.[28] In addition, there is evidence that peripheral nerve block may decrease the incidence of delirium, shorten hospital stays, and reduce morbidity and mortality.[28] Following the development of ultrasound guidance, the success rate of peripheral nerve block has improved.[29] Thus, peripheral nerve block may have an excellent effect on fast-track recovery.

Nowadays, the FN block, FIC block, and 3-in-1 FN block are popular peripheral nerve block techniques. Unfortunately, none of these nerve block techniques are ideal for hip fracture at present. According to multiple anatomical studies, the articular branches of FN, ON, and AON innervate the anterior hip joint, which plays an important role in the innervation of the hip capsule.[30-32] This suggests that they should be the main target of regional analgesia. The three main nerves can be anesthetized by 3-in-1 FN block and FIC block. However, the success rate of the obturator block with 3-in-1 FN block falls between 77-80%, while the rate with FIC block is 88%.[33] So, both FIC block and the 3-in-1 FN block may result in failure to anesthetize ON, and the FN block also cannot anesthetize ON.[33-35] As a result, the effectiveness of these three blocks is moderate at best. In addition, these three nerve block techniques may produce quadriceps weakness, which could slow mobilization and increase the incidence of falls.[36] Therefore, a new regional analgesia, one that can provide complete analgesia without significant motor dysfunction, should be put forward.

The PENG block, developed by Arango *et al*[12], is a novel peripheral nerve block for patients with hip fracture. When Arango *et al*[12] performed the PENG block in 5 patients, they found that the Numeric Rating Scale (NRS) for rest pain in 4 cases decreased from 4 points or above to 0 points, the reduction of NRS for dynamic pain in all 5 cases was more than 4 points, and the median reduction of pain was 7 points. Over 100 PENG blocks have been performed by Yu *et al*[37] for hip fracture and surgery, and these blocks were also found to be highly effective. Ince *et al*[38] combined PENG and lumbar erector spinae plane block to provide postoperative pain treatment in a 4-year-old child undergoing surgery for congenital hip dysplasia, and the FLACC score in postoperative 24h was less than 1 point without any need for additional analgesics. Recently some studies of PENG block have been published and suggested PENG block could provide effect analgesia with better preservation of motor function comparing with FN block or FIC block.[14 39]

These studies provide promising evidence about the effectiveness of PENG block for hip surgery. Perhaps most impressive is that this approach provides significant dynamic pain control with a motor-sparing effect, which makes the early mobilization possible. PENG block seems to meet the conditions for an ideal peripheral nerve block for geriatric patients with hip fracture. Thus, this trial is set to test whether PENG block is effective to enhance recovery in elderly patients with hip fracture.

To test the quality of recovery, a variety of measurement tools could be chosen. Traditionally, many clinical observational indexes are used to evaluate the effectiveness and safety of anesthesia in postoperative recovery, but most are focused on the physiological endpoints such as the incidence of complications, the length of hospital stays, the mortality, and so on. Although these indexes are objective and measure important data, evaluations from the patients' points of view are more humanized and are also important to be assessed. So, a patient-rated QoR-15 is suitable. It is a multidimensional measurement of quality of recovery demonstrated by high-quality evidence and includes five dimensions: pain, physical comfort, physical independence, psychological support, and emotional state. Stark *et al*[20] suggested there was no relation between the QoR-15 and patient age, which indicates that the QoR-15 could be used in elderly patients. In addition, according to the positive impact duration of the regional anesthesia, the time-frame of the measurement instrument should be the early postoperative time.[7] As the result, some common assessment, which resulted at postoperative Day-3 or later, may be not ideally suited. For these reasons, the QoR-15 at postoperative 24h was chosen as the primary outcome in this study.

This is a study using a randomized, parallel controlled, double-blind trial to compare QoR-15 between ultrasound-guided FN block and ultrasound-guided PENG block. It also explores the effectiveness and safety of PENG block in elderly patients after hip fracture surgery. The findings of this study may provide a new peripheral nerve analgesia for hip fracture, which could relieve pain without motor dysfunction to accelerate recovery. This will offer clinical evidence for the optimal analgesia method in Enhance Recovery After Surgery pathways for elderly patients with hip fracture.

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Contributions WL, JTW, and QHL conceived of the study, designed the study protocol, and drafted the manuscript. WL and QHL wrote the manuscript. WHM was in charge of coordination and direct implementation. JHL and HYW helped to develop the study measures and analyses. WL, JHL, HYW, and YHL performed the trial. YHO and JTW input the data and guaranteed the data quality. HYW and YHL provided statistical knowledge for the study's initiation. All authors contributed to and approved the final manuscript.

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REFERENCES

1 Fox KMMJ, Hawkes WG, Yu-Yahiro J, *et al*. Loss of bone density and lean body mass after hip fracture. *Osteoporos Int* 2000;11:31–5.

2 National Clinical Guideline Centre: The management of hip fracture in adults. *London: National Clinical Guideline Centre* 2017: Available from www.ncgc.ac.uk.

3 Gerbershagen HJ, Aduckathil S, van Wijck AJ, *et al*. Pain intensity on the first day after surgery: a prospective cohort study comparing 179 surgical procedures. *Anesthesiology* 2013;118:934–44.

4 Morrison RS, Magaziner J, McLaughlin MA, *et al*. The impact of post-operative pain on outcomes following hip fracture. *Pain* 2003;103:303–11.

5 Halaszynski TM. Pain management in the elderly and cognitively impaired patient: the role of regional anesthesia and analgesia. *Curr Opin Anaesthesiol* 2009; 22: 594–9.

6 James R, John A, David E, *et al*. A pre-emptive multimodal pathway featuring peripheral nerve block improves perioperative outcomes after major orthopedic surgery. *Reg Anesth Pain Med* 2008;33:510-7.

7 Ellis TA, Hammoud H, Dela Merced P, *et al*. Multimodal clinical pathway with adductor canal block decreases hospital length of stay, improves pain control, and reduces opioid consumption in total knee arthroplasty patients: a retrospective review. *J Arthroplasty* 2018;33:2440-8.

8 Fabi DW. Multimodal analgesia in the hip fracture patient. *J Orthop Trauma* 2016;30:S6-S11.

9 Unneby A, Svensson O, Gustafson Y, *et al*. Femoral nerve block in a representative sample of elderly people with hip fracture: a randomized controlled trial. *Injury* 2017;48:1542–9.

10 Dickman E, Ayvazyan S, Pearl M, *et al*. Ultrasound-guided fascia iliaca compartment block for hip fractures in the emergency department. *J Emerg Med* 2012;43:692–7.

11 Beaudoin FL, Haran JP, Liebmann O. A comparison of ultrasound-guided three-in-one femoral nerve block versus parenteral opioids alone for analgesia in emergency department patients with hip fractures: a randomized controlled trial. *Acad Emerg Med* 2013;20:584–91.

