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Complete List of Authors:	zhang, junfeng; Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Department of Anesthesiology wang, xiaofeng; Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Department of Anesthesiology zhang, hui; Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Department of Anesthesiology shu, zhuolin; Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Department of Anesthesiology jiang, wei; Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Department of Anesthesiology
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Comparison of combined lumbar and sacral plexus block with sedation versus general endotracheal anesthesia on postoperative outcomes in elderly patients undergoing hip fracture surgery: study protocol for a prospective, multicenter, randomized controlled trial

Junfeng Zhang[#], Xiaofeng Wang[#], Hui Zhang, Zhuolin Shu, Wei Jiang*

Department of Anesthesiology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai 200233, China

*Corresponding author: Wei Jiang MD, PhD. Address: 600 Yishan Road, Shanghai 200233, China. Tel: +86 21 64369181 ext. 58328; Fax: +86 21 64369181 ext. 58330. E-mail: jiangw@sjtu.edu.cn.

[#]These authors contributed equally to this work.

Email address of all authors:

JZ: Department of Anesthesiology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Email: zhangjunfeng@sjtu.edu.cn

XW: Department of Anesthesiology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Email: 240483680@qq.com

HZ: Department of Anesthesiology, Shanghai Jiao Tong University Affiliated Sixth

People's Hospital, Email: zhanghui12179@163.com

ZS: Department of Anesthesiology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Email:5883434@qq.com

WJ: Department of Anesthesiology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Email: jiangw@sjtu.edu.cn

ABSTRACT

Introduction Hip fracture in elderly people is a global public health problem, with substantial associated mortality and disability. Nearly all patients with hip fracture undergo surgical treatment, but choice of anesthesia for hip fracture surgery in elderly patients is still inconclusive. Ultrasound-guided combined lumbar and sacral plexus block has been widely used in hip fracture surgery in recent years, especially for some high-risk patients. However, it is not clear whether it can improve the postoperative prognosis of elderly patients with hip fracture.

Method and analysis This research project is a two-arm, parallel, multicenter, prospective randomized controlled trail. 1086 aged 77 and older scheduled for hip fracture surgery in five clinical trial centers will be randomized in a 1:1 ratio to receive either combined lumbar and sacral plexus block plus sedation or general endotracheal anesthesia. The primary outcome will be the postoperative 1-year all-cause mortality. The secondary outcomes will be the incidence of postoperative complications, high-sensitivity cardiac troponin, postoperative acute pain scores, early mobility after surgery, postoperative delirium, satisfaction with anesthesia, length of stay in ICU and hospital, and cost-effective outcomes. Assessments will be conducted in four steps: preoperative, intraoperative and in-hospital data collection and post-discharge telephone follow-up.

Ethics and dissemination This study has been supported by Shanghai Municipal Commission of Health and Family Planning Foundation for Key Developing Disciplines (2015ZB0103) and approved by the Ethics Committee of Shanghai Sixth

People's Hospital [No: 2016-28-(2)]. At the time of manuscript submission, the protocol version is v1.6 (March 2nd, 2018) with one subsequent approved amendment. Results will be disseminated via an international peer-reviewed publication.

Trial registration number NCT03318133.

Key words Elderly; Hip fracture; Lumbar plexus block; Sacral plexus block; General anesthesia

Strengths and limitations of this study

- This study will be the first prospective, multicenter, randomized controlled clinical trial to investigate the effect of the two anesthesia techniques on long-term prognostic indicators in elderly patients with hip fracture.
- The results of this study will help elucidate whether ultrasound-guided CLSB with sedative anesthesia can be safely used in hip fracture surgery and reduce the incidence of perioperative complications and improve long-term prognosis in elderly patients.
- Our study results will be limited to a Chinese population, and further studies on other ethnic backgrounds will be required.

1.BACKGROUND

Hip fracture is a global public health problem with an incidence of more than 1.6 million worldwide each year [1]. Owing to the global increase of the population aged 65 years and over, the total number of hip fracture is expected to surpass 6 million by 2050 [2]. While early surgery is the most effective treatment method, the postoperative

mortality and disability rates are still high [3]. Patients with hip fracture often have concurrent organ dysfunction, making anesthesia extremely risky, which is mainly associated with the high rates of pulmonary and cardiovascular complications [4, 5]. Seeking appropriate anesthesia technique is in urgent need to ensure that these patients can safely and effectively get through the perioperative period.

Most studies assessing the relationship between anesthesia technique and outcomes mainly focus on the comparisons between neuraxial anesthesia (including spinal and epidural anesthesia) and general endotracheal anesthesia. A previous study has shown that neuraxial anesthesia can avoid endotracheal intubation, reduce intraoperative blood loss and improve postoperative analgesia, while general endotracheal anesthesia can maintain a more stable hemodynamic state[6]. Some other investigations have shown that neuraxial anesthesia for hip fracture can reduce postoperative morbidity[7, 8], but two recent large-sample size observational studies deemed that neuraxial anesthesia could not significantly improve the prognosis of patients [9, 10]. However, all of the above are retrospective observational studies, in which anesthesiologists might have selected the anesthesia technique based on their practice style and a variety of patient-related factors. For example, patients with coagulation dysfunction would have contraindication to neuraxial anesthesia and must receive general anesthesia. Neuraxial anesthesia is thought to be less postoperative complications, so elderly or critically ill patients might be more likely to receive neuraxial anesthesia [11], rather than being randomly assigned to different anesthesia groups. Therefore, there could be selective bias that affected the clinical significance

of those results. In addition to general anesthesia and neuraxial anesthesia, ultrasound-guided lumbar and sacral plexus block has been widely used in hip fracture surgeries in recent years, especially for some high-risk patients with cardiopulmonary dysfunction [12-14]. Compared with neuraxial anesthesia, combined lumbar and sacral plexus block is associated with less sympathetic block and better cardiovascular function stability. In addition, combined lumbar and sacral plexus block plus sedation could avoid endotracheal intubation and thereby might reduce the complications related to the general endotracheal anesthesia. A recent small sample size retrospective study [14] compared the effect of general endotracheal anesthesia, neuraxial anesthesia and lumbar and sacral plexus block on the prognosis of patients with hip fracture, and the results showed that neuraxial anesthesia and lumbar and sacral plexus block anesthesia could reduce the total mortality, and there was no significant difference between neuraxial anesthesia and lumbar and sacral plexus block. But the number of elderly and high-ASA-grade patients in the lumbar and sacral plexus block group was significantly greater than that in the neuraxial anesthesia group, suggesting that when comparing the effect of these two anesthetic methods in similar conditions, combined lumbar and sacral plexus block might have more advantages. However, it is not clear whether ultrasound-guided combined lumbar and sacral plexus block with sedation can improve outcomes of elderly patients with hip fracture.

This paper describes the design of a prospective, multicenter, parallel, randomized controlled clinical trial to assess the effect of ultrasound-guided combined

lumbar and sacral plexus block plus sedation versus general endotracheal anesthesia on the postoperative outcome in elderly patients with hip fracture.

2. METHODS AND ANALYSIS

2.1. Study design

This will be a two-arm, parallel, multicenter, prospective, randomized controlled trial and the design of this study protocol has referred to the SPIRIT 2013 guideline [15, 16].

2.2. Study location

The study will be conducted in five teaching hospitals including Shang Sixth People's Hospital (Shanghai, China), Beijing Chaoyang Hospital (Beijing, China), Beijing Jishuitan Hospital (Beijing, China), First Affiliated Hospital of Wenzhou Medical University (Wenzhou, China), and Foshan Hospital of Traditional Chinese Medicine (Foshan, China).

2.3. Study population

Elderly patients scheduled for hip fracture surgery will be recruited voluntarily according to the inclusion and exclusion criteria below. All included patients are suitable for either general endotracheal anesthesia or combined lumbar and sacral plexus block plus sedation, which will not bring tendency to choose a specific type of anesthesia.

2.3.1. Inclusion criteria:

- Age ≥77 years old;
- First unilateral surgery for hip fracture including femoral neck, intertrochanteric

or subtrochanteric fracture;

- Patient with planned hip fracture surgery within 24-72 h;
- Patient without peripheral nerve block within 24 h prior to surgery;
- The ability to receive written informed consent from the patient or patient's legal representative.

2.3.2. **Exclusion criteria:**

- Refuse to participate;
- Unable to perform nerve block;
- Multiple trauma, multiple fractures or other fractures outside the inclusion criteria, such as pathological fractures, pelvic fractures, femur fractures;
- Prosthetic fracture;
- Scheduled for bilateral hip fracture surgery;
- Usage of bone-cement fixation in the surgery;
- With recent cerebral stroke (<3 months);
- Combined with active heart disease (unstable angina, acute myocardial infarction, recent myocardial infarction; decompensated heart failure; symptomatic arrhythmia; severe mitral or aortic stenotic heart disease);
- Patient with known severe lung and/or airway disease, acute respiratory failure, acute pulmonary infection, and acute attack of bronchial asthma;
- Current enrolment in another clinical trial;
- Contraindication for general endotracheal anesthesia(drug allergies to general anesthesia, difficult airway);

- Contraindication for lumbar and sacral plexus block(infection at the site of needle insertion, coagulopathy, allergy to local anesthetics).

2.4. Interventions

Eligible patients will be randomly assigned into either CLSB group receiving combined lumbar and sacral plexus block plus sedation or GA group receiving general anesthesia with endotracheal intubation (Figure 1). Standard anesthetic and surgical methods will be applied to ensure the consistency of treatment in the participating centers.

Figure legend

Fig. 1 CONSORT flowchart designed for subject enrollment(supplementary file)

In the CLSB group (combined lumbar and sacral plexus block with sedative anesthesia), the procedures will be performed as followed.

- Peripheral venous access for fluid infusion will be established;
- In the lateral decubitus position with the operated side uppermost, ultrasound-guided lumbar plexus block (L_{2-3} or/and L_{3-4} vertebral space level, 0.375% ropivacaine 25ml) will be performed, followed by sacral plexus block (0.375 % ropivacaine 20ml);
- 2.4.3. Radial arterial catheterization under local lidocaine anesthesia and arterial blood pressure monitoring will be performed. Blockade effectiveness will be evaluated 30 minutes after nerve block;
- After confirmation of satisfactory blockade, target-controlled infusion of propofol

will be used to maintain Ramsay sedation score between 5-6 points. $P_{ET}CO_2$ will be monitored through nasopharyngeal airway. Small-dose sufentanil (1-5μg each time) will be titrated to maintain spontaneous breathing.

- Experienced and qualified anesthesiologist will be designated to perform lumbar and sacral plexus block in order to ensure effective blockade. The intervention will be discontinued for a given patient and convert to general endotracheal anesthesia if the satisfactory blockade is not acquired. Patients will not be included for analysis if the surgical procedure changes during the operation.

In the GA group, the procedures will be performed as followed.

- Peripheral venous access for fluid infusion will be established;
- Radial arterial catheterization under local lidocaine anesthesia and arterial blood pressure monitoring will be conducted;
- Anesthesia will be induced with propofol (1.5-3mg/kg), cis-atracurium(0.1-0.15mg/kg), and sufentanil(0.2-0.6μg/kg) for tracheal intubation. Mechanical ventilation will be performed to maintain normal $P_{ET}CO_2$.
- Sevoflurane, propofol and sufentanil will be used to maintain anesthesia during surgery, while cis-atracurium will be added as needed.

During surgery, fluid infusion and blood transfusion will be used to maintain stable hemodynamics. Perioperative arterial pressure lower than 30% of the baseline will be defined as hypotension, upon which ephedrine or phenylephrine will be administrated. The type and dosage of infusion depends on anesthesiologist's experience. Blood transfusion will be given according to blood loss and Hb level

(80-100g/L) [17]. Following surgery, patients will be sent to the postanesthesia care unit (PACU) and then transferred to orthopedic ward or ICU according to the local procedures of each clinical centre. Postoperative analgesia can be administrated with regard to the routine clinical practice of each trial site, aiming to maintain a VAS pain score ≤3.

To improve adherence to intervention protocols, fixed protocols will be used and relevant staff will be trained.

2.5. Endpoints

2.5.1. Primary endpoint

Postoperative 1-year all-cause mortality (follow-up time points are set as 1 month, 3 months, 6 months and 1 year after surgery);

2.5.2. Secondary endpoints

2.5.2.1. Duration of surgery;

2.5.2.2. Occurrence of intraoperative complications, including:

- Intraoperative hypotension and vasopressor dosage;
- Intraoperative arrhythmia, myocardial ischemia, myocardial infarction, massive hemorrhage, pulmonary embolism and hypoxemia;
- Intraoperative blood loss and blood transfusion volume;

2.5.2.3. High-sensitivity cardiac troponin T(hs-cTnT), measured on 1 day before surgery,1 and 3 days after surgery;

2.5.2.4. MMSE assessed on 1 day before surgery;

2.5.2.5. Early mobility after surgery;

2.5.2.6. Incidence of various complications and CCI during hospitalization after surgery;

2.5.2.7. Postoperative analgesic effectiveness within two days after the surgery;

2.5.2.8. Incidence of delirium on 1, 2 and 3 days after surgery, diagnosed by CAM-CR;

2.5.2.9. SOFA, assessed on 1 day before surgery,1 and 3 after surgery;

2.5.2.10. Length of stay in ICU and hospital;

2.5.3. Other observational variables:

2.5.3.1. Satisfaction with anesthesia care on day 3 after surgery.

2.5.3.2. Economic parameters including total cost in hospital and expenditure for anesthesia;

2.5.3.3. Functional recovery on day 30 after discharge and surgery, evaluated by Barthel Activities of Daily Living Index;

2.5.3.4. Post-discharge destination, and incidence of complications and adverse events.

2.6. Participant timeline

For a given participant, assessment will be performed one day prior to surgery and again on the day of surgery to confirm whether qualified for enrollment. Randomization will perform on the day of surgery. And then intervention will be performed. The patients will be followed up 1, 2 and 3 days after surgery and on the day of discharge. Telephone follow-up will be conducted at 1, 3, 6 and 12 months after surgery.

2.7. Power and Sample Size Calculation

We estimate the sample size under the assumption of the validity of the proportional-hazards regression model [18, 19]. We take significance level 0.05 and power 0.80. Patients will be randomly assigned to one of the two anesthesia groups in five different centers (hospitals). The total number of patients needed for this study is 868 (with 434 patients in each of the two groups). With that many patients, we can ensure a power of 0.8 with level of significance 0.05 when the mortality rate of 55% for the GA group and a decrease of mortality rate for the GLSB group as low as 15%. In this study, only patients with age 77 years or older will be included, so we expect the actual mortality rate of the GA group will be higher than 55% [14]. When the mortality rate of the GA group is only 45%, the above calculated sample size can still detect a 20% improvement in the CLSB group with the power of at least 0.80. In consideration of the possible lost to follow up, we add an additional 20% to the above calculated sample size. So the total number of patients needed for this study is 1086.