12 Girón-Arango L, Peng PWH, Chin KJ, *et al*. Pericapsular nerve group (PENG) block for hip fracture. *Reg Anesth Pain Med* 2018;43:859–63.

13 Morrison C, Brown B, Lin D-Y, *et al*. Analgesia and anesthesia using the pericapsular nerve group block in hip surgery and hip fracture: a scoping review.*Reg Anesth Pain Med* 2020;0:1-7.

14 Lin DY, Morrison C, Brown B, *et al*. Pericapsular nerve group (PENG) block provides improved short-term analgesia compared with the femoral nerve block in hip fracture surgery: a single-center double-blinded randomized comparative trial. *Reg Anesth Pain Med* 2021;46:398–403.

15 Chan AW, Tetzlaff JM, Gøtzsche PC, *et al*. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. *BMJ* 2013;346:e7586

16 Girard TD, Thompson JL, Pandharipande PP, *et al*. Clinical phenotypes of delirium during critical illness and severity of subsequent long- term cognitive impairment: a prospective cohort study. *Lancet Respir Med* 2018;6:213–22.

17 Mistry T, Bapurao SK. Gray zone of pericapsular nerve group (PENG) block. *J Clin Anesth* 2019; 58:123-4.

18 Black ND, Chin KJ. Pericapsular nerve group (PENG) block: Comments and practical considerations. *J Clin Anesth*

2019;56:143-4.

19 Marhofer P, Schrogendorfer K, Koinig H, *et al.* Ultrasonographic guidance improves sensory block and onset time of three-in-one blocks. *Anesth Analg* 1997; 85: 854–7.

20 Stark PA, Myles PS, Burke JA, *et al.* Development and psychometric evaluation of a postoperative quality of recovery score: the QoR-15. *Anesthesiology* 2013;118:1332-40.

21 Bu XS, Jing Z, Zuo YX. Validation of the Chinese Version of the Quality of Recovery-15 Score and Its Comparison with the Post-Operative Quality Recovery Scale. *Patient* 2016;9:251–9.

22 Matthew, Dean, Edwards, *et al*. Effect of Adductor Canal Block Versus Femoral Nerve Block on Quadriceps Strength, Function, and Postoperative Pain After Anterior Cruciate Ligament Reconstruction: A Systematic Review of Level 1 Studies. *Am J Sports Med* 2020;48:2305-13.

23 Myles PS, Myles DB, Galagher W, *et al.* Minimal clinically important difference for three quality of recovery scales. *Anesthesiology* 2016;125:39–45.

24 Gomes T, Tadrous M, Mamdani MM, *et al.* The burden of opioid-related mortality in the United States. *JAMA Network Open* 2018;1:e180217.

25 Wetzel M, Hockenberry J, Raval MV. Interventions for postsurgical opioid prescribing: a systematic review. *JAMA Surg* 2018;153:948-54.

26 Birke H, Ekholm O, Sjøgren P, *et al.* Long-term opioid therapy in Denmark: a disappointing journey. *Eur J Pain* 2017;21:1516–27.

27 Simoni AH, Nikolajsen L, Olesen AE, *et al.* Opioid use after hip fracture surgery: a Danish nationwide cohort study from 2005 to 2015. *Eur J Pain* 2019;23:1309-17.

28 Scurrah A, Shiner CT, Stevens JA, *et al.* Regional nerve blockade for early analgesic management of elderly patients with hip fracture - a narrative review. *Anaesthesia* 2017;73:769–83.

29 Reid N, Stella J, Ryan M, *et al*. Use of ultrasound to facilitate accurate femoral nerve block in the emergency department. *Emerg Med Australas* 2009;21:124–30.

30 Short AJ, Barnett JJG, Gofeld M, *et al.* Anatomic study of innervation of the anterior hip capsule：implication for image-guided intervention. *Reg Anesth Pain Med* 2018;43:186-92.

31 Birnbaum K , Prescher A , Hessler S , *et al.* The sensory innervation of the hip joint - an anatomical study. *Surg Radiol Anat* 1997;19:371-5.

32 Gerhardt M, Johnson K, Atkinson R, *et al.* Characterisation and classification of the neural anatomy in the human hip joint. *Hip Int* 2012;22:75–81.

33 Ali AM, Tahoun HM, Ahmed AA, *et al.* Comparative study between the analgesic efficacies of nerve stimulator-guided 3-in-1 block, ultrasonographic-guided 3-in-1 block and posterior approach lumbar plexus block following total hip arthroplasty. *Egyptian J Anaesth* 2003;19:39–43.

34 Dolan J, Williams A, Murney E , *et al.* Ultrasound guided fascia iliaca block: a comparison with the loss of resistance technique. *Reg Anesth Pain Med* 2008;33:526-31.

35 Swenson JD, Davis JJ, Stream JO, *et al.* Local anesthetic injection deep to the fascia iliaca at the level of the inguinal ligament: the pattern of distribution and effects on the obturator nerve. *J Clin Anesth* 2015;27:652-7.

36 Kuang M, Ma J, Fu L, *et al.* Is Adductor Canal Block Better Than Femoral Nerve Block in Primary Total Knee Arthroplasty? A GRADE Analysis of the Evidence Through a Systematic Review and Meta-Analysis. *J Arthroplasty* 2017;32:3238–48.

37 Yu HC, Moser JJ, Chu AY, *et al.* Inadvertent quadriceps weakness following the pericapsular nerve group (PENG) block. *Reg Anesth Pain Med* 2019;44:611–3.

38 Ince I, Kilicaslan A, Kutlu E, *et al.* Combined pericapsular nerve block(PENG) and lumbar erector spinae plane(ESP) blockfor congenital hip dislocation surgery. *J Clin Anesth* 2020;61:109671.

39 Aliste J, Layera S, Bravo D, *et al*. Randomized comparison between pericapsular nerve group (PENG) block and suprainguinal fascia iliaca block for total hip arthroplasty. *Reg Anesth Pain Med* 2021;46:874-8.

Table 1 Trial process chart

Items	The time before surgery	30 min After block	Postoperative 6h	Postoperative 12h	Postoperative 18h	Postoperative 24h	Postoperative 48h
Inclusion criteria	×						
Exclusion criteria	×						
Informed consent	×						
Randomization and allocation	×						
The rest pain score	×	×	×	×	×	×	×
The dynamic pain score	×	×	×	×	×	×	×
The strength of quadriceps		×	×	×	×	×	×
The consumption morphine			×	×	×	×	×
The rescue analgesic use			×	×	×	×	×
The time of the bolus			×	×	×	×	×
The time of bolus pressing during the lockout time			×	×	×	×	×
The first out-of-bed time			×	×	×	×	×
The postoperative complications			×	×	×	×	×
others	×	×	×	×	×	×	×

Figure 1 The flow diagram for this trial. ASA: American Society of Anesthesiologists class; MMSE: Mini- Mental State Examination; VAS: Visual Analogue Scale; PENG: Pericapsular nerve group; FN: Femoral nerve; PCIA: Patient controlled intravenous analgesia; QoR-15: Quality of Recovery-15.

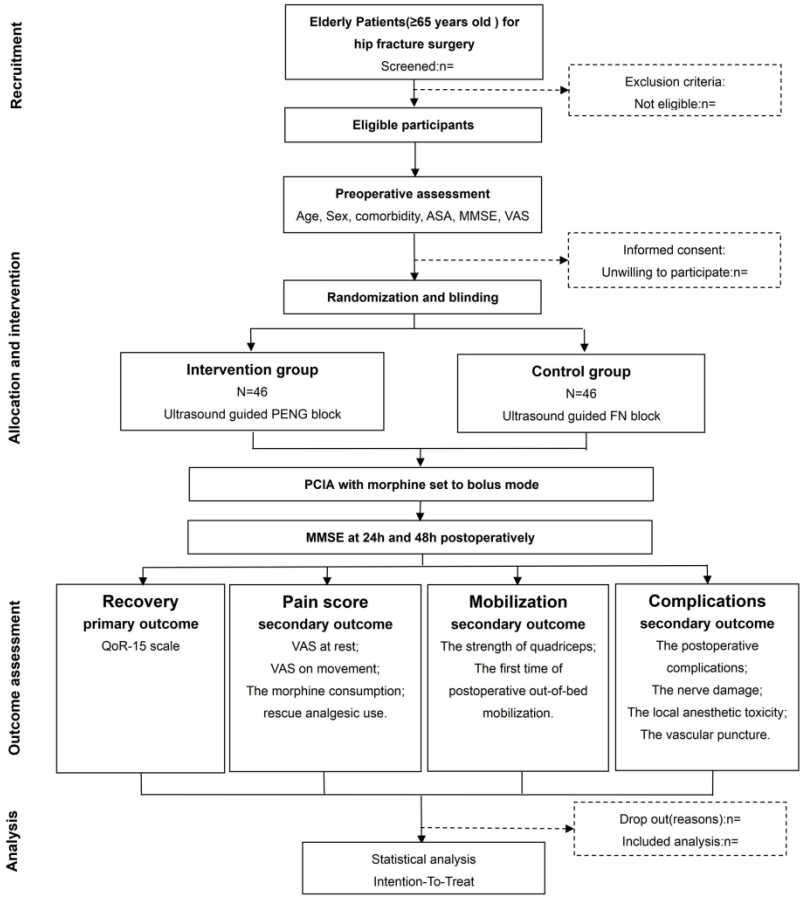

Figure 1 The flow diagram for this trial. ASA: American Society of Anesthesiologists class; MMSE: Mini- Mental State Examination; VAS: Visual analogue scale; PENG: Pericapsular nerve group; FN: Femoral nerve; PCIA: Patient controlled intravenous analgesia; QoR-15: quality of recovery-15.

209x296mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

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Instructions to authors

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

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	P1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	P1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	P1
Protocol version	#3	Date and version identifier	P1
Funding	#4	Sources and types of financial, material, and other support	P8
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	P1, P8

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	N/A
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	N/A
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)	P6
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	P2
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	P2
Objectives	#7	Specific objectives or hypotheses	P2-P3
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)	P3 P5-P6
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be	P3

		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)	P3
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	P4- P5
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)	P4- P6
Interventions: adherence	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	P4- P5
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	P3-P4
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	P5
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)	P5 Figure 1
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	P5-P6
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	P3

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	P5
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	P5
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	P4-P5
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	P4-P5
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	P6
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, if not in the protocol	P5 P7-P8

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	P6-P7
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	P6
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	P6-P7
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	P6-P7
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)	P6-P7
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	P6
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	P6
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	P6
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	P6

Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	P6
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)	P6
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	P3
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	P6
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	P8
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	P6,P9
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	N/A
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, reporting in results databases, or other data sharing arrangements), including any publication restrictions	P9
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	P8

Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A

Appendices

Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	P3
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

BMJ Open

The effects of pericapsular nerve group (PENG) block on postoperative recovery in elderly patients with hip fracture: study protocol for a randomized, parallel controlled, double-blind trial

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Secondary Subject Heading:	Rehabilitation medicine
Keywords:	Anaesthesia in orthopaedics < ANAESTHETICS, Pain management < ANAESTHETICS, Hip < ORTHOPAEDIC & TRAUMA SURGERY, Rehabilitation medicine < INTERNAL MEDICINE

The effects of pericapsular nerve group (PENG) block on postoperative recovery in elderly patients with hip fracture: study protocol for a randomized, parallel controlled, double-blind trial

Wei Luo,[1] Jianhui Liang,[1] Jieting Wu,[2] Quehua Luo,[3] Huiyi Wu,[1] Yanhua Ou,[1] Yuhui Li,[1] Wuhua Ma.[1]

ABSTRACT

Introduction Hip fracture is a common and serious emergency in the elderly, and it is associated with severe pain, significant morbidity and mortality. The use of peripheral nerve block can relieve pain effectively and reduce opioid requirements, which may accelerate patient's recovery. The pericapsular nerve group (PENG) block has been found to provide an effective blockade to the hip joint with a potential motor-sparing effect, so we hypothesized that the PENG block may be an effective tool to enhance the recovery in elderly patients after hip fracture surgery.

Methods and analysis This study is a single centered, randomized, parallel controlled, double-blind trial. A total of 92 elderly patients scheduled for hip fracture surgery will be divided into two groups at random to receive either ultrasound-guided femoral nerve block or ultrasound-guided PENG block. The primary outcome will be to compare the Quality of Recovery-15 scores at 24h postoperatively between the two groups. The secondary outcomes will include measuring and comparing the strength of the quadriceps, the visual analogue scale at rest and on movement, the total morphine consumption, the rescue analgesic, the first time of postoperative out-of-bed mobilization, and complications.

Ethics and dissemination This study was approved by the Institutional Review Board of the Ethics Committee of The First Affiliated Hospital of Guangzhou University of Chinese Medicine on 15 December 2020 (Reference K2020-110). The results of this study will be published in peer-reviewed international journals.

Trial registration number ChiCTR2100042341.

Key words Quality of recovery, Hip fracture, Pericapsular nerve group block, Elderly patients

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Strengths and limitations of this study

- This study was done to investigate the effects of pericapsular nerve group block on the quality of recovery in elderly patients after hip fracture surgery.
- The primary outcome is Quality of Recovery-15, which can assess multiple domains of recovery.
- Both objective and subjective quality of recovery in the postoperative 24h are included.
- A limitation of this study is that Quality of Recovery-15 score could be influenced by delirium, which is a common complication in elderly patients with hip fracture.
- Though objective and subjective outcomes are recorded ,measurements are incomplete. For example, some level of neuroinflammatory markers could be the evaluation of recovery.