2.8. Randomization and blinding

Upon the receipt of informed consents, patients will be randomly assigned to the two groups in any one of the five centers. Sequentially numbered sealed opaque envelops with group allocation inside altered anesthetist to use CLSB or GA. The R program (other software packages) will be used to generate randomization with a 1:1 allocation stratified by the treatment hospital by variable block algorithm with random blocks of size four, six or eight. The envelopes will be placed in the patient's chart before the start of each procedure by a doctor of the research team. The research staff

who will interview patients postoperatively are blinded for the allocated treatment. The statistician will be blinded. A spreadsheet linking the patient number and name will be password protected and kept on a research computer. The blind can be lift upon the patient's request at the end of the follow up. The recruitment will stop when the total number of patients reaches 1086. The subjects and intervention performers (anesthesiologists) know the grouping, but the follow-up personnel and statistical analysts do not know the randomized grouping and intervention.

2.9. Data collection and management

Data will be collected in four steps: preoperative, intraoperative and in-hospital data collection and post-discharge telephone follow-up.

2.9.1. Preoperative data:

2.9.1.1. Basic information including name, admission number, height, weight, gender, age, blood pressure, heart rate and ASA grade.

2.9.1.2. Preoperative information including diagnosis, type of surgery, type and dosage of anticoagulants, and days passed until surgery.

2.9.1.3. Preoperative complications and medication related to cardiovascular disease, stroke, respiratory disease, kidney disease, diabetes, Parkinson's disease, and deep venous thrombosis of lower extremity if any.

2.9.1.4. Preoperative examination results including blood gas analysis, ECG, echocardiography, blood routine testing, liver and kidney function testing, coagulation testing (D-dimer), Pro-BNP, hs-cTnT, lower extremity vascular ultrasonography.

2.9.1.5. Preoperative evaluation results including MMSE, CAM-CR, SOFA and

Barthel Index.

2.9.2. Intraoperative data

2.9.2.1. Duration of surgery, incidence of intraoperative hypotension, and vasoactive drug dosage.

2.9.2.2. Intraoperative blood loss, blood transfusion volume, and intraoperative fluid infusion volume.

2.9.2.3. Intraoperative arrhythmia (sinus bradycardia, sinus tachycardia, ventricular arrhythmia, atrial arrhythmia, etc.), myocardial ischemia, and myocardial infarction,.

2.9.2.4. Intraoperative complications: massive hemorrhage, pulmonary embolism, allergic reaction, hypoxemia, bronchospasm, gastric reflux and aspiration.

2.9.2.5. Intraoperative convertion of anesthesia and the relevant causes.

2.9.3. In-hospital data

2.9.3.1. Postoperative complications including incidence and severity of various complications and the CCI [20] value at discharge. Complications were assessed and graded using the Clavien-Dindo classification. CCI will be derived from these features at discharge, using the CCI calculator available online (www.assessurgery.com). Complications include:

- Myocardial ischemia, myocardial infarction, heart failure, arrhythmia;
- Pulmonary infection, respiratory failure, pulmonary embolism;
- Postoperative delirium;
- Cerebral ischemia, cerebrovascular accident;
- Renal failure, urinary retention;

- Regurgitation and pulmonary aspiration;
- Postoperative nausea and vomiting (PONV);
- Postoperative bleeding and 24h postoperative drainage volume;
- Reoperation.

2.9.3.2. The intensity of postoperative pain at rest and on movement will be assessed with Visual Analogue Scale (VAS) (0 no pain, 10 worst possible pain) at 24 and 48 hours after surgery.

2.9.3.3. Earlier mobilization and postoperative hip rehabilitation: the daily degree of maximal hip flexion and abduction will be recorded [21]. The day after surgery, all 2 groups will start an identical physical therapy regimen. The patients will perform passive and active hip flexion and abduction exercises twice daily. Patients will be encouraged to get out of bed as soon as possible and try ambulation with a walker. The maximal degree of hip flexion and abduction tolerated by each patient will be recorded for three days. The day of first ambulation will be also recorded for each group.

2.9.3.4. SOFA [22] will be evaluated on 1 and 3 day after surgery.

2.9.3.5. CAM-CR will be evaluated on 1, 2 and 3 day after surgery [23].

2.9.3.6. Length of ICU stay, length of hospital stay, total hospitalization cost, and expenditure for anesthesia.

2.9.3.7. Satisfaction with anesthesia care will be assessed on postoperative day 3 or the day of discharge (whichever occurs first) via the Bauer Patient Satisfaction Questionnaire [24].

2.9.4. Post-discharge follow-up data

2.9.4.1. Telephone follow-up will be performed on 1, 3, 6 and 12 months after surgery to collect the following information.

- Discharge destinations. Disposition status after discharge will be classified as follows: dead, nursing home (e.g., skilled nursing facility, intermediate care facility, extended care facility, nursing home), community dwelling (e.g., home alone, home with others), or other.
- Dead or not, specific cause and time.
- Incidence of complications and adverse events: heart, lungs, brain, liver, kidney, four limbs, hospitalization, etc.

2.9.4.2. Barthel Index for evaluation of functional recovery will be collected on day 30 after surgery.

Preoperative, intraoperative and in-hospital data will be collected from the electronic medical record, monitor machines and relevant manual records by one of the research staff. Telephone follow-up will be conducted by the research team. Data will be securely managed by an independent contract research organization (Shanghai Ruihui Biotech Co., Ltd, Shanghai). Data monitoring will be conducted by an independent third party, who will direct safety oversight and convene a meeting to review adverse events at 25%, 50% and 75% of enrolment or earlier if so needed. Sites will report any related adverse events to the Ethics Committee.

2.10. Statistical analysis

Demographics information will be compared for patients of the two groups to

ensure the data are balanced. Student t-test will be used for quantitative variables such as age, delay in surgery and heart rate, blood pressure. Chi-square test will be used for categorical variables such as Sex, ASA classification grades. The intensity pain VAS scores will be analyzed using repeated measure ANOVA. The effects of different covariates on the mortality rates measured at 1month, 3 months, 6 months and 12 months will be assessed using a logistic regression model. Logistic regression or ordinary multiple regression method will also be used to assess the effects of the covariate on the secondary and other outcomes as well. The proportional-hazards regression model will be used to compare the survival times of the patients in the two groups and to assess the effects of the covariates.

2.11. Access to data

During the study, data will be stored in a password-protected system and can be accessed by the research staff who sign the confidential disclosure agreements. Data without patient identification will be publicly accessible after the study.

2.12. Confidentiality

Each participant will be given an identification number and referred by the identification number throughout the study and in all study-related information. Those information will be securely stored in a password-protected access system provided by a local supplier. Relevant paper records will be stored in a locked cabinet in an access-controlled room. All records containing any patients' personal identifiers will be separately stored similarly as above.

2.13. Trial status

At the time of manuscript submission, the study is in the preparation phase for recruitment.

3. DISCUSSION

Choice of anesthesia for hip fracture surgery in elderly patients is still inconclusive. General anesthesia with endotracheal intubation is a common procedure for hip fracture surgery, with advantages of wide indications and maintaining relatively stable hemodynamics. Compared with general endotracheal anesthesia, neuraxial anesthesia avoids endotracheal intubation. But vertebral degeneration and anatomical abnormalities in elderly patients often make neuraxial anesthesia puncture difficult, and most of these patients are taking anticoagulants, which are the contraindication of neuraxial anesthesia. So the neuraxial anesthesia has limitations in application for the elderly patient. The principle for anesthesia selection is to reduce or avoid the effect of anesthesia on systemic and vital organ functions as much as possible when meeting the needs of surgery. Previous lumbar and sacral plexus block depends on blind puncture technique and cannot ensure the clinical effectiveness. However, ultrasound visualization technology has promoted the wide application of lumbar and sacral plexus block. Combined lumbar and sacral plexus block with sedative anesthesia has gradually become alternative approach for hip fracture surgery in elderly patients, and this anesthetic technique has been massively applied in our department and achieved satisfactory clinical results in recent years, but there is few reliable clinical evidence on whether it can be safely used for hip fracture surgery in elderly patients and improve the short-term or long-term prognosis. Thus, we have

designed this trial protocol to illustrate the clinical value of combined lumbar and sacral plexus block with sedative anesthesia in elderly patients undergoing hip fracture surgery. In this study, we will observe the effect of the two anesthetic methods (general endotracheal anesthesia or combined lumbar and sacral plexus block plus sedation on the early prognostic indicators in elderly patients with hip fracture, including postoperative complications, postoperative analgesic effect, postoperative early mobility, postoperative delirium, patient's satisfaction to anesthesia and length of stay in ICU and hospital. This study will be the first prospective, multicenter, randomized controlled clinical trial to investigate the effect of the two anesthesia techniques on long-term prognostic indicators in elderly patients with hip fracture, including postoperative 1-year all-cause mortality and incidence of complications and adverse events. The results of this study will help elucidate whether ultrasound-guided combined lumbar and sacral plexus block with sedative anesthesia can be safely used in hip fracture surgery in elderly patients and can reduce the incidence of perioperative complications and improve long-term prognosis, so as to solve the troubling clinical problem and provide a theoretical basis for elderly patients undergoing hip fracture surgery to choose the best anesthetic method.

Abbreviations

ASA: American Society of Anesthesiologists; GA: General anesthesia; CLSB: Combined lumbar plexus and sacral plexus block; PACU: Postanesthesia care unit; ICU: Intensive care unit; CCI：Comprehensive complication index; SOFA: Sequential

organ failure assessment; CAM-CR: The confusion assessment method Chinese reversion; MMSE: Mini-mental state examination; ECG: echocardiography; Pro-BNP: Pro brain natriuretic peptide; hs-cTnT: High-sensitivity cardiac troponin T; PONV: Postoperative nausea and vomiting; VAS: Visual analog scale

Contributors JZ and WJ designed the study and wrote the protocol. HZ and XW performed statistical analysis. HZ, XW and ZS were involved in protocol conception and design and manuscript revision. WJ is the principal investigator of this clinical trial. All authors read and approved the final version of the manuscript.

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Data sharing statement No additional data are available.

Patient consent Obtained.

Competing interests None declared.

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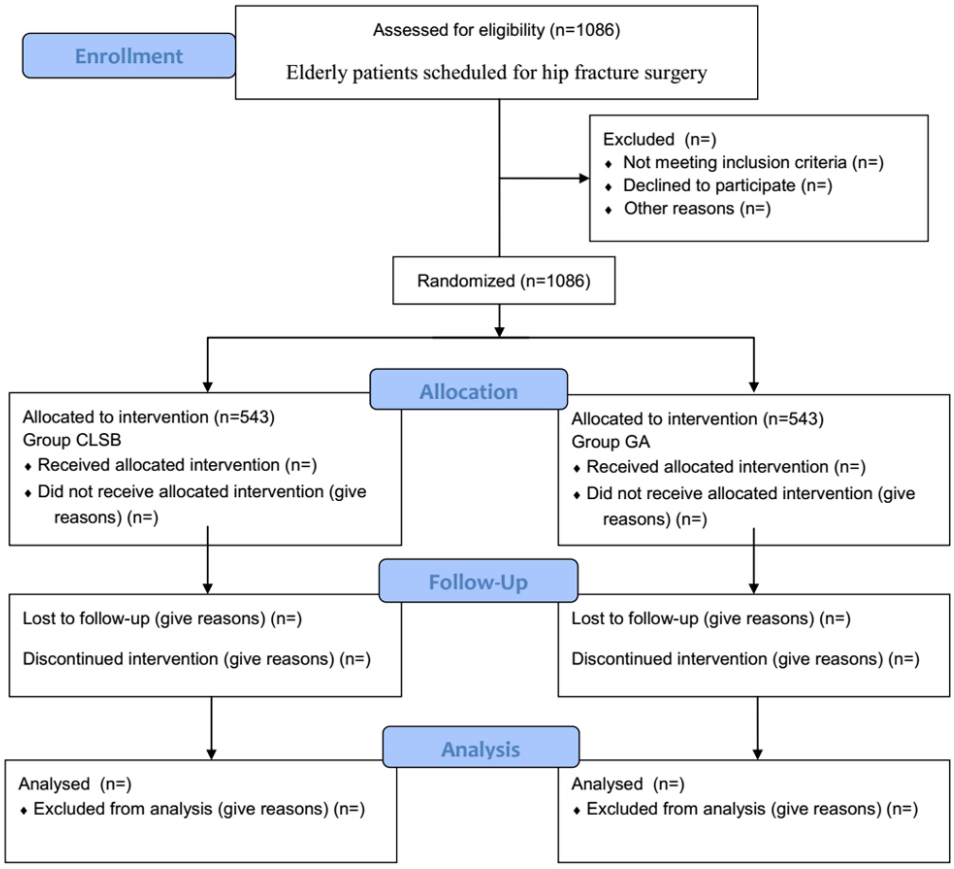