INTRODUCTION

Hip fracture is one of the most serious medical emergencies in the elderly patients, associated with high morbidity and mortality.[1] Surgery has been the generally-accepted treatments for hip fracture.[2] However, the overwhelming pain after hip fracture surgery[3] can significantly increase both postoperative complications and mortality, which utterly delay the post-surgical recovery.[4] Therefore, proper analgesics has been identified as a major priority in the management of hip fracture.[2]

In elderly patients, peripheral nerve blocks are effective analgesia techniques with fewer side effects.[5] Compared with traditional intravenous opioids during the initial postoperative period, a multimodal pathway featuring a peripheral nerve block can improve control of dynamic pain, accelerate mobilization and reduce the opioid-related adverse effects, which may result in fewer complications and improved perioperative outcomes after major orthopedic surgery.[6-8]

Among peripheral nerve block techniques for dealing with hip fracture, ultrasound-guided femoral nerve (FN) block, fascia iliac compartment (FIC) block, and 3-in-1 FN block are widely used. However, the obturator nerve (ON) and the accessory obturator nerve (AON) have often failed to exhibit adequate blockade from these blocks, the effectiveness of these blocks is only moderate accompanied by decreasing the strength of quadriceps.[9-11]

In 2018 Arango *et al* found out a new regional technique for hip fractures: ultrasound-guided pericapsular nerve group (PENG) block.[12] They concluded that this technique could provide an effective blockade to the articular branches of FN, ON, and AON, with a potential motor-sparing effect. Many studies indicated that the PENG block could provide sufficient analgesia with no to minimal opioid requirements at postoperative 24h.[13-15] A study showed that the patients receiving PENG block experienced better postoperative pain relief coupled with quadriceps strength improvement compared to those receiving FN block.[16] Encouraged by this outcome, we hypothesize that PENG block may provide a better recovery for hip fractures, especially in the elderly patients. Therefore, this randomized, parallel controlled, double-blind trial is set to compare the Quality of Recovery-15 (QoR-15) scores at 24h postoperatively between two groups to investigate whether PENG block enhances recovery in elderly patients after hip fracture surgery.

METHODS AND ANALYSIS

Primary aims

The primary aim of this trial is to investigate whether PENG block effectively enhances recovery in elderly patients after hip fracture surgery.

Secondary aims

The secondary aims are to investigate whether PENG block results in a motor-sparing effect, a reduction in pain score at rest and on movement, a decrease in total morphine consumption and the rescue analgesic, an improvement in the first time of postoperative out-of-bed mobilization, and a decrease in complications.

Trial design

This is a single centered, randomized, parallel controlled, double-blind trial. The study will be conducted at The First Affiliated Hospital of Guangzhou University of Chinese Medicine and has been registered with the Chinese Clinical Trial Registry (ChiCTR2100042341). The methods and results of this study will be reported according to the Standard Protocol Items: Recommendations for Interventional Trials and 2013 statement.[17] The flow diagram for this trial is presented in figure 1.

Eligibility criteria

Recruitment

Elderly patients (≥ 65 years old) with hip fracture who are selected for hip surgery at The First Affiliated Hospital of Guangzhou University of Chinese Medicine will be recruited for this study. Inclusion was initiated in March 2021. The expected study completion date is March 2023.

Inclusion criteria

Patients will be included if they: (1) are cognitively intact; (2) have an American Society of Anesthesiologists physical status (ASA) between I-Ⅲ and (3) have a body mass index (BMI) between 18-30kg/m^2.

Exclusion criteria

Patients will be excluded if they: (1) refuse to participate in the study; (2) have an allergy or contraindication to the drug or anesthetic technique in this study; (3) have dementia; (4) have multiple traumas; (5) have severe deafness and vision problems, communication difficulties; (6) have an infection near the block site; (7) are obese (BMI > 30 kg/m^2) or (8) have clinically significant neurological, cardiovascular, renal, or hepatic disease (ASA Ⅳ-Ⅴ).

Informed consent

According to the inclusion and exclusion criteria， patients will be assessed by members of the research team the day before the surgery. Once patients are eligible, researchers will fully explain the study, including the implications, known adverse effects, any risks in taking part, and constraints of the protocol, to the eligible patients and their families and answer any questions. If patients agree to enroll, written informed consent will be obtained from the participants and their proxies. Participants can choose to withdraw from the trial at any time and for any reason. Permission will be obtained from each patient regarding the use of their data for statistical analysis.

Preoperative management

In accordance with national guideline,[2] patients in both groups will be receiving standard care to accelerate recovery. The pathway includes rapid assessment from the Emergency Department, adequate pain control, assessment of bone health and falls, multidisciplinary management, surgical procedures, and mobilization strategies. The ASA status classification will be evaluated, and preoperative cognitive assessment will be performed by using the Mini-Mental State Examination (MMSE).[18] Opioid use will be avoided except for severe pain. Patients who participate in this study will also avoid the use of premedication.

Intraoperative management

After entering the operating room, continuous electrocardiogram, noninvasive intermittent blood pressure, and pulse oxygen saturation will be monitored. The patients will be given 4 L/min of oxygen through a mask. In order to reduce any pain or anxiety during the nerve blockade, 0.5 μg/kg of fentanyl will be given intravenously.
The blockade for both groups will be performed by the same experienced anesthesiologist. Before local anesthesia, the anesthesiologist will obtain the sequence from a sealed envelope and perform the blockade according to the allocated information. The anesthesia for the surgery will be performed after the block and will be managed by a second anesthesiologist. For both groups, spinal anesthesia will be chosen as the main anesthetic technique and will be provided with 0.5% bupivacaine 1.2 mL to 1.8 mL (6 mg to 9 mg) at the L3-L4 interspace, and the sensory block will be controlled at T8-T10.

Ultrasound-guided pericapsular nerve group block

With patients in a supine position, PENG block will be performed as described by Arango *et al.*[12] The anterior inferior iliac spine, the femoral artery, the pectineus muscle, the iliopubic eminence, the iliopsoas muscle, and tendon will be observed using a curvilinear low-frequency ultrasound probe. The puncture site will be set 0.5-1.0 cm away from the lateral of the ultrasound probe. After 2 ml of 1% lidocaine is injected for local anesthesia, a 22-gauge, 80-mm needle will be inserted carefully in an in-plane approach from lateral to inner. After the tip of the needle is placed the musculofascial plane between the tendon of the psoas muscle anteriorly and the pubic ramus posteriorly, which is between the iliopubic eminence and anterior inferior iliac spine,[19 20] 1mL of 0.9% saline solution will be injected to ensure that the solution will be spread in the plane beneath the iliopsoas muscle. After negative aspiration, a total volume of 20 mL of 0.375% ropivacaine will be slowly injected every 5 mL. The spread of the ropivacaine is in the musculofascial plane towards the iliopubic eminence with the iliopsoas tendon lifted up.[19] The ultrasound view of the fluid spread in the plane will be observed to ensure that the ropivacaine is injected right in the targeted location.

Ultrasound-guided femoral nerve block

With the patients in a supine position, FN block will be performed as described by Marhofer *et al.*[21] A linear high-frequency probe will be used to visualize the femoral artery and the FN. The puncture site will be set 0.5-1.0 cm away from the lateral of the ultrasound probe. After 2 ml of 1% lidocaine is injected for local anesthesia, a 22-gauge, 80-mm needle will be inserted carefully in an in-plane approach from lateral to inner. After the tip of the needle is placed next to the FN, a total volume of 20 mL of 0.375% ropivacaine will be slowly injected after negative aspiration every 5 mL. The ultrasound view of the fluid spread will be observed to ensure that the ropivacaine is injected around the FN.

Postoperative management and follow-up

After surgery, when participants are transferred to the ward, vital signs (heart rate, noninvasive blood pressure, pulse oxygen saturation, and respiratory rate) will be monitored. Over the course of postoperative 48h, a patient controlled intravenous analgesia (PCIA) with morphine will be started when the operation concludes and set to the bolus only mode (bolus 1.0 mg, lockout 6 min, maximum dosage 15mg/4h). All participants will receive 1 g paracetamol every 6h as a part of postoperative multimodal analgesia. In case of nausea or vomiting, 5mg of tropisetron will be intravenously injected.

Outcome measurement

Before a series of clinical-scale evaluations and analgesia are evaluated and recorded by an estimator, who is blinded to the group assignments, patients will first be tested with the MMSE on postoperative Day-1 and Day-2.

The primary outcome measurement of this study will be the QoR-15 scores answered by patients at 24h postoperatively.[22 23] The questionnaire contains 15 items concerning the patient's quality of recovery. Each item is scored on an 11-point scale ranging from 0 to 10, with a total possible score of up to 150 points. The mean value and standard deviation (SD) will be used for descriptive analysis.

The secondary outcomes will include the strength of the quadriceps, the visual analogue scale (VAS) of both resting and dynamic pain, the total morphine consumption, the rescue analgesic, the first time of postoperative out-of-bed mobilization, and any complications. To test the strength of quadriceps, patients will be asked to extend the knee of the affected limb while supporting the knee under the popliteal fossa 30 min after the blockade, and at 6h, 12h, 18h, 24h and 48h postoperatively. The quadriceps strength will be graded to a 6-point scale: 5, normal strength; 4, extension against gravity and light resistance; 3, extension against gravity; 2, extension against gravity eliminated; 1, muscle twitch; 0, paralysis.[24] At the time before and 30 min after the blockade, and at 6h, 12h, 18h, 24h and 48h postoperatively, the pain scores at rest and on movement will be assessed, respectively. After patients have been resting in bed for 15 min, VAS at rest will be assessed. When VAS on movement is assessed, participants will be asked to perform the operative hip flexion to 45 degrees. Using an 11-point numerical rating scale, the VAS ranges from 0 = no pain to 10 = unbearable pain. The total morphine consumption in PCIA and the time of the bolus will be recorded. If the participants do not feel pain relief after injection of morphine from the PCIA, they will receive rescue anesthetic as required by the assessment. The time and the dosage of analgesics in the first 48h will be recorded. A physiotherapist will evaluate the patients' postoperative ability; including the time taken for a patient to get out of bed, and perform physiotherapy exercises. Any postoperative complications, such as pneumonia, deep vein thrombosis, myocardial infarction, cerebrovascular accident, and so on, will be recorded and treated. Additionally, any PENG block complications such as nerve damage, local anesthetic toxicity, and vascular puncture will be recorded. A diagram of participant recruitment and secondary outcomes measurement is shown in table 1.

Randomization and blinding

At the beginning of this study, a randomization sequence will be generated by SAS 9.0 statistical software and assign the participants to either the control group (ultrasound-guided FN block group) or the intervention group (ultrasound-guided PENG block group) at a 1:1 ratio. An independent statistician will conceal the sequence (including allocated group, random numbers, and intervention information) from the researcher, who will assess the subjects, in identical opaque and sealed envelopes.

The effect of the block will be evaluated and recorded by an investigator who is blinded in the block performance analysis.

Sample size estimation

Based on the results of preliminary experiments, the QoR-15 scores (mean difference ± SD) of elderly patients for 24h were 88.25 ± 8.32 in the FN block group and 98.97 ± 10.37 in the PENG block group. Myles *et al*[25] found that the minimal clinically important difference for the QoR-15 is 8.0. Therefore, to detect the effect size (power = 0.8) with the type 1 error of 5% (α=0.05), a dropout rate of 10% and a non-inferiority or superiority margin of 8, a sample size of 92 participants is required. As a result, 46 participants per group will be recruited for this study.

Reporting of adverse events

Participants will be seen daily for the duration of the study. All adverse events and other unintended effects of the trial will be recorded. If any serious complications occur, researchers will be informed immediately, medical practitioners will then take proper measures to ensure the safety of patients. After the treatment, the allocated group of the patient will be revealed, and the evaluation about the correlation between adverse events and intervention will be discussed comprehensively. All details of any serious adverse events will be recorded and reported to the ethics committee.

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

Ethics and declarations

This trial received ethical approval from the Institutional Review Board of the Ethics Committee of The First Affiliated Hospital of Guangzhou University of Chinese Medicine on 15 December 2020 (Reference K2020-110). This study has been registered at the Chinese Clinical Trial Registry (ChiCTR2100042341). The trial will be conducted in accordance with the Declaration of Helsinki 1996, principles of good clinical practice, and the Department of Health Research Governance Framework for Health and Social Care. The researchers will send regular reports about the progress and any changes to this trial to the Institutional Review Board of the Ethics Committee of The First Affiliated Hospital of Guangzhou University of Chinese Medicine. The results of this study will be published in peer-reviewed international journals.

Data management and monitoring

Demographic data and mental assessment data, QoR-15 data and information on pain scores, mobilization assessment data, and information about complications will be collected and input into an electronic database. An independent researcher will guarantee the data quality during the process. All data of outcomes will be input into another independent database and will be double-checked to promote data quality. Any individual privacy information will be deleted to protect confidentiality. After data storage, only researchers will have direct access to the final trial dataset. The progress and safety of this study will be monitored monthly by the data monitoring committee (DMC), which is composed of two independent experts outside the study. The clinical experts will be able to access the unblinded data. The DMC will be able to give suggestions regarding safety, and will also have authority to terminate the trial. The final trial dataset will be managed by The First Affiliated Hospital of Guangzhou University of Chinese Medicine. Accessing the dataset will require the written permission of the corresponding author.