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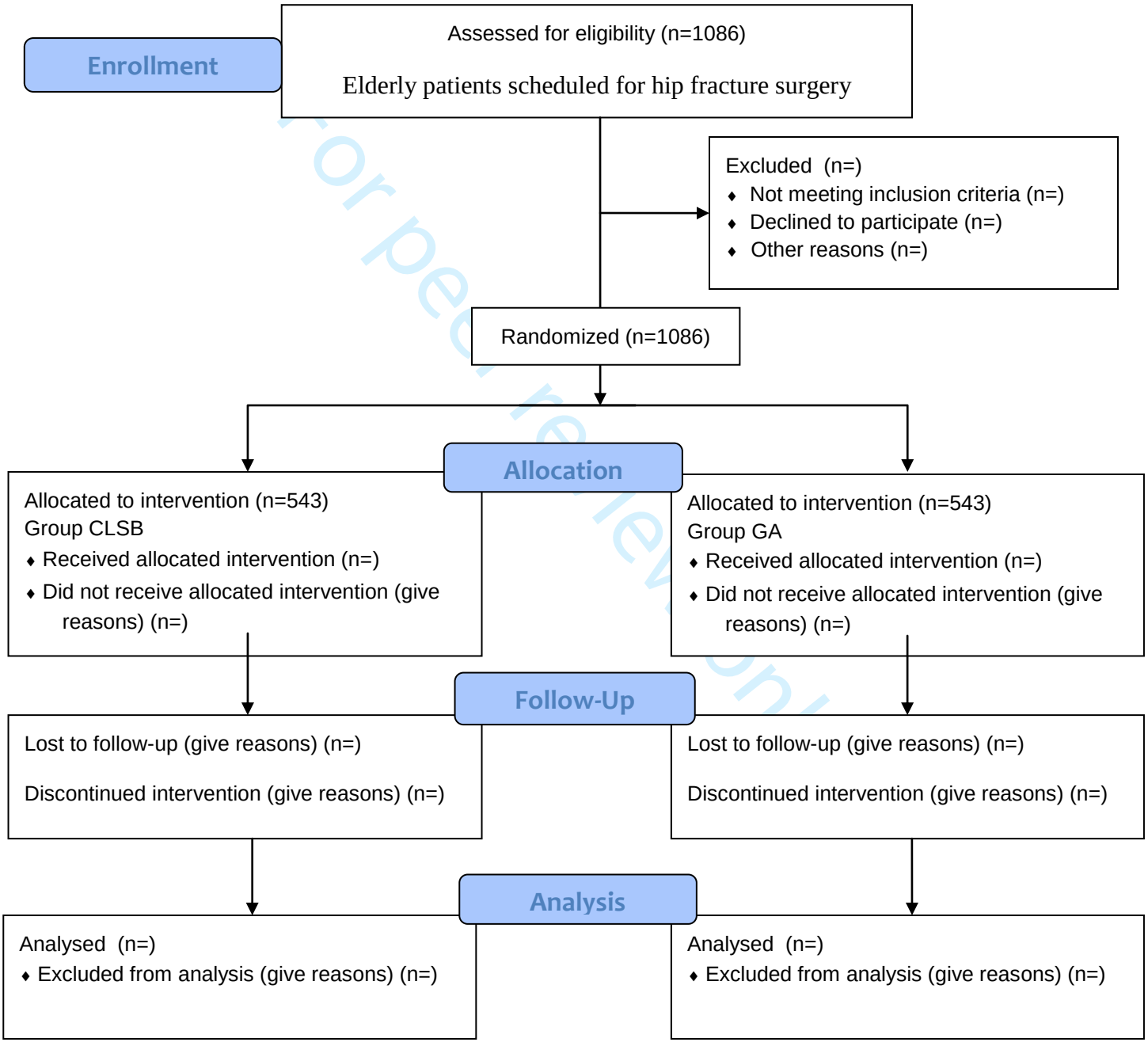
CONSORT
TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	20
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	20
Funding	4	Sources and types of financial, material, and other support	21
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	20
	5b	Name and contact information for the trial sponsor	1
	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	
	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)	

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	2-3
	6b	Explanation for choice of comparators	3-4
Objectives	7	Specific objectives or hypotheses	5-6
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, noninferiority, exploratory)	5-6
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	6
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)	6-7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-9
	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)	9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	
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	9-10
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)	10

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	10-11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6
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	11-12
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	11-12
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11-12
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	11-12
Methods: Data collection, management, and analysis			
Data collection methods	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	12-15
	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	12-15

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	16
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16
	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)	16
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15
	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	15
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	
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	19-20
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)	20

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	19-20
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	
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	16-17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	21
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	
Dissemination policy	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	20
	31b	Authorship eligibility guidelines and any intended use of professional writers	20
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	20
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	
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	

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Comparison of combined lumbar and sacral plexus block with sedation versus general anesthesia on postoperative outcomes in elderly patients undergoing hip fracture surgery(CLSB-HIPELD): study protocol for a prospective, multicenter, randomized controlled trial

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Keywords:	Hip fracture, Elderly, Lumbar plexus block, Sacral plexus block, General anesthesia

Comparison of combined lumbar and sacral plexus block with sedation versus general anesthesia on postoperative outcomes in elderly patients undergoing hip fracture surgery(CLSB-HIPELD): study protocol for a prospective, multicenter, randomized controlled trial

Junfeng Zhang[#], Xiaofeng Wang[#], Hui Zhang, Zhuolin Shu, Wei Jiang*

Department of Anesthesiology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai 200233, China

*Corresponding author: Wei Jiang MD, PhD. Address: 600 Yishan Road, Shanghai 200233, China. Tel: +86 21 64369181 ext. 58328; Fax: +86 21 64369181 ext. 58330. E-mail: jiangw@sjtu.edu.cn.

[#]These authors contributed equally to this work.

Email address of all authors:

JZ: Department of Anesthesiology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Email: zhangjunfeng@sjtu.edu.cn

XW: Department of Anesthesiology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Email: 240483680@qq.com

HZ: Department of Anesthesiology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Email: zhanghui12179@163.com

ZS: Department of Anesthesiology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Email:5883434@qq.com

WJ: Department of Anesthesiology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Email: jiangw@sjtu.edu.cn

ABSTRACT

Introduction Hip fracture in elderly people is a global public health problem, with substantial associated mortality and disability. Nearly all patients with hip fracture undergo surgical treatment, but optimal anesthesia for hip fracture surgery in elderly patients is still inconclusive. Ultrasound-guided combined lumbar and sacral plexus block has been widely used in hip fracture surgery in recent years, especially for some high-risk patients. However, it is not clear whether it can improve the postoperative outcomes of elderly patients with hip fracture.

Method and analysis This research project is a two-arm, parallel, multicenter, prospective randomized controlled trail. A total of 1086 patients aged 77 and older scheduled for hip fracture surgery in five clinical trial centers of China will be randomized in a 1:1 ratio to receive either combined lumbar and sacral plexus block plus sedation or general anesthesia. The primary outcome will be the postoperative 1-year all-cause mortality. The secondary outcomes will be the incidence of postoperative complications, high-sensitivity cardiac troponin T, early mobility after surgery, postoperative VAS pain scores, postoperative delirium, length of stay in ICU and hospital, cost-effective outcomes, Barthel Index and incidence of adverse events after discharge. Assessments will be conducted in four steps: preoperative, intraoperative and in-hospital data collection and post-discharge telephone follow-up.

Ethics and dissemination This study has been supported by Shanghai Municipal Commission of Health and Family Planning Foundation for Key Developing Disciplines (2015ZB0103) and approved by the Ethics Committee of Shanghai Sixth

People's Hospital [No: 2016-28-(2)]. At the time of manuscript submission, the protocol version is v1.6 (March 2nd, 2018) with one subsequent approved amendment. Results will be disseminated via an international peer-reviewed publication.

Trial registration number NCT03318133.

Key words Elderly; Hip fracture; Lumbar plexus block; Sacral plexus block; General anesthesia

Strengths and limitations of this study

- This study will be the first prospective, multicenter, randomized controlled clinical trial to investigate the effect of the two anesthesia techniques on long-term prognostic indicators in elderly patients with hip fracture.
- The results of this study will help elucidate whether CLSB plus sedation could be safely used in hip fracture surgery and reduce the incidence of perioperative complications and improve long-term outcome in elderly patients.
- Our study results will be limited to Chinese population, and further studies on other ethnic backgrounds will be required.

1.BACKGROUND

Hip fracture is a global public health problem with an incidence of more than 1.6 million worldwide each year.[1] Owing to the global increase of the population aged 65 years and over, the total number of hip fracture is expected to surpass 6 million by 2050.[2] While early surgery is the most effective treatment method, the postoperative mortality and disability rates are still high.[3] The elderly patients with hip fracture frequently have multiple comorbidities, which put these patients at high risk of

morbidity and mortality after anesthesia.[4 5] Seeking appropriate anesthesia technique is in urgent need to ensure that these patients can safely and effectively get through the perioperative period.

Most studies assessing the relationship between anesthesia technique and outcomes mainly focus on the comparisons between neuraxial anesthesia (including spinal and epidural anesthesia) and general anesthesia (with an endotracheal tube or a laryngeal mask airway). A recently updated systematic review and meta-analysis has found no difference between regional versus general anesthesia, but they also supposed that the number of participants included in the review was insufficient to eliminate a difference between the two techniques in the majority of outcomes studied.[6] Some other investigations have shown that neuraxial anesthesia for hip fracture can reduce postoperative morbidity,[7 8] but two recent large-sample size observational studies deemed that neuraxial anesthesia could not significantly improve the prognosis of patients.[9 10] However, all of the above are retrospective observational studies, in which anesthesiologists might have selected the anesthesia technique based on their practice style and a variety of patient-related factors. For example, patients with coagulation dysfunction would have contraindication to neuraxial anesthesia and must receive general anesthesia. Neuraxial anesthesia is thought to be less postoperative complications, so elderly or critically ill patients might be more likely to receive neuraxial anesthesia,[11] rather than being randomly assigned to different anesthesia groups. Therefore, there could be selective bias that affected the clinical significance of those results. In addition to general anesthesia and

neuraxial anesthesia, ultrasound-guided lumbar and sacral plexus block has been widely used in hip fracture surgeries in recent years, especially for some high-risk patients with cardiopulmonary dysfunction.[12-14] Compared with neuraxial anesthesia, combined lumbar and sacral plexus block is associated with less sympathetic block and better cardiovascular function stability. In addition, combined lumbar and sacral plexus block plus sedation could avoid endotracheal intubation or laryngeal mask airway(LMA) insertion and thereby might reduce the complications related to the general anesthesia. A recent small sample size retrospective study compared the effect of general endotracheal anesthesia, neuraxial anesthesia and lumbar and sacral plexus block on the prognosis of patients with hip fracture, and the results showed that neuraxial anesthesia and combined lumbar and sacral plexus block could reduce the total mortality, and there was no significant difference between neuraxial anesthesia and combined lumbar and sacral plexus block.[14] But the number of elderly and high-ASA-grade patients in the combined lumbar and sacral plexus block group was significantly greater than that in the neuraxial anesthesia group, suggesting that when comparing the effect of these two anesthetic methods in similar conditions, combined lumbar and sacral plexus block might have more advantages. However, it is not clear whether ultrasound-guided combined lumbar and sacral plexus block plus sedation could improve outcomes of elderly patients with hip fracture.

This paper describes the design of a prospective, multicenter, parallel, randomized controlled clinical trial to assess the effect of ultrasound-guided combined lumbar and sacral plexus block plus sedation versus general anesthesia on the

postoperative outcomes in elderly patients with hip fracture.

2. METHODS AND ANALYSIS

2.1. Patient and public involvement

Patients and public were not involved in the design or conduct of the study. Dissemination of the general results (no personal data) would be made on demand.

2.2. Study design

This will be a two-arm, parallel, multicenter, prospective, randomized controlled trial and the design of this study protocol has referred to the SPIRIT 2013 guideline.[15] [16]

2.3. Study location

The study will be conducted in five teaching hospitals including Shanghai Sixth People's Hospital (Shanghai, China), Beijing Chaoyang Hospital (Beijing, China), Beijing Jishuitan Hospital (Beijing, China), First Affiliated Hospital of Wenzhou Medical University (Wenzhou, China), and Foshan Hospital of Traditional Chinese Medicine (Foshan, China).

2.4. Study population

Although elderly population was considered to be people older than 65 years in the present studies, introduction to aging population is latening owing to increasing life expectancy. As shown in a recent study, age is the primary risk factor on first year mortality in patients older than 75 years old with hip fracture. In addition, China wants to increase its citizens' average life expectancy to 77.3 by 2020 and 79 by 2030, up from 76.34 in 2015, according to "Plan of Health China 2030" published in 2015.

We thus used 77 years as an age cutoff for inclusion criteria in this study because optimal selection of anesthesia technique in this age group might have more clinical significance.

Elderly patients above 77 years scheduled for hip fracture surgery will be recruited voluntarily according to the inclusion and exclusion criteria. All included patients are suitable for either general anesthesia or combined lumbar and sacral plexus block plus sedation, which will not bring tendency to choose a specific type of anesthesia.

2.4.1. Inclusion criteria:

- Age ≥77 years old;
- First unilateral surgery for hip fracture including femoral neck, intertrochanteric or subtrochanteric fracture;
- Patient with planned hip fracture surgery within 24-72 h;
- Patient without peripheral nerve block within 24 h prior to surgery or patients with preoperative peripheral nerve blockade but its effect had faded away at the beginning of the operation.
- The ability to receive written informed consent from the patient or patient's legal representative.

2.4.2. Exclusion criteria:

- Refuse to participate;
- Unable to perform nerve block;
- Multiple trauma, multiple fractures or other fractures outside the inclusion criteria,

such as pathological fractures, pelvic fractures, femur fractures;

- Prosthetic fracture;
- Scheduled for bilateral hip fracture surgery;
- Usage of bone-cement fixation in the surgery;
- With recent cerebral stroke (<3 months);
- Concomitant active heart disease (unstable angina, acute myocardial infarction, recent myocardial infarction; decompensated heart failure; symptomatic arrhythmia; severe mitral or aortic stenotic heart disease);
- Patient with known severe lung and/or airway disease, acute respiratory failure, acute pulmonary infection, and acute attack of bronchial asthma;
- Current enrolment in another clinical trial;
- Contraindication for general anesthesia (drug allergies to general anesthesia, difficult airway);
- Contraindication for lumbar and sacral plexus block (infection at the site of needle insertion, coagulopathy, allergy to local anesthetics).

2.5. Interventions

Eligible patients will be randomly assigned into either CLSB group receiving combined lumbar and sacral plexus block plus sedation or GA group receiving general anesthesia with endotracheal intubation or LMA (Figure 1). Standard anesthetic and surgical methods will be applied to ensure the consistency of treatment in the participating centers. Experienced and qualified anesthesiologists in every clinical centers will be specifically designated to perform combined lumbar-sacral plexus

block plus sedative anesthesia or GA in order to minimize the potential bias. To improve adherence to intervention protocol, study personnel are trained to follow the study protocol in accordance with the Good Clinical Practice (GCP) principles.

In the CLSB group (Combined lumbar-sacral plexus block with sedative anesthesia), the procedures will be performed as followed.

- Peripheral venous access for fluid infusion will be established;
- In the lateral decubitus position with the operated side uppermost, ultrasound-guided lumbar plexus block (L_{2-3} or/and L_{3-4} vertebral space level, 0.375% ropivacaine 25ml) will be performed, followed by sacral plexus block (0.375 % ropivacaine 20ml); We used the nerve stimulator to confirm the needle's correct position by a quadratus femoris twitch for lumbar plexus block and hamstring, leg, or foot twitches for sacral plexus block at a current within 0.4–0.6 mA, followed by relevant volume of 0.375% ropivacaine that was slowly injected in 5 ml increments to surround the target nerve under ultrasound monitoring.
- Radial arterial catheterization under local lidocaine anesthesia and arterial blood pressure monitoring will be performed. Blockade effectiveness will be evaluated 30 minutes after nerve block; The intervention will be discontinued for a given patient and convert to general anesthesia with endotracheal intubation or LMA if the satisfactory blockade is not acquired. These patients are still followed up for further statistical analysis according to the formal protocol because they have been randomly allocated.
- After confirmation of satisfactory blockade, target-controlled infusion of propofol

will be used to maintain Ramsay sedation score between 4-5 points. $P_{ET}CO_2$ will be monitored through nasopharyngeal airway. Small-dose sufentanil (1-5μg each time) will be titrated to maintain spontaneous breathing.

In the GA group, the procedures will be performed as followed.

- Peripheral venous access for fluid infusion will be established;
- Radial arterial catheterization under local lidocaine anesthesia and arterial blood pressure monitoring will be conducted;
- Anesthesia will be induced with propofol (1.5-3mg/kg), rocuronium(0.3-0.9mg/kg), and sufentanil (0.2-0.6μg/kg) for tracheal intubation or LMA insertion. Mechanical ventilation will be performed to maintain normal $P_{ET}CO_2$. Sevoflurane, propofol and sufentanil will be used to maintain anesthesia, while rocuronium will be added as needed.

During surgery, fluid infusion and blood transfusion will be used to maintain stable hemodynamics. Perioperative arterial pressure lower than 30% of the baseline will be defined as hypotension, upon which ephedrine or phenylephrine will be administrated. The type and dosage of infusion depends on anesthesiologist's experience. Blood transfusion will be given according to blood loss and hemoglobin concentration(Hb) level (80-100g/L).[17] Following surgery, patients will be sent to the postanesthesia care unit (PACU) and then transferred to orthopedic ward or intensive care unit(ICU) according to the local procedures of each clinical center. Postoperative analgesia can be administrated with regard to the routine clinical practice of each trial site, aiming to maintain a Visual Analogue Scale (VAS) pain score ≤3.

2.6. Outcomes and measurements

2.6.1. Primary outcome

Postoperative 1-year all-cause mortality (follow-up time points are set as 1 month, 3 months, 6 months and 1 year after surgery);

2.6.2. Secondary outcomes

2.6.2.1. Occurrence of intraoperative complications, including:

- Intraoperative hypotension and vasopressor dosage;
- Intraoperative arrhythmia, myocardial ischemia, myocardial infarction, massive hemorrhage, pulmonary embolism and hypoxemia;
- Intraoperative blood loss and blood transfusion volume;

2.6.2.2. High-sensitivity cardiac troponin T(hs-cTnT), measured on the 1 and 3 days after surgery;

2.6.2.3. Early mobility after surgery;

2.6.2.4. Incidence of various complications and Comprehensive Complication Index (CCI) [18] during hospitalization after surgery;

2.6.2.5. Postoperative analgesic effectiveness within three days after the surgery;

2.6.2.6. Incidence of delirium on the 1, 2 and 3 days after surgery, diagnosed with Confusion Assessment Method(CAM); [19]

2.6.2.7. Sequential Organ Failure Assessment(SOFA), [20] assessed on the 1 and 3 days after surgery;

2.6.2.8. Length of stay in ICU and hospital;

2.6.3. Other observational variables:

2.6.3.1. Economic parameters including total cost in hospital and expenditure for anesthesia;

2.6.3.2. Functional recovery on the 30 days after surgery, evaluated by Barthel Activities of Daily Living Index (Barthel Index);

2.6.3.3. Post-discharge destination, and incidence of complications and adverse events after discharge.

2.7. Participant timeline

For a given participant, assessment will be performed one day prior to surgery and again on the day of surgery to confirm whether qualified for enrollment. Randomization will perform on the day of surgery. And then intervention will be performed. The patients will be followed up on the 1, 2 and 3 days after surgery and on the day of discharge. Telephone follow-up will be conducted at the 1, 3, 6 and 12 months after surgery.

2.8. Power and Sample Size Calculation

We estimate the sample size using the formula by Schoendeld under the assumption of the validity of the proportional-hazards regression model.[21 22] We take significance level 0.05 and power 0.80. Patients will be randomly assigned to one of the two anesthesia groups in five different clinical centers. The total number of patients needed for this study is 868 (with 434 patients in each of the two groups). With these patients, we can ensure a power of 0.8 with level of significance 0.05 when the mortality rate of 55% for the GA group and a decrease of mortality rate for the GLSB group as low as 15%. In this study, only patients with age 77 years or older

will be included, so we expect the actual mortality rate of the GA group will be higher than 55%.[14] When the mortality rate of the GA group is only 45%, the above calculated sample size can still detect a 20% improvement in the CLSB group with the power of at least 0.80. In consideration of the possible lost to follow up, we add an additional 20% to the above calculated sample size. So the total number of patients needed for this study is 1086.

2.9. Randomization and blinding

Upon the receipt of informed consents, the patients will be randomly assigned to the two groups in any one of the five centers. Sequentially numbered sealed opaque envelops with group allocation inside altered anesthesiologist to use CLSB or GA. The R program will be used to generate randomization block allocation for each of the five centers with randomly selected block sizes of four, six, and eight. The envelopes will be placed in the patient's chart before the start of each procedure by a doctor of the research team. The research staff who will interview patients postoperatively are blinded for the allocated treatment. The statistician will be blinded. A spreadsheet linking the patient number and name will be password protected and kept on a research computer. The recruitment will stop when the total number of patients reaches 1086. The subjects and intervention performers (anesthesiologists) know the randomized allocation, but the follow-up personnel and statistician was blinded to the randomized allocation and intervention.

2.10. Data collection and management

Data will be collected in four steps: preoperative, intraoperative and in-hospital

data collection and post-discharge telephone follow-up.

2.10.1. Preoperative data:

2.10.1.1. Basic information including name, admission number, height, weight, gender, age, blood pressure, heart rate and ASA grade (American Society of Anesthesiologists grade).

2.10.1.2. Preoperative information including diagnosis, type of surgery, type and dosage of anticoagulants, and days passed until surgery.

2.10.1.3. Preoperative complications and medication related to cardiovascular disease, stroke, respiratory disease, kidney disease, diabetes, Parkinson's disease, and deep venous thrombosis of lower extremity if any.

2.10.1.4. Preoperative examination results including blood gas analysis, ECG, echocardiography, blood routine testing, liver and kidney function testing, coagulation testing (D-dimer), Pro-BNP, hs-cTnT, and lower extremity vascular ultrasonography.

2.10.1.5. Preoperative evaluation including MMSE (Mini-mental State Examination), SOFA and Barthel Index, all of which might be associated with the postoperative complications.

2.10.2. Intraoperative data

2.10.2.1. Duration of surgery, incidence of intraoperative hypotension or hypertension, and vasoactive drug dosage.

2.10.2.2. Intraoperative blood loss, blood transfusion volume, and intraoperative fluid infusion volume.

2.10.2.3. Intraoperative arrhythmia (sinus bradycardia, sinus tachycardia, ventricular

arrhythmia, atrial arrhythmia, etc.), myocardial ischemia, and myocardial infarction.

2.10.2.4. Intraoperative complications: massive hemorrhage, pulmonary embolism, allergic reaction, hypoxemia, bronchospasm, gastric reflux and aspiration.

2.10.2.5. Intraoperative conversion of anesthesia and the relevant causes.

2.10.3. In-hospital data

2.10.3.1. High-sensitivity cardiac troponin T(hs-cTnT), measured on the 1 and 3 days after surgery;

2.10.3.2. Earlier mobilization and postoperative hip rehabilitation: the daily degree of maximal hip flexion and abduction will be recorded.[23] The day after surgery, all 2 groups will start an identical physical therapy regimen. The patients will perform passive and active hip flexion and abduction exercises twice daily. Patients will be encouraged to get out of bed as soon as possible and try ambulation with a walker. The maximal degree of hip flexion and abduction tolerated by each patient will be recorded for three days. The day of first ambulation will be also recorded for each group.

2.10.3.3. Postoperative complications including incidence and severity of various complications and the CCI [18] value at discharge. Complications were assessed and graded using the Clavien-Dindo classification. CCI will be derived from these features at discharge, using the CCI calculator available online (www.assessurgery.com). Complications include:

- Myocardial ischemia, myocardial infarction, heart failure, arrhythmia;
- Pulmonary infection, respiratory failure, pulmonary embolism;

- Postoperative delirium;
- Cerebral ischemia, cerebrovascular accident;
- Renal failure, urinary retention;
- Regurgitation and pulmonary aspiration;
- Postoperative nausea and vomiting (PONV);
- Postoperative bleeding and 24h postoperative drainage volume;
- Reoperation.

2.10.3.4. The intensity of postoperative pain at rest and on movement will be assessed with Visual Analogue Scale (VAS) (0 no pain, and 10 worst possible pain) at the 24, 48, and 72 hours after surgery.

2.10.3.6. CAM will be evaluated on the 1, 2 and 3 days after surgery.

2.10.3.7. SOFA [20] will be evaluated on the 1 and 3 days after surgery.

2.10.3.8. Length of ICU stay, length of hospital stay, total hospitalization cost, and expenditure for anesthesia.

2.10.4. Post-discharge follow-up data

2.10.4.1. Telephone follow-up will be performed on the 1, 3, 6 and 12 months after surgery to collect the following information.

- Discharge destinations. Disposition status after discharge will be classified as follows: dead, nursing home (e.g., skilled nursing facility, intermediate care facility, extended care facility, nursing home), community dwelling (e.g., home alone, home with others), or other.
- Dead or not, specific cause and time.

- Incidence of complications and adverse events: heart, lungs, brain, liver, kidney, four limbs, and hospitalization, etc.

2.10.4.2. Barthel Index for evaluation of functional recovery will be collected on the 30 days after surgery.

2.11. Data and safety monitoring

Preoperative, intraoperative and in-hospital data will be collected from the electronic medical record, monitor machines and relevant manual records by one of the research staff. Telephone follow-up will be conducted by the research team. Data will be securely managed by an independent contract research organization (Shanghai Ruihui Biotech Co., Ltd, Shanghai). All serious adverse events, as well as all non-serious adverse events that are unexpected and judged to be related to the study treatment, will be recorded in the study database and reported as required to local IRBs and to the Shanghai Jiao Tong University Affiliated Sixth People's Hospital IRB. Data and safety monitoring will be the responsibility of the study director/principle investigator(PI), the study biostatistician, site clinical directors and an independent Data and Safety Monitoring Board(DSMB) selected by the study PI. The DSMB will be composed of 5-7 independent, multidisciplinary experts who are not have subordinate relationships with the PI or any member of the study team. The DSMB will review study implementation and the occurrence of adverse events.

2.12. Statistical analysis

The data will be analyzed using intention-to-treat approach. Demographics information will be compared between the two groups to ensure the data are balanced.

Student t-test will be used for quantitative variables such as age, and heart rate, blood pressure. Chi-square test will be used for categorical variables such as Sex, ASA classification grades. The VAS pain scores will be analyzed using repeated measure ANOVA to test the effects of treatment, time, and the interaction effect. The effects of different covariates on the mortality rates measured at 1 month, 3 months, 6 months and 12 months will be assessed using a logistic regression model. Either logistic regression or ordinary multiple regression method will also be used to assess the effects of the covariate on the secondary and other outcomes as well depending on the type of dependent variable. The proportional-hazards regression model will be used to compare the survival time of the patients in the two groups and to assess the effects of the covariates.

2.13. Access to data

During the study, data will be stored in a password-protected system and can be accessed by the research staff who sign the confidential disclosure agreement. Data without patient identification will be publicly accessible after the study.

2.14. Confidentiality

Each participant will be given an identification number and referred by the identification number throughout the study and in all study-related information. This information will be securely stored in a password-protected access system provided by a local supplier. Relevant paper records will be stored in a locked cabinet in an access-controlled room. All records containing any patients' personal identifiers will be separately stored similarly as above.

2.15. Trial status

At the time of manuscript submission, the study is in the preparation phase for recruitment. It is planned to be completed by 2021.

3. DISCUSSION

Choice of anesthesia for hip fracture surgery in elderly patients is still inconclusive. General anesthesia with endotracheal intubation or LMA is a common procedure for hip fracture surgery, with advantages of wide indications and maintaining relatively stable hemodynamics. Compared with general anesthesia, neuraxial anesthesia avoids endotracheal intubation or LMA insertion. Vertebral degeneration and anatomical abnormalities in elderly patients often make neuraxial anesthesia puncture difficult, and most of these patients are taking anticoagulants, which are the contraindication of neuraxial anesthesia. So the neuraxial anesthesia has limitations in application for the elderly patient. The principle for anesthesia selection is to reduce or avoid the effect of anesthesia on systemic and vital organ functions as much as possible when meeting the needs of surgery. Previous lumbar and sacral plexus block depends on blind puncture technique and cannot ensure the clinical effectiveness. However, ultrasound visualization technology has promoted the wide application of lumbar and sacral plexus block. Combined lumbar and sacral plexus block with sedative anesthesia has gradually become alternative approach for hip fracture surgery in elderly patients, and this anesthetic technique has been extensively applied in our department and achieved satisfactory clinical results in recent years, but there is few reliable clinical evidence on whether it can be safely used for hip fracture

surgery in elderly patients and improve the short-term or long-term outcomes. Thus, we have designed this protocol to illustrate the clinical significance of combined lumbar and sacral plexus block with sedative anesthesia in elderly patients undergoing hip fracture surgery. In this study, we will observe the effect of the two anesthetic methods (general anesthesia or combined lumbar and sacral plexus block plus sedation on the early prognostic indicators in elderly patients with hip fracture, including postoperative complications, postoperative analgesic effect, postoperative early mobility, postoperative delirium, and length of stay in ICU and hospital. This study will be the first prospective, multicenter, randomized controlled clinical trial to investigate the effect of the two anesthesia techniques on long-term prognostic outcomes in elderly patients with hip fracture, including postoperative 1-year all-cause mortality and incidence of complications and adverse events. The results of this study will help elucidate whether ultrasound-guided combined lumbar and sacral plexus block with sedative anesthesia can be safely used in hip fracture surgery in elderly patients and can reduce the incidence of perioperative complications and improve long-term prognosis, so as to solve the troubling clinical problem and provide a theoretical basis for elderly patients undergoing hip fracture surgery to choose the optimal anesthetic method.

Abbreviations

ASA grade: American Society of Anesthesiologists grade; GA: General anesthesia; CLSB: Combined Lumbar and Sacral Plexus Block; PACU: Postanesthesia Care Unit; Hb: Hemoglobin Concentration; ICU: Intensive Care Unit; CCI: Comprehensive

Complication Index; SOFA: Sequential Organ Failure Assessment; CAM: The Confusion Assessment method; MMSE: Mini-mental State Examination; ECG: Echocardiography; Pro-BNP: Pro Brain Natriuretic Peptide; hs-cTnT: High-sensitivity cardiac Troponin T; PONV: Postoperative Nausea and Vomiting; VAS: Visual Analog Scale

Contributors JZ and WJ designed the study and wrote the protocol. HZ and XW performed statistical analysis. HZ, XW and ZS were involved in protocol conception and design and manuscript revision. WJ is the principal investigator of this clinical trial. All authors read and approved the final version of the manuscript.