Statistical analysis

All allocated subjects with available data will be analysed. According to the variable type and distribution, data will be presented as mean and SD, frequency and proportion, or median and interquartile range (25th-75th percentile). Based on the $\chi 2$ test or Fisher's exact test, categorical variables will be evaluated. The parametric t-test, the Wilcoxon rank-sum test, or the Kruskal-Wallis test will be used to analyse differences between the two groups in continuous variables. Non-normal distributions will be assessed with the Mann-Whitney U test. To manage missing data, mean completer and regression will be used. A p value of <0.05 will be considered statistically significant, and results will be presented with 95% CIs. Analysis of data will be performed with SPSS software V.21.0 (developed by IBM Corp, Armonk, New York, USA).

Discussion

Hip fracture is often associated with serious pain. Lack of sufficient pain treatment can lead to not only the deceleration of recovery after surgery, but also high risk of cardiovascular adverse events and long-term chronic pain.[4] Because of this, adequate pain treatment is needed in the perioperative period for more effective recovery.

Opioid use could be appropriate for the requirement of pain relief after surgery, so it has been the mainstay of potent analgesia for hip fractures worldwide in the past 20 years.[26-28] Simoni *et al*[29] found that 26.8% of patients redeemed one or more opioid prescriptions before surgery, and 61.8% received opioid therapy postoperatively. However, opioid-related adverse events are more common among the elderly, occurring in 80% of patients. These adverse events, including cognitive impairment and increased fall risk (and in some cases, mortality) seriously delay rehabilitation after surgery. In addition, opioids offer pain relief at rest but are ineffective at addressing pain on movement.

Therefore, to reduce related adverse events and improve patients' experience, neuraxial techniques have been recommended. Consistent evidence has suggested that regional analgesia techniques can reduce pain by providing reasonable, rapid-onset and site-specific analgesia, which is more effective than traditional systemic analgesia.[30] In addition, there is evidence that peripheral nerve block may decrease the incidence of delirium, shorten hospital stays, and reduce morbidity and mortality.[30] Following the development of ultrasound guidance, the success rate of peripheral nerve block has improved.[31] Thus, peripheral nerve block may have an excellent effect on fast-track recovery.

Nowadays, the FN block, FIC block, and 3-in-1 FN block are popular peripheral nerve block techniques. Unfortunately, none of these nerve block techniques are ideal for hip fracture at present. According to multiple anatomical studies, the articular branches of FN, ON, and AON innervate the anterior hip joint, which plays an important role in the innervation of the hip capsule.[32-34] This suggests that they should be the main target of regional analgesia. The three main nerves can be anesthetized by 3-in-1 FN block and FIC block. However, the success rate of the obturator block with 3-in-1 FN block falls between 77-80%, while the rate with FIC block is 88%.[35] So, both FIC block and the 3-in-1 FN block may result in failure to anesthetize ON, and the FN block also cannot anesthetize ON.[35-37] As a result, the effectiveness of these three blocks is moderate. In addition, these three nerve block techniques may produce quadriceps weakness, which could slow mobilization and increase the incidence of falls.[38] Therefore, a new regional analgesia, one that can provide complete analgesia without significant motor dysfunction, should be put forward.

The PENG block, developed by Arango *et al*[12], is a novel peripheral nerve block for patients with hip fracture. When Arango *et al*[12] performed the PENG block in 5 patients, they found that the Numeric Rating Scale (NRS) for rest pain in 4 cases decreased from 4 points or above to 0 points, the reduction of NRS for dynamic pain in all 5 cases was more than 4 points, and the median reduction of pain was 7 points. Over 100 PENG blocks have been performed by Yu *et al*[39] for hip fracture and surgery, and these blocks were also found to be highly effective. Ince *et al*[40] combined PENG and lumbar erector spinae plane block to provide postoperative pain treatment in a 4-year-old child undergoing surgery for congenital hip dysplasia, and the FLACC score in postoperative 24h was less than 1 point without any need for additional analgesics. Recently some studies of PENG block have been published and suggested PENG block could provide effect analgesia with better preservation of motor function comparing with FN block or FIC block.[16 41]

These studies provide promising evidence about the effectiveness of PENG block for hip surgery. Perhaps most impressive is that this approach provides significant dynamic pain control with a motor-sparing effect, which makes the early mobilization possible. PENG block seems to meet the conditions for an ideal peripheral nerve

block for geriatric patients with hip fracture. Thus, this trial is set to test whether PENG block is effective to enhance recovery in elderly patients with hip fracture.

To test the quality of recovery, a variety of measurement tools could be chosen. Traditionally, many clinical observational indexes are used to evaluate the effectiveness and safety of anesthesia in postoperative recovery, but most are focused on the physiological endpoints such as the incidence of complications, the length of hospital stays, the mortality, and so on. Although these indexes are objective and measure important data, evaluations from the patients' points of view are more humanized and are also important to be assessed. So, a patient-rated QoR-15 is suitable. It is a multidimensional measurement of quality of recovery demonstrated by high-quality evidence and includes five dimensions: pain, physical comfort, physical independence, psychological support, and emotional state. Stark *et al*[22] suggested there was no relation between the QoR-15 and patient age, which indicates that the QoR-15 could be used in elderly patients. In addition, according to the positive impact duration of the regional anesthesia, the time-frame of the measurement instrument should be the early postoperative time.[7] As the result, some common assessment, which resulted at postoperative Day-3 or later, may be not ideally suited. For these reasons, the QoR-15 at postoperative 24h was chosen as the primary outcome in this study.

This is a study using a randomized, parallel controlled, double-blind trial to compare QoR-15 between ultrasound-guided FN block and ultrasound-guided PENG block. It also explores the effectiveness and safety of PENG block in elderly patients after hip fracture surgery. The findings of this study may provide a new peripheral nerve analgesia for hip fracture, which could relieve pain without motor dysfunction to accelerate recovery. This will offer clinical evidence for the optimal analgesia method in Enhance Recovery After Surgery pathways for elderly patients with hip fracture.

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Contributions WL, JTW, and QHL conceived of the study, designed the study protocol, and drafted the manuscript. WL and QHL wrote the manuscript. WHM was in charge of coordination and direct implementation. JHL and HYW helped to develop the study measures and analyses. WL, JHL, HYW, and YHL performed the trial. YHO and JTW input the data and guaranteed the data quality. HYW and YHL provided statistical knowledge for the study's initiation. All authors contributed to and approved the final manuscript.

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REFERENCES

1 Fox KMMJ, Hawkes WG, Yu-Yahiro J, *et al.* Loss of bone density and lean body mass after hip fracture. *Osteoporos Int* 2000;11:31–5.