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Data sharing statement No additional data are available.

Patient consent Obtained.

Competing interests None declared.

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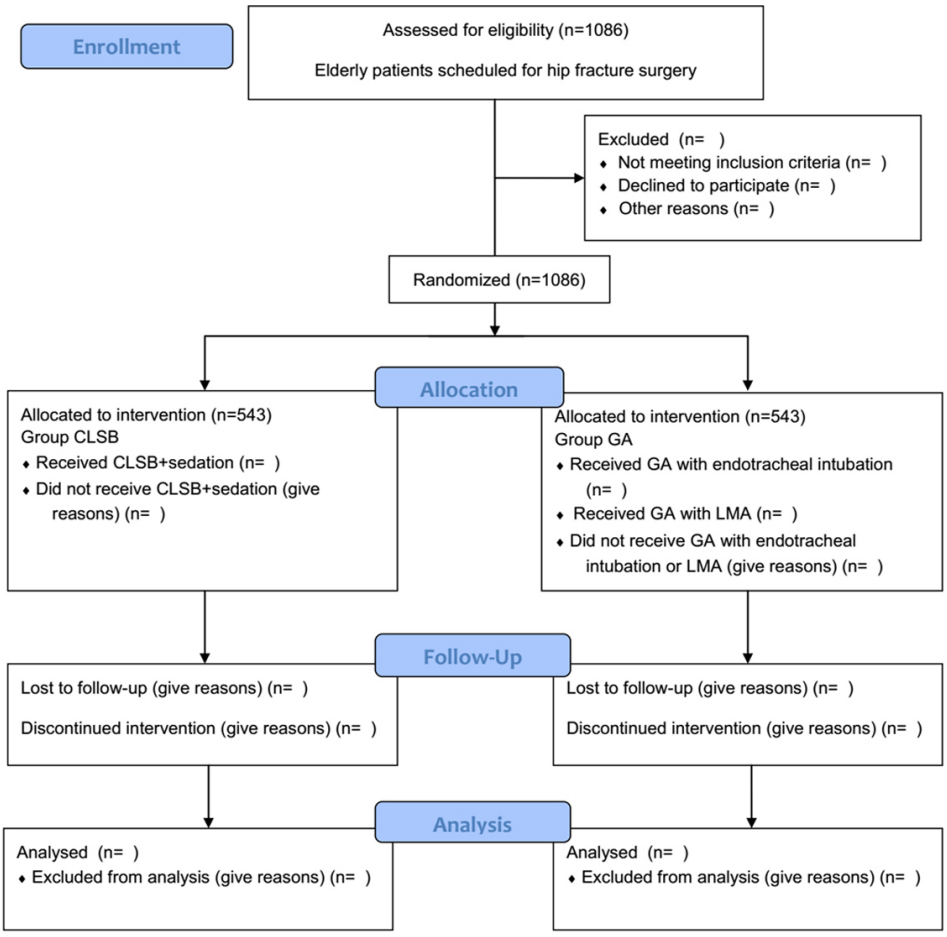
Figure legend

Fig. 1 CONSORT flowchart designed for subject enrollment



100x99mm (300 x 300 DPI)

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2-3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3-6
	2b	Specific objectives or hypotheses	5-6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6-10
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	n/a
Participants	4a	Eligibility criteria for participants	7-8
	4b	Settings and locations where the data were collected	n/a
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8-11
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	11-12
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n/a
Sample size	7a	How sample size was determined	12-13
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n/a
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	13
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	13
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	13
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	13
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	13

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	n/a
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	17-18
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	n/a
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	n/a
	13b	For each group, losses and exclusions after randomisation, together with reasons	n/a
Recruitment	14a	Dates defining the periods of recruitment and follow-up	12
	14b	Why the trial ended or was stopped	n/a
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	n/a
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	n/a
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	n/a
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	n/a
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	n/a
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	n/a
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	n/a
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	n/a
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	n/a
Other information			
Registration	23	Registration number and name of trial registry	2-3
Protocol	24	Where the full trial protocol can be accessed, if available	3
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	21

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

Comparison of combined lumbar and sacral plexus block with sedation versus general anesthesia on postoperative outcomes in elderly patients undergoing hip fracture surgery(CLSB-HIPELD): study protocol for a prospective, multicenter, randomized controlled trial

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Comparison of combined lumbar and sacral plexus block with sedation versus general anesthesia on postoperative outcomes in elderly patients undergoing hip fracture surgery(CLSB-HIPELD): study protocol for a prospective, multicenter, randomized controlled trial

Junfeng Zhang[#], Xiaofeng Wang[#], Hui Zhang, Zhuolin Shu, Wei Jiang*

Department of Anesthesiology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai 200233, China

*Corresponding author: Wei Jiang MD, PhD. Address: 600 Yishan Road, Shanghai 200233, China. Tel: +86 21 64369181 ext. 58328; Fax: +86 21 64369181 ext. 58330. E-mail: jiangw@sjtu.edu.cn.

[#]These authors contributed equally to this work.

Email address of all authors:

JZ: Department of Anesthesiology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Email: zhangjunfeng@sjtu.edu.cn

XW: Department of Anesthesiology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Email: 240483680@qq.com

HZ: Department of Anesthesiology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Email: zhanghui12179@163.com

ZS: Department of Anesthesiology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Email:5883434@qq.com

WJ: Department of Anesthesiology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Email: jiangw@sjtu.edu.cn

ABSTRACT

Introduction Hip fracture in elderly people is a global public health problem, with substantial associated mortality and disability. Nearly all patients with hip fracture undergo surgical treatment, but optimal anesthesia for hip fracture surgery in elderly patients is still inconclusive. Ultrasound-guided combined lumbar and sacral plexus block has been widely used in hip fracture surgery in recent years, especially for some high-risk patients. However, it is not clear whether it can improve the postoperative outcomes of elderly patients with hip fracture.

Method and analysis This research project is a two-arm, parallel, multicenter, prospective randomized controlled trail. A total of 1086 patients aged 75 and older scheduled for hip fracture surgery in five clinical trial centers of China will be randomized in a 1:1 ratio to receive either combined lumbar and sacral plexus block plus sedation or general anesthesia. The primary outcome will be the postoperative 1-year all-cause mortality. The secondary outcomes will be the incidence of postoperative complications, high-sensitivity cardiac troponin T, early mobility after surgery, postoperative VAS pain scores, postoperative delirium, length of stay in ICU and hospital, cost-effective outcomes, Barthel Index and incidence of adverse events after discharge. Assessments will be conducted in four steps: preoperative, intraoperative and in-hospital data collection and post-discharge telephone follow-up.

Ethics and dissemination This study has been supported by Shanghai Municipal Commission of Health and Family Planning Foundation for Key Developing Disciplines (2015ZB0103) and approved by the Ethics Committee of Shanghai Sixth

People's Hospital [No: 2016-28-(2)]. At the time of manuscript submission, the protocol version is v1.6 (March 2nd, 2018) with one subsequent approved amendment. Results will be disseminated via an international peer-reviewed publication.

Trial registration number NCT03318133.

Key words Elderly; Hip fracture; Lumbar plexus block; Sacral plexus block; General anesthesia

Strengths and limitations of this study

- This study will be the first prospective, multicenter, randomized controlled clinical trial to investigate the effect of the two anesthesia techniques on long-term prognostic indicators in elderly patients with hip fracture.
- The results of this study will help elucidate whether CLSB plus sedation could be safely used in hip fracture surgery and reduce the incidence of perioperative complications and improve long-term outcome in elderly patients.
- Our study results will be limited to Chinese population, and further studies on other ethnic backgrounds will be required.

1.BACKGROUND

Hip fracture is a global public health problem with an incidence of more than 1.6 million worldwide each year [1]. Owing to the global increase of the population aged 65 years and over, the total number of hip fracture is expected to surpass 6 million by 2050 [2]. While early surgery is the most effective treatment method, the postoperative mortality and disability rates are still high [3]. The elderly patients with hip fracture frequently have multiple comorbidities, which put these patients at high risk of

morbidity and mortality after anesthesia [4, 5]. Seeking appropriate anesthesia technique is in urgent need to ensure that these patients can safely and effectively get through the perioperative period.

Most studies assessing the relationship between anesthesia technique and outcomes mainly focus on the comparisons between neuraxial anesthesia (including spinal and epidural anesthesia) and general anesthesia (with an endotracheal tube or a laryngeal mask airway). A recently updated systematic review and meta-analysis has found no difference between regional versus general anesthesia, but they also supposed that the number of participants included in the review was insufficient to eliminate a difference between the two techniques in the majority of outcomes studied[6]. Some other investigations have shown that neuraxial anesthesia for hip fracture can reduce postoperative morbidity[7, 8], but two recent large-sample size observational studies deemed that neuraxial anesthesia could not significantly improve the prognosis of patients [9, 10]. However, all of the above are retrospective observational studies, in which anesthesiologists might have selected the anesthesia technique based on their practice style and a variety of patient-related factors. For example, patients with coagulation dysfunction would have contraindication to neuraxial anesthesia and must receive general anesthesia. Neuraxial anesthesia is thought to be less postoperative complications, so elderly or critically ill patients might be more likely to receive neuraxial anesthesia[11], rather than being randomly assigned to different anesthesia groups. Therefore, there could be selective bias that affected the clinical significance of those results. In addition to general anesthesia and

neuraxial anesthesia, ultrasound-guided lumbar and sacral plexus block has been widely used in hip fracture surgeries in recent years, especially for some high-risk patients with cardiopulmonary dysfunction [12-14]. Compared with neuraxial anesthesia, combined lumbar and sacral plexus block is associated with less sympathetic block and better cardiovascular function stability. In addition, combined lumbar and sacral plexus block plus sedation could avoid endotracheal intubation or laryngeal mask airway(LMA) insertion and thereby might reduce the complications related to the general anesthesia. A recent small sample size retrospective study [14] compared the effect of general endotracheal anesthesia, neuraxial anesthesia and lumbar and sacral plexus block on the prognosis of patients with hip fracture, and the results showed that neuraxial anesthesia and combined lumbar and sacral plexus block could reduce the total mortality, and there was no significant difference between neuraxial anesthesia and combined lumbar and sacral plexus block. But the number of elderly and high-ASA-grade patients in the combined lumbar and sacral plexus block group was significantly greater than that in the neuraxial anesthesia group, suggesting that when comparing the effect of these two anesthetic methods in similar conditions, combined lumbar and sacral plexus block might have more advantages. However, it is not clear whether ultrasound-guided combined lumbar and sacral plexus block plus sedation could improve outcomes of elderly patients with hip fracture.

This paper describes the design of a prospective, multicenter, parallel, randomized controlled clinical trial to assess the effect of ultrasound-guided combined lumbar and sacral plexus block plus sedation versus general anesthesia on the

postoperative outcomes in elderly patients with hip fracture.

2. METHODS AND ANALYSIS

2.1. Patient and public involvement

Patients and public were not involved in the design or conduct of the study. We do not have any specific plans to disseminate our results to patients.

2.2. Study design

This will be a two-arm, parallel, multicenter, prospective, randomized controlled trial and the design of this study protocol has referred to the SPIRIT 2013 guideline [15, 16].

2.3. Study location

The study will be conducted in five teaching hospitals including Shang Sixth People's Hospital (Shanghai, China), Beijing Chaoyang Hospital (Beijing, China), Beijing Jishuitan Hospital (Beijing, China), First Affiliated Hospital of Wenzhou Medical University (Wenzhou, China), and Foshan Hospital of Traditional Chinese Medicine (Foshan, China).

2.4. Study population

Although elderly population was considered to be people older than 65 years in the present studies, introduction to aging population is latening owing to increasing life expectancy. As shown in a recent study[17], age is the primary risk factor on first year mortality in patients older than 75 years old with hip fractures. In addition, China wants to increase its citizens' average life expectancy to 77.3 by 2020 and 79 by 2030, up from 76.34 in 2015, according to "Plan of Health China 2030" published in 2015.

We thus used 75 years as an age cutoff for inclusion criteria in this study because optimal selection of anesthesia technique in this age group might have more clinical significance.

Elderly patients above 75 years scheduled for hip fracture surgery will be recruited voluntarily according to the inclusion and exclusion criteria below. All included patients are suitable for either general endotracheal anesthesia or combined lumbar and sacral plexus block plus sedation, which will not bring tendency to choose a specific type of anesthesia.

2.4.1. Inclusion criteria:

- Age ≥75 years old;
- First unilateral surgery for hip fracture including femoral neck, intertrochanteric or subtrochanteric fracture;
- Patient with planned hip fracture surgery within 24-72 h;
- Patient without peripheral nerve block within 24 h prior to surgery or patients with preoperative peripheral nerve blockade but its effect had faded away at the beginning of the operation.
- The ability to receive written informed consent from the patient or patient's legal representative.

2.4.2. Exclusion criteria:

- Refuse to participate;
- Unable to perform nerve block;
- Multiple trauma, multiple fractures or other fractures outside the inclusion criteria,

such as pathological fractures, pelvic fractures, femur fractures;

- Prosthetic fracture;
- Scheduled for bilateral hip fracture surgery;
- Usage of bone-cement fixation in the surgery;
- With recent cerebral stroke (<3 months);
- Concomitant active heart disease (unstable angina, acute myocardial infarction, recent myocardial infarction; decompensated heart failure; symptomatic arrhythmia; severe mitral or aortic stenotic heart disease);
- Patient with known severe lung and/or airway disease, acute respiratory failure, acute pulmonary infection, and acute attack of bronchial asthma;
- Current enrolment in another clinical trial;
- Contraindication for general endotracheal anesthesia (drug allergies to general anesthesia, difficult airway);
- Contraindication for lumbar and sacral plexus block (infection at the site of needle insertion, coagulopathy, allergy to local anesthetics).

2.5. Interventions

Eligible patients will be randomly assigned into either CLSB group receiving combined lumbar and sacral plexus block plus sedation or GA group receiving general anesthesia with endotracheal intubation or LMA (Figure 1). Standard anesthetic and surgical methods will be applied to ensure the consistency of treatment in the participating centers. Experienced and qualified anesthesiologists in every clinical centers will be specifically designated to perform combined lumbar-sacral plexus

block plus sedative anesthesia or GA in order to minimize the potential bias. To improve adherence to intervention protocols, study personnel are trained to follow the study protocol in accordance with the Good Clinical Practice (GCP) principles.

In the CLSB group (Combined lumbar-sacral plexus block with sedative anesthesia), the procedures will be performed as followed.

- Peripheral venous access for fluid infusion will be established;
- In the lateral decubitus position with the operated side uppermost, ultrasound-guided lumbar plexus block (L_{2-3} or/and L_{3-4} vertebral space level, 0.375% ropivacaine 25ml) will be performed, followed by sacral plexus block (0.375 % ropivacaine 20ml); We used the nerve stimulator to confirm the needle's correct position by a quadratus femoris twitch for lumbar plexus block and hamstring, leg, or foot twitches for sacral plexus block at a current within 0.4–0.6 mA, followed by relevant volume of 0.375% ropivacaine that was slowly injected in 5 ml increments to surround the target nerve under ultrasound monitoring.
- Radial arterial catheterization under local lidocaine anesthesia and arterial blood pressure monitoring will be performed. Blockade effectiveness will be evaluated 30 minutes after nerve block; The intervention will be discontinued for a given patient and convert to general anesthesia with endotracheal intubation or LMA if the satisfactory blockade is not acquired. These patient are still followed up for further statistical analysis according to the formal protocol because they have been randomly allocated.
- After confirmation of satisfactory blockade, target-controlled infusion of propofol

will be used to maintain Ramsay sedation score between 3-4 points. $P_{ET}CO_2$ will be monitored through nasopharyngeal airway. Small-dose sufentanil (1-2μg each time) will be titrated to maintain spontaneous breathing.

In the GA group, the procedures will be performed as followed.

- Peripheral venous access for fluid infusion will be established;
- Radial arterial catheterization under local lidocaine anesthesia and arterial blood pressure monitoring will be conducted;
- Anesthesia will be induced with propofol (1.5-3mg/kg), rocuronium(0.3-0.9mg/kg), and sufentanil (0.2-0.6μg/kg) for tracheal intubation or LMA insertion. Mechanical ventilation will be performed to maintain normal $P_{ET}CO_2$.
- Sevoflurane, propofol and sufentanil will be used to maintain anesthesia during surgery, while rocuronium will be added as needed.

During surgery, fluid infusion and blood transfusion will be used to maintain stable hemodynamics. Perioperative arterial pressure lower than 30% of the baseline will be defined as hypotension, upon which ephedrine or phenylephrine will be administrated. The type and dosage of infusion depends on anesthesiologist's experience. Blood transfusion will be given according to blood loss and hemoglobin concentration(Hb) level (80-100g/L) [18]. Following surgery, patients will be sent to the postanesthesia care unit (PACU) and then transferred to orthopedic ward or intensive care unit(ICU) according to the local procedures of each clinical center. Postoperative analgesia can be administrated with regard to the routine clinical

practice of each trial site, aiming to maintain a Visual Analogue Scale (VAS) pain score ≤3.

2.6. Outcomes and measurements

2.6.1. Primary outcome

Postoperative 1-year all-cause mortality (follow-up time points are set as 1 month, 3 months, 6 months and 1 year after surgery);

2.6.2. Secondary outcomes

2.6.2.1. Occurrence of intraoperative complications, including:

- Intraoperative hypotension and vasopressor dosage;
- Intraoperative arrhythmia, myocardial ischemia, myocardial infarction, massive hemorrhage, pulmonary embolism and hypoxemia;
- Intraoperative blood loss and blood transfusion volume;

2.6.2.2. High-sensitivity cardiac troponin T(hs-cTnT), measured on the 1 and 3 days after surgery;

2.6.2.3. Early mobility after surgery;

2.6.2.4. Incidence of various complications and Comprehensive Complication Index (CCI) [19] during hospitalization after surgery;

2.6.2.5. Postoperative analgesic effectiveness within three days after the surgery;

2.6.2.6. Incidence of delirium on the 1, 2 and 3 days after surgery, diagnosed with Confusion Assessment Method(CAM)[20];

2.6.2.7. Sequential Organ Failure Assessment(SOFA) [21], assessed on the 1 and 3 days after surgery;

2.6.2.8. Bauer Patient Satisfaction Questionnaire[22], assessed on the 3 days after surgery;

2.6.2.9. Length of stay in ICU and hospital;

2.6.3. Other observational variables:

2.6.3.1. Economic parameters including total cost in hospital and expenditure for anesthesia;

2.6.3.2. Functional recovery on the 30 days after surgery, evaluated by Barthel Activities of Daily Living Index (Barthel Index);

2.6.3.3. Post-discharge destination, and incidence of complications and adverse events after discharge.

2.7. Participant timeline

For a given participant, assessment will be performed one day prior to surgery and again on the day of surgery to confirm whether qualified for enrollment. Randomization will perform on the day of surgery. And then intervention will be performed. The patients will be followed up on the 1, 2 and 3 days after surgery and on the day of discharge. Telephone follow-up will be conducted at the 1, 3, 6 and 12 months after surgery.

2.8. Power and Sample Size Calculation

We estimate the sample size using the formula by Schoendeld under the assumption of the validity of the proportional-hazards regression model [23, 24]. We take significance level 0.05 and power 0.80. Patients will be randomly assigned to one of the two anesthesia groups in five different clinical centers. The total number of patients needed for this study is 868 (with 434 patients in each of the two groups).

With that many patients, we can ensure a power of 0.8 with level of significance 0.05 when the mortality rate of 55% for the GA group and a decrease of mortality rate for the GLSB group as low as 15%. In this study, only patients with age 75 years or older will be included, so we expect the actual mortality rate of the GA group will be higher than 55% [14]. When the mortality rate of the GA group is only 45%, the above calculated sample size can still detect a 20% improvement in the CLSB group with the power of at least 0.80. In consideration of the possible lost to follow up, we add an additional 20% to the above calculated sample size. So the total number of patients needed for this study is 1086.

2.9. Randomization and blinding

Upon the receipt of informed consents, patients will be randomly assigned to the two groups in any one of the five centers. Sequentially numbered sealed opaque envelops with group allocation inside altered anesthetist to use CLSB or GA. The R program will be used to generate randomization block allocation for each of the five centers with randomly selected block sizes of four, six, and eight. The envelopes will be placed in the patient's chart before the start of each procedure by a doctor of the research team. The research staff who will interview patients postoperatively are blinded for the allocated treatment. The statistician will be blinded. A spreadsheet linking the patient number and name will be password protected and kept on a research computer. The recruitment will stop when the total number of patients reaches 1086. The subjects and intervention performers (anesthesiologists) know the randomized allocation, but the follow-up personnel and statistician was blinded to the

randomized allocation and intervention.

2.10. Data collection and management

Data will be collected in four steps: preoperative, intraoperative and in-hospital data collection and post-discharge telephone follow-up.

2.10.1. Preoperative data:

2.10.1.1. Basic information including name, admission number, height, weight, gender, age, blood pressure, heart rate and ASA grade (American Society of Anesthesiologists grade).

2.10.1.2. Preoperative information including diagnosis, type of surgery, type and dosage of anticoagulants, and days passed until surgery.

2.10.1.3. Preoperative complications and medication related to cardiovascular disease, stroke, respiratory disease, kidney disease, diabetes, Parkinson's disease, and deep venous thrombosis of lower extremity if any.

2.10.1.4. Preoperative examination results including blood gas analysis, ECG, echocardiography, blood routine testing, liver and kidney function testing, coagulation testing (D-dimer), Pro-BNP, hs-cTnT, and lower extremity vascular ultrasonography.

2.10.1.5. Preoperative evaluation results including MMSE (Mini-mental State Examination), SOFA and Barthel Index, all of which might be associated with the postoperative complications.

2.10.2. Intraoperative data

2.10.2.1. Duration of surgery, incidence of intraoperative hypotension or hypertension, and vasoactive drug dosage.

2.10.2.2. Intraoperative blood loss, blood transfusion volume, and intraoperative fluid infusion volume.

2.10.2.3. Intraoperative arrhythmia (sinus bradycardia, sinus tachycardia, ventricular arrhythmia, atrial arrhythmia, etc.), myocardial ischemia, and myocardial infarction.

2.10.2.4. Intraoperative complications: massive hemorrhage, pulmonary embolism, allergic reaction, hypoxemia, bronchospasm, gastric reflux and aspiration.

2.10.2.5. Intraoperative conversion of anesthesia and the relevant causes.

2.10.3. In-hospital data

2.10.3.1. High-sensitivity cardiac troponin T(hs-cTnT), measured on the 1 and 3 days after surgery;

2.10.3.2. Earlier mobilization and postoperative hip rehabilitation: the daily degree of maximal hip flexion and abduction will be recorded [25]. The day after surgery, all 2 groups will start an identical physical therapy regimen. The patients will perform passive and active hip flexion and abduction exercises twice daily. Patients will be encouraged to get out of bed as soon as possible and try ambulation with a walker. The maximal degree of hip flexion and abduction tolerated by each patient will be recorded for three days. The day of first ambulation will be also recorded for each group.

2.10.3.3. Postoperative complications including incidence and severity of various complications and the CCI [19] value at discharge. Complications were assessed and graded using the Clavien-Dindo classification. CCI will be derived from these features at discharge, using the CCI calculator available online

(www.assessurgery.com). Complications include:

- Myocardial ischemia, myocardial infarction, heart failure, arrhythmia;
- Pulmonary infection, respiratory failure, pulmonary embolism;
- Postoperative delirium;
- Cerebral ischemia, cerebrovascular accident;
- Renal failure, urinary retention;
- Regurgitation and pulmonary aspiration;
- Postoperative nausea and vomiting (PONV);
- Postoperative bleeding and 24h postoperative drainage volume;
- Reoperation.

2.10.3.4. The intensity of postoperative pain at rest and on movement will be assessed with Visual Analogue Scale (VAS) (0 no pain, and 10 worst possible pain) at the 24, 48, and 72 hours after surgery.

2.10.3.6. CAM will be evaluated on the 1, 2 and 3 days after surgery.

2.10.3.7. SOFA [21] will be evaluated on the 1 and 3 days after surgery.

2.10.3.8. Bauer Patient Satisfaction Questionnaire will be assessed on the 3 days after surgery.

2.10.3.9. Length of ICU stay, length of hospital stay, total hospitalization cost, and expenditure for anesthesia.

2.10.4. Post-discharge follow-up data

2.10.4.1. Telephone follow-up will be performed on the 1, 3, 6 and 12 months after surgery to collect the following information.

- Discharge destinations. Disposition status after discharge will be classified as follows: dead, nursing home (e.g., skilled nursing facility, intermediate care facility, extended care facility, nursing home), community dwelling (e.g., home alone, home with others), or other.
- Dead or not, specific cause and time.
- Incidence of complications and adverse events: heart, lungs, brain, liver, kidney, four limbs, and hospitalization, etc.

2.10.4.2. Barthel Index for evaluation of functional recovery will be collected on the 30 days after surgery.

2.11. Data and safety monitoring

Preoperative, intraoperative and in-hospital data will be collected from the electronic medical record, monitor machines and relevant manual records by one of the research staff. Telephone follow-up will be conducted by the research team. Data will be securely managed by an independent contract research organization (Shanghai Ruihui Biotech Co., Ltd, Shanghai). All serious adverse events, as well as all non-serious adverse events that are unexpected and judged to be related to the study treatment, will be recorded in the study database and reported as required to local IRBs and to the Shanghai Jiao Tong University Affiliated Sixth People's Hospital IRB. Data and safety monitoring will be the responsibility of the study director/principle investigator(PI), the study biostatistician, site clinical directors and an independent Data and Safety Monitoring Board(DSMB) selected by the study PI. The DSMB will be composed of 5-7 independent, multidisciplinary experts who are not have

subordinate relationships with the PI or any member of the study team. The DSMB will review study implementation and the occurrence of adverse events.

2.12. Statistical analysis

The data will be analyzed using intention-to-treat approach. Demographics information will be compared for patients of the two groups to ensure the data are balanced. Student t-test will be used for quantitative variables such as age, and heart rate, blood pressure. Chi-square test will be used for categorical variables such as Sex, ASA classification grades. The VAS pain scores will be analyzed using repeated measure ANOVA to test the effects of treatment, time, and the interaction effect. The effects of different covariates on the mortality rates measured at 1 month, 3 months, 6 months and 12 months will be assessed using a logistic regression model. The primary analysis model will be Cox regression model with covariates. Either logistic regression or ordinary multiple regression method will also be used to assess the effects of the covariate on the secondary and other outcomes as well depending on the type of dependent variable. The proportional-hazards regression model will be used to compare the survival times of the patients in the two groups and to assess the effects of the covariates.

2.13. Access to data

During the study, data will be stored in a password-protected system and can be accessed by the research staff who sign the confidential disclosure agreements. Data without patient identification will be publicly accessible after the study.

2.14. Confidentiality

Each participant will be given an identification number and referred by the identification number throughout the study and in all study-related information. This information will be securely stored in a password-protected access system provided by a local supplier. Relevant paper records will be stored in a locked cabinet in an access-controlled room. All records containing any patients' personal identifiers will be separately stored similarly as above.

2.15. Trial status

At the time of manuscript submission, the study is in the preparation phase for recruitment.

3. DISCUSSION

Choice of anesthesia for hip fracture surgery in elderly patients is still inconclusive. General anesthesia with endotracheal intubation or LMA is a common procedure for hip fracture surgery, with advantages of wide indications and maintaining relatively stable hemodynamics. Compared with general anesthesia, neuraxial anesthesia avoids endotracheal intubation or LMA insertion. But vertebral degeneration and anatomical abnormalities in elderly patients often make neuraxial anesthesia puncture difficult, and most of these patients are taking anticoagulants, which are the contraindication of neuraxial anesthesia. So the neuraxial anesthesia has limitations in application for the elderly patient. The principle for anesthesia selection is to reduce or avoid the effect of anesthesia on systemic and vital organ functions as much as possible when meeting the needs of surgery. Previous lumbar and sacral plexus block depends on blind puncture technique and cannot ensure the clinical

effectiveness. However, ultrasound visualization technology has promoted the wide application of lumbar and sacral plexus block. Combined lumbar and sacral plexus block with sedative anesthesia has gradually become alternative approach for hip fracture surgery in elderly patients, and this anesthetic technique has been massively applied in our department and achieved satisfactory clinical results in recent years, but there is few reliable clinical evidence on whether it can be safely used for hip fracture surgery in elderly patients and improve the short-term or long-term outcomes. Thus, we have designed this trial protocol to illustrate the clinical value of combined lumbar and sacral plexus block with sedative anesthesia in elderly patients undergoing hip fracture surgery. In this study, we will observe the effect of the two anesthetic methods (general endotracheal anesthesia or combined lumbar and sacral plexus block plus sedation on the early prognostic indicators in elderly patients with hip fracture, including postoperative complications, postoperative analgesic effect, postoperative early mobility, postoperative delirium, patient's satisfaction to anesthesia and length of stay in ICU and hospital. This study will be the first prospective, multicenter, randomized controlled clinical trial to investigate the effect of the two anesthesia techniques on long-term prognostic indicators in elderly patients with hip fracture, including postoperative 1-year all-cause mortality and incidence of complications and adverse events. The results of this study will help elucidate whether ultrasound-guided combined lumbar and sacral plexus block with sedative anesthesia can be safely used in hip fracture surgery in elderly patients and can reduce the incidence of perioperative complications and improve long-term prognosis, so as to solve the

troubling clinical problem and provide a theoretical basis for elderly patients undergoing hip fracture surgery to choose the optimal anesthetic method.