2 National Clinical Guideline Centre: The management of hip fracture in adults. *London: National Clinical Guideline Centre* 2017: Available from www.ncgc.ac.uk.

3 Gerbershagen HJ, Aduckathil S, van Wijck AJ, *et al.* Pain intensity on the first day after surgery: a prospective cohort study comparing 179 surgical procedures. *Anesthesiology* 2013;118:934–44.

4 Morrison RS, Magaziner J, McLaughlin MA, *et al.* The impact of post-operative pain on outcomes following hip fracture. *Pain* 2003;103:303–11.

5 Halaszynski TM. Pain management in the elderly and cognitively impaired patient: the role of regional anesthesia and analgesia. *Curr Opin Anaesthesiol* 2009; 22: 594–9.

6 James R, John A, David E, *et al.* A pre-emptive multimodal pathway featuring peripheral nerve block improves perioperative outcomes after major orthopedic surgery. *Reg Anesth Pain Med* 2008;33:510-7.

7 Ellis TA, Hammoud H, Dela Merced P, *et al.* Multimodal clinical pathway with adductor canal block decreases hospital length of stay, improves pain control, and reduces opioid consumption in total knee arthroplasty patients: a retrospective review. *J Arthroplasty* 2018;33:2440-8.

8 Fabi DW. Multimodal analgesia in the hip fracture patient. *J Orthop Trauma* 2016;30:S6-S11.

9 Unneby A, Svensson O, Gustafson Y, *et al.* Femoral nerve block in a representative sample of elderly people with hip fracture: a randomized controlled trial. *Injury* 2017;48:1542–9.

10 Dickman E, Ayvazyan S, Pearl M, *et al.* Ultrasound-guided fascia iliaca compartment block for hip fractures in the emergency department. *J Emerg Med* 2012;43:692–7.

11 Beaudoin FL, Haran JP, Liebmann O. A comparison of ultrasound-guided three-in-one femoral nerve block versus parenteral opioids alone for analgesia in emergency department patients with hip fractures: a randomized controlled trial. *Acad Emerg Med* 2013;20:584–91.

12 Girón-Arango L, Peng PWH, Chin KJ, *et al.* Pericapsular nerve group (PENG) block for hip fracture. *Reg Anesth Pain Med* 2018;43:859–63.

13 Sandri M, Blasi A, De Blasi RA. PENG block and LIA as a possible anesthesia technique for total hip arthroplasty. *J Anesth* 2020;34:472–5.

14 Fusco P, Di Carlo S, Paladini G, *et al.* Could the combination of PENG block and LIA be a useful analgesic strategy in the treatment of postoperative pain for hip replacement surgery? *Reg Anesth Pain Med* 2019;44:531.

15 Reza PC, Garcia PD, Vazquez MG, *et al.* Pericapsular nerve group block for hip surgery. *Minerva Anestesiol* 2020;86:463–5.

16 Lin DY, Morrison C, Brown B, *et al.* Pericapsular nerve group (PENG) block provides improved short-term analgesia compared with the femoral nerve block in hip fracture surgery: a single-center double-blinded randomized comparative trial. *Reg Anesth Pain Med* 2021;46:398–403.

17 Chan AW, Tetzlaff JM, Gøtzsche PC, *et al.* SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. *BMJ* 2013;346:e7586

18 Girard TD, Thompson JL, Pandharipande PP, *et al.* Clinical phenotypes of delirium during critical illness and severity of subsequent long- term cognitive impairment: a prospective cohort study. *Lancet Respir Med* 2018;6:213–22.

19 Mistry T, Bapurao SK. Gray zone of pericapsular nerve group (PENG) block. *J Clin Anesth* 2019; 58:123-4.

20 Black ND, Chin KJ. Pericapsular nerve group (PENG) block: Comments and practical considerations. *J Clin Anesth* 2019;56:143-4.

21 Marhofer P, Schrogendorfer K, Koinig H, *et al.* Ultrasonographic guidance improves sensory block and onset time of three-in-one blocks. *Anesth Analg* 1997; 85: 854–7.

22 Stark PA, Myles PS, Burke JA, *et al.* Development and psychometric evaluation of a postoperative quality of recovery score: the QoR-15. *Anesthesiology* 2013;118:1332-40.

23 Bu XS, Jing Z, Zuo YX. Validation of the Chinese Version of the Quality of Recovery-15 Score and Its Comparison with the Post-Operative Quality Recovery Scale. *Patient* 2016;9:251–9.

24 Matthew, Dean, Edwards, *et al*. Effect of Adductor Canal Block Versus Femoral Nerve Block on Quadriceps Strength, Function, and Postoperative Pain After Anterior Cruciate Ligament Reconstruction: A Systematic Review of Level 1 Studies. *Am J Sports Med* 2020;48:2305-13.

25 Myles PS, Myles DB, Galagher W, *et al.* Minimal clinically important difference for three quality of recovery scales. *Anesthesiology* 2016;125:39–45.

26 Gomes T, Tadrous M, Mamdani MM, *et al.* The burden of opioid-related mortality in the United States. *JAMA Network Open* 2018;1:e180217.

27 Wetzel M, Hockenberry J, Raval MV. Interventions for postsurgical opioid prescribing: a systematic review. *JAMA Surg* 2018;153:948-54.

28 Birke H, Ekholm O, Sjøgren P, *et al.* Long-term opioid therapy in Denmark: a disappointing journey. *Eur J Pain* 2017;21:1516–27.

29 Simoni AH, Nikolajsen L, Olesen AE, *et al.* Opioid use after hip fracture surgery: a Danish nationwide cohort study from 2005 to 2015. *Eur J Pain* 2019;23:1309-17.

30 Scurrah A, Shiner CT, Stevens JA, *et al.* Regional nerve blockade for early analgesic management of elderly patients with hip fracture - a narrative review. *Anaesthesia* 2017;73:769–83.

31 Reid N, Stella J, Ryan M, *et al*. Use of ultrasound to facilitate accurate femoral nerve block in the emergency department. *Emerg Med Australas* 2009;21:124–30.

32 Short AJ, Barnett JJG, Gofeld M, *et al.* Anatomic study of innervation of the anterior hip capsule：implication for image-guided intervention. *Reg Anesth Pain Med* 2018;43:186-92.

33 Birnbaum K , Prescher A , Hessler S , *et al.* The sensory innervation of the hip joint - an anatomical study. *Surg Radiol Anat* 1997;19:371-5.

34 Gerhardt M, Johnson K, Atkinson R, *et al.* Characterisation and classification of the neural anatomy in the human hip joint. *Hip Int* 2012;22:75–81.

35 Ali AM, Tahoun HM, Ahmed AA, *et al.* Comparative study between the analgesic efficacies of nerve stimulator-guided 3-in-1 block, ultrasonographic-guided 3-in-1 block and posterior approach lumbar plexus block following total hip arthroplasty. *Egyptian J Anaesth* 2003;19:39–43.