Abbreviations

ASA grade: American Society of Anesthesiologists grade; GA: General anesthesia; CLSB: Combined Lumbar and Sacral Plexus Block; PACU: Postanesthesia Care Unit; Hb: Hemoglobin Concentration; ICU: Intensive Care Unit; CCI: Comprehensive Complication Index; SOFA: Sequential Organ Failure Assessment; CAM: The Confusion Assessment method; MMSE: Mini-mental State Examination; ECG: Echocardiography; Pro-BNP: Pro Brain Natriuretic Peptide; hs-cTnT: High-sensitivity cardiac Troponin T; PONV: Postoperative Nausea and Vomiting; VAS: Visual Analog Scale

Contributors JZ and WJ designed the study and wrote the protocol. HZ and XW performed statistical analysis. HZ, XW and ZS were involved in protocol conception and design and manuscript revision. WJ is the principal investigator of this clinical trial. All authors read and approved the final version of the manuscript.

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Data sharing statement No additional data are available.

Patient consent Obtained.

Competing interests None.

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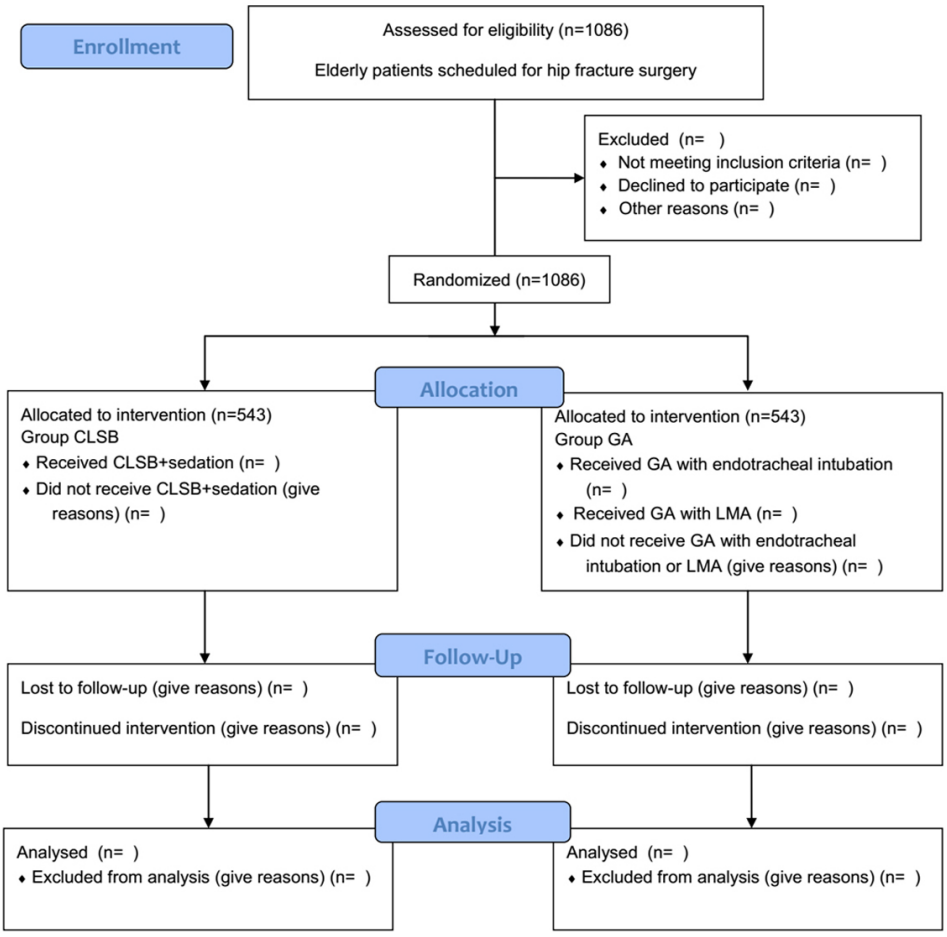
Figure legend

Fig. 1 CONSORT flowchart designed for subject enrollment



100x99mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	3	Date and version identifier	3
Funding	4	Sources and types of financial, material, and other support	2-3
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	21
	5b	Name and contact information for the trial sponsor	n/a
	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
	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)	6

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	3-6
	6b	Explanation for choice of comparators	4-5
Objectives	7	Specific objectives or hypotheses	5-6
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, noninferiority, exploratory)	6
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	6
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)	7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-11
	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)	9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	n/a
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9-11
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	11-12
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)	10,12,24

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	12-13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6-7
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	13-14
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	13-14
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	13-14
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13-14
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	13-14
Methods: Data collection, management, and analysis			
Data collection methods	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	14-18
	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	n/a

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	17-18
Statistical methods	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	18
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	18
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	n/a
Methods: Monitoring			
Data monitoring	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	17-18
	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	n/a
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	17-18
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2-3
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)	2-3

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	18-19
	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	18-19
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	21
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18
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	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	3
	31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
	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	n/a
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

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Comparison of combined lumbar and sacral plexus block with sedation versus general anesthesia on postoperative outcomes in elderly patients undergoing hip fracture surgery(CLSB-HIPELD): study protocol for a prospective, multicenter, randomized controlled trial

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Comparison of combined lumbar and sacral plexus block with sedation versus general anesthesia on postoperative outcomes in elderly patients undergoing hip fracture surgery (CLSB-HIPELD): study protocol for a prospective, multicenter, randomized controlled trial

Junfeng Zhang[#], Xiaofeng Wang[#], Hui Zhang, Zhuolin Shu, Wei Jiang*

Department of Anesthesiology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai 200233, China

*Corresponding author: Wei Jiang MD, PhD. Address: 600 Yishan Road, Shanghai 200233, China. Tel: +86 21 64369181 ext. 58328; Fax: +86 21 64369181 ext. 58330. E-mail: jiangw@sjtu.edu.cn.

[#]These authors contributed equally to this work.

Email address of all authors:

JZ: Department of Anesthesiology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Email: zhangjunfeng@sjtu.edu.cn

XW: Department of Anesthesiology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Email: 240483680@qq.com

HZ: Department of Anesthesiology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Email: zhanghui12179@163.com

ZS: Department of Anesthesiology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Email:5883434@qq.com

WJ: Department of Anesthesiology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Email: jiangw@sjtu.edu.cn

ABSTRACT

Introduction Hip fracture in elderly people is a global public health problem, with substantial associated mortality and disability. Nearly all patients with hip fracture undergo surgical treatment, but optimal anesthesia for hip fracture surgery in elderly patients is still inconclusive. Ultrasound-guided combined lumbar and sacral plexus block has been widely used in hip fracture surgery in recent years, especially for some high-risk patients. However, it is not clear whether it can improve the postoperative outcomes of elderly patients with hip fracture.

Method and analysis This research project is a two-arm, parallel, multicenter, prospective randomized controlled trail. A total of 1086 patients aged 75 and older scheduled for hip fracture surgery in five clinical trial centers of China will be randomized in a 1:1 ratio to receive either combined lumbar and sacral plexus block plus sedation or general anesthesia. The primary outcome will be the postoperative 1-year all-cause mortality. The secondary outcomes will be the incidence of postoperative complications, high-sensitivity cardiac troponin T, early mobility after surgery, postoperative VAS pain scores, postoperative delirium, length of stay in ICU and hospital, cost-effective outcomes, Barthel Index and incidence of adverse events after discharge. Assessments will be conducted in four steps: preoperative, intraoperative and in-hospital data collection and post-discharge telephone follow-up.

Ethics and dissemination This study has been supported by Shanghai Municipal Commission of Health and Family Planning Foundation for Key Developing Disciplines (2015ZB0103) and approved by the Ethics Committee of Shanghai Sixth

People's Hospital [No: 2016-28-(2)]. At the time of manuscript submission, the protocol version is v1.6 (March 2nd, 2018) with one subsequent approved amendment. Results will be disseminated via an international peer-reviewed publication.

Trial registration number NCT03318133.

Key words Elderly; Hip fracture; Lumbar plexus block; Sacral plexus block; General anesthesia

Strengths and limitations of this study

- This study will be the first prospective, multicenter, randomized controlled clinical trial to investigate the effect of the two anesthesia techniques on long-term prognostic indicators in elderly patients with hip fracture.
- The results of this study will help elucidate whether CLSB plus sedation could be safely used in hip fracture surgery and reduce the incidence of perioperative complications and improve long-term outcome in elderly patients.
- Our study results will be limited to Chinese population, and further studies on other ethnic backgrounds will be required.

1.BACKGROUND

Hip fracture is a global public health problem with an incidence of more than 1.6 million worldwide each year [1]. Owing to the global increase of the population aged 65 years and over, the total number of hip fracture is expected to surpass 6 million by 2050 [2]. While early surgery is the most effective treatment method, the postoperative mortality and disability rates are still high [3]. The elderly patients with hip fracture frequently have multiple comorbidities, which put these patients at high risk of

morbidity and mortality after anesthesia [4, 5]. Seeking appropriate anesthesia technique is in urgent need to ensure that these patients can safely and effectively get through the perioperative period.

Most studies assessing the relationship between anesthesia technique and outcomes mainly focus on the comparisons between neuraxial anesthesia (including spinal and epidural anesthesia) and general anesthesia (with an endotracheal tube or a laryngeal mask airway). A recently updated systematic review and meta-analysis has found no difference between regional versus general anesthesia, but they also supposed that the number of participants included in the review was insufficient to eliminate a difference between the two techniques in the majority of outcomes studied[6]. Some other investigations have shown that neuraxial anesthesia for hip fracture can reduce postoperative morbidity[7, 8], but two recent large-sample size observational studies deemed that neuraxial anesthesia could not significantly improve the prognosis of patients [9, 10]. However, all of the above are retrospective observational studies, in which anesthesiologists might have selected the anesthesia technique based on their practice style and a variety of patient-related factors. For example, patients with coagulation dysfunction would have contraindication to neuraxial anesthesia and must receive general anesthesia. Neuraxial anesthesia is thought to be less postoperative complications, so elderly or critically ill patients might be more likely to receive neuraxial anesthesia[11], rather than being randomly assigned to different anesthesia groups. Therefore, there could be selection bias that affected the clinical significance of those results. In addition to general anesthesia and neuraxial anesthesia, ultrasound-

guided lumbar and sacral plexus block has been widely used in hip fracture surgeries in recent years, especially for some high-risk patients with cardiopulmonary dysfunction [12-14]. Compared with neuraxial anesthesia, combined lumbar and sacral plexus block is associated with less sympathetic block and better cardiovascular function stability. In addition, combined lumbar and sacral plexus block plus sedation could avoid endotracheal intubation or laryngeal mask airway(LMA) insertion and thereby might reduce the complications related to the general anesthesia. A recent small sample size retrospective study [14] compared the effect of general endotracheal anesthesia, neuraxial anesthesia and lumbar and sacral plexus block on the prognosis of patients with hip fracture, and the results showed that neuraxial anesthesia and combined lumbar and sacral plexus block could reduce the total mortality, and there was no significant difference between neuraxial anesthesia and combined lumbar and sacral plexus block. But the number of elderly and high-ASA-grade patients in the combined lumbar and sacral plexus block group was significantly greater than that in the neuraxial anesthesia group, suggesting that when comparing the effect of these two anesthetic methods in similar conditions, combined lumbar and sacral plexus block might have more advantages. However, it is not clear whether ultrasound-guided combined lumbar and sacral plexus block plus sedation could improve outcomes of elderly patients with hip fracture.

This paper describes the design of a prospective, multicenter, parallel, randomized controlled clinical trial to assess the effect of ultrasound-guided combined lumbar and sacral plexus block plus sedation versus general anesthesia on the postoperative

outcomes in elderly patients with hip fracture.

2. METHODS AND ANALYSIS

2.1. Patient and public involvement

Patients and public were not involved in the design or conduct of the study. We do not have any specific plans to disseminate our results to patients.

2.2. Study design

This will be a two-arm, parallel, multicenter, prospective, randomized controlled trial and the design of this study protocol has referred to the SPIRIT 2013 guideline [15, 16].

2.3. Study location

The study will be conducted in five teaching hospitals including Shang Sixth People's Hospital (Shanghai, China), Beijing Chaoyang Hospital (Beijing, China), Beijing Jishuitan Hospital (Beijing, China), First Affiliated Hospital of Wenzhou Medical University (Wenzhou, China), and Foshan Hospital of Traditional Chinese Medicine (Foshan, China).

2.4. Study population

Although elderly population was considered to be people older than 65 years in the present studies, introduction to aging population is latening owing to increasing life expectancy. As shown in a recent study[17], age is the primary risk factor on first year mortality in patients older than 75 years old with hip fractures. In addition, China wants to increase its citizens' average life expectancy to 77.3 by 2020 and 79 by 2030, up from 76.34 in 2015, according to "Plan of Health China 2030" published in 2015.

We thus used 75 years as an age cutoff for inclusion criteria in this study because optimal selection of anesthesia technique in this age group might have more clinical significance.

Elderly patients above 75 years scheduled for hip fracture surgery will be recruited voluntarily according to the inclusion and exclusion criteria below. All included patients are suitable for either general endotracheal anesthesia or combined lumbar and sacral plexus block plus sedation, which will not bring tendency to choose a specific type of anesthesia.

2.4.1. Inclusion criteria:

- Age ≥75 years old;
- First unilateral surgery for hip fracture including femoral neck, intertrochanteric or subtrochanteric fracture;
- Patient with planned hip fracture surgery within 24-72 h;
- Patient without peripheral nerve block within 24 h prior to surgery or patients with preoperative peripheral nerve blockade but its effect had faded away at the beginning of the operation.
- The ability to receive written informed consent from the patient or patient's legal representative.

2.4.2. Exclusion criteria:

- Refuse to participate;
- Unable to perform nerve block;
- Multiple trauma, multiple fractures or other fractures outside the inclusion criteria,

such as pathological fractures, pelvic fractures, femur fractures;

- Prosthetic fracture;
- Scheduled for bilateral hip fracture surgery;
- Usage of bone-cement fixation in the surgery;
- With recent cerebral stroke (<3 months);
- Concomitant active heart disease (unstable angina, acute myocardial infarction, recent myocardial infarction; decompensated heart failure; symptomatic arrhythmia; severe mitral or aortic stenotic heart disease);
- Patient with known severe lung and/or airway disease, acute respiratory failure, acute pulmonary infection, and acute attack of bronchial asthma;
- Current enrolment in another clinical trial;
- Contraindication for general endotracheal anesthesia (drug allergies to general anesthesia, difficult airway);
- Contraindication for lumbar and sacral plexus block (infection at the site of needle insertion, coagulopathy, allergy to local anesthetics).