36 Dolan J, Williams A, Murney E , *et al.* Ultrasound guided fascia iliaca block: a comparison with the loss of resistance technique. *Reg Anesth Pain Med* 2008;33:526-31.

37 Swenson JD, Davis JJ, Stream JO, *et al.* Local anesthetic injection deep to the fascia iliaca at the level of the inguinal ligament: the pattern of distribution and effects on the obturator nerve. *J Clin Anesth* 2015;27:652-7.

38 Kuang M, Ma J, Fu L, *et al.* Is Adductor Canal Block Better Than Femoral Nerve Block in Primary Total Knee Arthroplasty? A GRADE Analysis of the Evidence Through a Systematic Review and Meta-Analysis. *J Arthroplasty* 2017;32:3238–48.

39 Yu HC, Moser JJ, Chu AY, *et al.* Inadvertent quadriceps weakness following the pericapsular nerve group (PENG) block. *Reg Anesth Pain Med* 2019;44:611–3.

40 Ince I, Kilicaslan A, Kutlu E, *et al.* Combined pericapsular nerve block(PENG) and lumbar erector spinae plane(ESP)

blockfor congenital hip dislocation surgery. *J Clin Anesth* 2020;61:109671.

41 Aliste J, Layera S, Bravo D, *et al*. Randomized comparison between pericapsular nerve group (PENG) block and suprainguinal fascia iliaca block for total hip arthroplasty. *Reg Anesth Pain Med* 2021;46:874-8.

Table 1 Trial process chart

Items	The time before surgery	30 min After block	Postoperative 6h	Postoperative 12h	Postoperative 18h	Postoperative 24h	Postoperative 48h
Inclusion criteria	×						
Exclusion criteria	×						
Informed consent	×						
Randomization and allocation	×						
The rest pain score	×	×	×	×	×	×	×
The dynamic pain score	×	×	×	×	×	×	×
The strength of quadriceps		×	×	×	×	×	×
The consumption morphine			×	×	×	×	×
The rescue analgesic use			×	×	×	×	×
The time of the bolus			×	×	×	×	×
The time of bolus pressing during the lockout time			×	×	×	×	×
The first out-of-bed time			×	×	×	×	×
The postoperative complications			×	×	×	×	×
others	×	×	×	×	×	×	×

Figure 1 The flow diagram for this trial. ASA: American Society of Anesthesiologists class; MMSE: Mini- Mental State Examination; VAS: Visual Analogue Scale; PENG: Pericapsular nerve group; FN: Femoral nerve; PCIA: Patient controlled intravenous analgesia; QoR-15: Quality of Recovery-15.

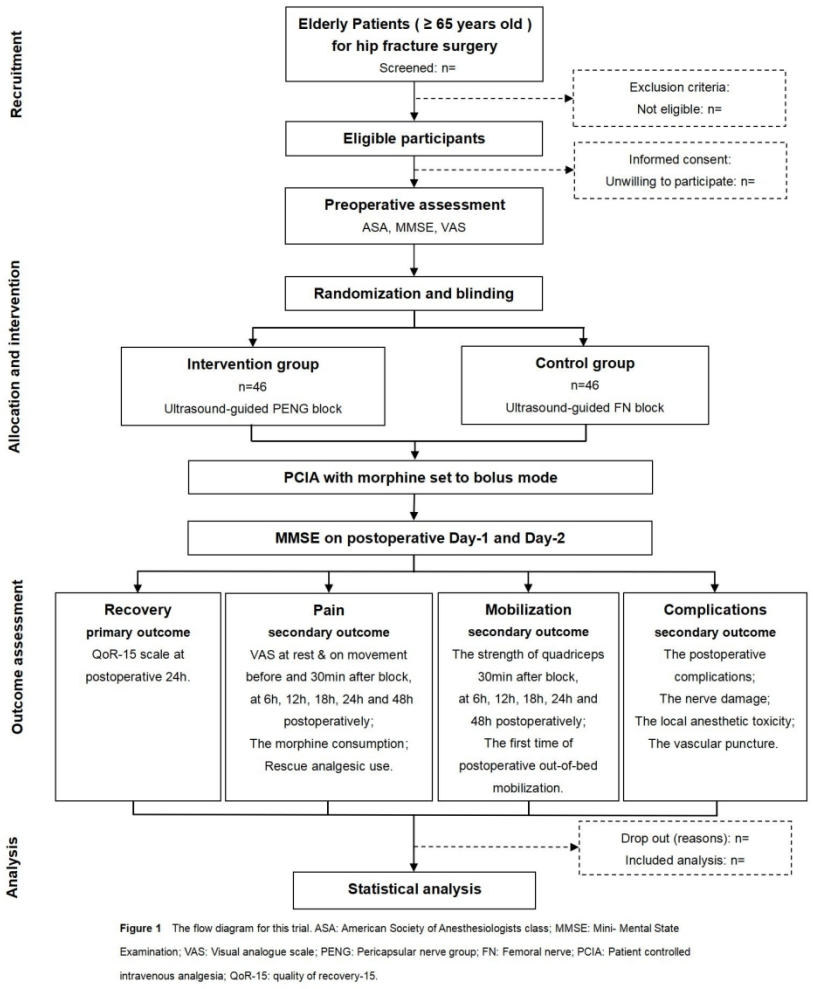

Figure 1 The flow diagram for this trial. ASA: American Society of Anesthesiologists class; MMSE: Mini- Mental State Examination; VAS: Visual analogue scale; PENG: Pericapsular nerve group; FN: Femoral nerve; PCIA: Patient controlled intravenous analgesia; QoR-15: quality of recovery-15.

Figure 1

209x296mm (192 x 192 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

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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.

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

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	P1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	P1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	P1
Protocol version	#3	Date and version identifier	P1
Funding	#4	Sources and types of financial, material, and other support	P8
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	P1, P8

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	N/A
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	N/A
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)	P6
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	P2
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	P2
Objectives	#7	Specific objectives or hypotheses	P2-P3
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)	P3 P5-P6
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be	P3

		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)	P3-P4
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	P4- P5
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)	P4- P6
Interventions: adherence	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	P4- P5
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	P3
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	P4-P5
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)	P5 Figure 1
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	P5
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	P3

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	P5
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	P5
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	P4-P5
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	P4-P5
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	P5-P6
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, if not in the protocol	P4-P5 P7-P8

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	P6
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	P6
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	P6
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	P6
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)	P6
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	P6
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	P6
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	P5-P6
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	P6

Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	P1,P6
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)	P6
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	P3
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	P6
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	P8
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	P6,P9
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	N/A
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, reporting in results databases, or other data sharing arrangements), including any publication restrictions	P9
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	P8

Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A

Appendices

Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	P3
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