2.5. Interventions

Eligible patients will be randomly assigned into either CLSB group receiving combined lumbar and sacral plexus block plus sedation or GA group receiving general anesthesia with endotracheal intubation or LMA (Figure 1). Standard anesthetic and surgical methods will be applied to ensure the consistency of treatment in the participating centers. Experienced and qualified anesthesiologists in every clinical centers will be specifically designated to perform combined lumbar-sacral plexus block

plus sedative anesthesia or GA in order to minimize the potential bias. To improve adherence to intervention protocols, study personnel are trained to follow the study protocol in accordance with the Good Clinical Practice (GCP) principles.

In the CLSB group (Combined lumbar-sacral plexus block with sedative anesthesia), the procedures will be performed as followed.

- Peripheral venous access for fluid infusion will be established;
- In the lateral decubitus position with the operated side uppermost, ultrasound-guided lumbar plexus block (L_{2-3} or/and L_{3-4} vertebral space level, 0.375% ropivacaine 25ml) will be performed, followed by sacral plexus block (0.375 % ropivacaine 20ml); We used the nerve stimulator to confirm the needle's correct position by a quadratus femoris twitch for lumbar plexus block and hamstring, leg, or foot twitches for sacral plexus block at a current within 0.4–0.6 mA, followed by relevant volume of 0.375% ropivacaine that was slowly injected in 5 ml increments to surround the target nerve under ultrasound monitoring.
- Radial arterial catheterization under local lidocaine anesthesia and arterial blood pressure monitoring will be performed. Blockade effectiveness will be evaluated 30 minutes after nerve block; The intervention will be discontinued for a given patient and convert to general anesthesia with endotracheal intubation or LMA if the satisfactory blockade is not acquired. These patient are still followed up for further statistical analysis according to the formal protocol because they have been randomly allocated.
- After confirmation of satisfactory blockade, target-controlled infusion of propofol

will be used to maintain Ramsay sedation score between 3-4 points. $P_{ET}CO_2$ will be monitored through nasopharyngeal airway. Small-dose sufentanil (1-2μg each time) will be titrated to maintain spontaneous breathing.

In the GA group, the procedures will be performed as followed.

- Peripheral venous access for fluid infusion will be established;
- Radial arterial catheterization under local lidocaine anesthesia and arterial blood pressure monitoring will be conducted;
- Anesthesia will be induced with propofol (1.5-3mg/kg), rocuronium(0.3-0.9mg/kg), and sufentanil (0.2-0.6μg/kg) for tracheal intubation or LMA insertion. Mechanical ventilation will be performed to maintain normal $P_{ET}CO_2$.
- Sevoflurane, propofol and sufentanil will be used to maintain anesthesia during surgery, while rocuronium will be added as needed.

During surgery, fluid infusion and blood transfusion will be used to maintain stable hemodynamics. Perioperative arterial pressure lower than 30% of the baseline will be defined as hypotension, upon which ephedrine or phenylephrine will be administrated. The type and dosage of infusion depends on anesthesiologist's experience. Blood transfusion will be given according to blood loss and hemoglobin concentration(Hb) level (80-100g/L)[18]. Following surgery, patients will be sent to the postanesthesia care unit (PACU) and then transferred to orthopedic ward or intensive care unit(ICU) according to the local procedures of each clinical center. Postoperative analgesia can be administrated with regard to the routine clinical practice of each trial site, aiming to maintain a Visual Analogue Scale (VAS) pain score ≤3.

2.6. Outcomes and measurements

2.6.1. Primary outcome

Postoperative 1-year all-cause mortality (follow-up time points are set as 1 month, 3 months, 6 months and 1 year after surgery);

2.6.2. Secondary outcomes

2.6.2.1. Occurrence of intraoperative complications, including:

- Intraoperative hypotension and vasopressor dosage;
- Intraoperative arrhythmia, myocardial ischemia, myocardial infarction, massive hemorrhage, pulmonary embolism and hypoxemia;
- Intraoperative blood loss and blood transfusion volume;

2.6.2.2. High-sensitivity cardiac troponin T(hs-cTnT), measured on the 1 and 3 days after surgery;

2.6.2.3. Early mobility after surgery;

2.6.2.4. Incidence of various complications and Comprehensive Complication Index (CCI) [19] during hospitalization after surgery;

2.6.2.5. Postoperative analgesic effectiveness within three days after the surgery;

2.6.2.6. Incidence of delirium on the 1, 2 and 3 days after surgery, diagnosed with Confusion Assessment Method(CAM)[20];

2.6.2.7. Sequential Organ Failure Assessment(SOFA) [21], assessed on the 1 and 3 days after surgery;

2.6.2.8. Bauer Patient Satisfaction Questionnaire[22], assessed on the 3 days after surgery;

2.6.2.9. Length of stay in ICU and hospital;

2.6.3. Other observational variables:

2.6.3.1. Economic parameters including total cost in hospital and expenditure for anesthesia;

2.6.3.2. Functional recovery on the 30 days after surgery, evaluated by Barthel Activities of Daily Living Index (Barthel Index);

2.6.3.3. Post-discharge destination, and incidence of complications and adverse events after discharge.

2.7. Participant timeline

For a given participant, assessment will be performed one day prior to surgery and again on the day of surgery to confirm whether qualified for enrollment. Randomization will perform on the day of surgery. And then intervention will be performed. There will be an initial accrual period of about 1.5 year. The patients will be followed up on the 1, 2 and 3 days after surgery and on the day of discharge. The total follow-up period will be set as 1 year and the telephone follow-up will be conducted at the 1, 3, 6 and 12 months after surgery.

2.8. Power and Sample Size Calculation

We estimate the sample size using the formula by Schoendeld under the assumption of the validity of the proportional-hazards regression model [23, 24]. We take significance level 0.05 and power 0.80. Patients will be randomly assigned to one of the two anesthesia groups in five different clinical centers. The total number of patients needed for this study is 868 (with 434 patients in each of the two groups). With that many patients, we can ensure a power of 0.8 with level of significance 0.05 when the

mortality rate of 55% for the GA group and a relative decrease of mortality rate for the GLSB group as low as 15%. In this study, only patients with age 75 years or older will be included, so we expect the actual mortality rate of the GA group will be higher than 55% [14]. When the mortality rate of the GA group is only 45%, the above calculated sample size can still detect a 20% improvement in the CLSB group with the power of at least 0.80. In consideration of the possible lost to follow up, we add an additional 20% to the above calculated sample size. So the total number of patients needed for this study is 1086.

2.9. Randomization and blinding

Upon the receipt of informed consents, patients will be randomly assigned to the two groups in any one of the five centers. Sequentially numbered sealed opaque envelops with group allocation inside altered anesthetist to use CLSB or GA. The R program will be used to generate randomization block allocation for each of the five centers with randomly selected block sizes of four, six, and eight. The envelopes will be placed in the patient's chart before the start of each procedure by a doctor of the research team. The research staff who will interview patients postoperatively are blinded for the allocated treatment. The statistician will be blinded. A spreadsheet linking the patient number and name will be password protected and kept on a research computer. The recruitment will stop when the total number of patients reaches 1086. The subjects and intervention performers (anesthesiologists) know the randomized allocation, but the follow-up personnel and statistician was blinded to the randomized allocation and intervention.

2.10. Data collection and management

Data will be collected in four steps: preoperative, intraoperative and in-hospital data collection and post-discharge telephone follow-up.

2.10.1. Preoperative data:

2.10.1.1. Basic information including name, admission number, height, weight, gender, age, blood pressure, heart rate and ASA grade (American Society of Anesthesiologists grade).

2.10.1.2. Preoperative information including diagnosis, type of surgery, type and dosage of anticoagulants, and days passed until surgery.

2.10.1.3. Preoperative complications and medication related to cardiovascular disease, stroke, respiratory disease, kidney disease, diabetes, Parkinson's disease, and deep venous thrombosis of lower extremity if any.

2.10.1.4. Preoperative examination results including blood gas analysis, ECG, echocardiography, blood routine testing, liver and kidney function testing, coagulation testing (D-dimer), Pro-BNP, hs-cTnT, and lower extremity vascular ultrasonography.

2.10.1.5. Preoperative evaluation results including MMSE (Mini-mental State Examination), SOFA and Barthel Index, all of which might be associated with the postoperative complications.

2.10.2. Intraoperative data

2.10.2.1. Duration of surgery, incidence of intraoperative hypotension or hypertension, and vasoactive drug dosage.

2.10.2.2. Intraoperative blood loss, blood transfusion volume, and intraoperative fluid

infusion volume.

2.10.2.3. Intraoperative arrhythmia (sinus bradycardia, sinus tachycardia, ventricular arrhythmia, atrial arrhythmia, etc.), myocardial ischemia, and myocardial infarction.

2.10.2.4. Intraoperative complications: massive hemorrhage, pulmonary embolism, allergic reaction, hypoxemia, bronchospasm, gastric reflux and aspiration.

2.10.2.5. Intraoperative conversion of anesthesia and the relevant causes.

2.10.3. In-hospital data

2.10.3.1. High-sensitivity cardiac troponin T(hs-cTnT), measured on the 1 and 3 days after surgery;

2.10.3.2. Earlier mobilization and postoperative hip rehabilitation: the daily degree of maximal hip flexion and abduction will be recorded [25]. The day after surgery, all 2 groups will start an identical physical therapy regimen. The patients will perform passive and active hip flexion and abduction exercises twice daily. Patients will be encouraged to get out of bed as soon as possible and try ambulation with a walker. The maximal degree of hip flexion and abduction tolerated by each patient will be recorded for three days. The day of first ambulation will be also recorded for each group.

2.10.3.3. Postoperative complications including incidence and severity of various complications and the CCI [19] value at discharge. Complications were assessed and graded using the Clavien-Dindo classification. CCI will be derived from these features at discharge, using the CCI calculator available online (www.assessurgery.com). Complications include:

- Myocardial ischemia, myocardial infarction, heart failure, arrhythmia;

- Pulmonary infection, respiratory failure, pulmonary embolism;
- Postoperative delirium;
- Cerebral ischemia, cerebrovascular accident;
- Renal failure, urinary retention;
- Regurgitation and pulmonary aspiration;
- Postoperative nausea and vomiting (PONV);
- Postoperative bleeding and 24h postoperative drainage volume;
- Reoperation.

2.10.3.4. The intensity of postoperative pain at rest and on movement will be assessed with Visual Analogue Scale (VAS) (0 no pain, and 10 worst possible pain) at the 24, 48, and 72 hours after surgery.

2.10.3.6. CAM will be evaluated on the 1, 2 and 3 days after surgery.

2.10.3.7. SOFA [21] will be evaluated on the 1 and 3 days after surgery.

2.10.3.8. Bauer Patient Satisfaction Questionnaire will be assessed on the 3 days after surgery.

2.10.3.9. Length of ICU stay, length of hospital stay, total hospitalization cost, and expenditure for anesthesia.

2.10.4. Post-discharge follow-up data

2.10.4.1. Telephone follow-up will be performed on the 1, 3, 6 and 12 months after surgery to collect the following information.

- Discharge destinations. Disposition status after discharge will be classified as follows: dead, nursing home (e.g., skilled nursing facility, intermediate care facility, extended care facility, nursing home), community dwelling (e.g., home alone,

home with others), or other.

- Dead or not, specific cause and time.
- Incidence of complications and adverse events: heart, lungs, brain, liver, kidney, four limbs, and hospitalization, etc.

2.10.4.2. Barthel Index for evaluation of functional recovery will be collected on the 30 days after surgery.

2.11. Data and safety monitoring

Preoperative, intraoperative and in-hospital data will be collected from the electronic medical record, monitor machines and relevant manual records by one of the research staff. Telephone follow-up will be conducted by the research team. Data will be securely managed by an independent contract research organization (Shanghai Ruihui Biotech Co., Ltd, Shanghai). All serious adverse events, as well as all non-serious adverse events that are unexpected and judged to be related to the study treatment, will be recorded in the study database and reported as required to local IRBs and to the Shanghai Jiao Tong University Affiliated Sixth People's Hospital IRB. Data and safety monitoring will be the responsibility of the study director/principle investigator(PI), the study biostatistician, site clinical directors and an independent Data and Safety Monitoring Board(DSMB) selected by the study PI. The DSMB will be composed of 5-7 independent, multidisciplinary experts who are not have subordinate relationships with the PI or any member of the study team. The DSMB will review study implementation and the occurrence of adverse events.

2.12. Statistical analysis

The data will be analyzed using intention-to-treat approach. Demographics information will be compared for patients of the two groups to ensure the data are balanced. Student t-test will be used for quantitative variables such as age, and heart rate, blood pressure. Chi-square test will be used for categorical variables such as Sex, ASA classification grades. The VAS pain scores will be analyzed using repeated measure ANOVA to test the effects of treatment, time, and the interaction effect. The effects of different covariates on the mortality rates measured at 1 month, 3 months, 6 months and 12 months will be assessed using a logistic regression model. The primary analysis model will be Cox regression model with covariates. Either logistic regression or ordinary multiple regression method will also be used to assess the effects of the covariate on the secondary and other outcomes as well depending on the type of dependent variable. The proportional-hazards regression model will be used to compare the survival times of the patients in the two groups and to assess the effects of the covariates. Statistical significance will be defined for P value<0.05 (two tailed).

2.13. Access to data

During the study, data will be stored in a password-protected system and can be accessed by the research staff who sign the confidential disclosure agreements. Data without patient identification will be publicly accessible after the study.

2.14. Confidentiality

Each participant will be given an identification number and referred by the identification number throughout the study and in all study-related information. This information will be securely stored in a password-protected access system provided by

a local supplier. Relevant paper records will be stored in a locked cabinet in an access-controlled room. All records containing any patients' personal identifiers will be separately stored similarly as above.

2.15. Trial status

At the time of manuscript submission, the study is in the preparation phase for recruitment.

3. DISCUSSION

Choice of anesthesia for hip fracture surgery in elderly patients is still inconclusive. General anesthesia with endotracheal intubation or LMA is a common procedure for hip fracture surgery, with advantages of wide indications and maintaining relatively stable hemodynamics. Compared with general anesthesia, neuraxial anesthesia avoids endotracheal intubation or LMA insertion. But vertebral degeneration and anatomical abnormalities in elderly patients often make neuraxial anesthesia puncture difficult, and most of these patients are taking anticoagulants, which are the contraindication of neuraxial anesthesia. So the neuraxial anesthesia has limitations in application for the elderly patient. The principle for anesthesia selection is to reduce or avoid the effect of anesthesia on systemic and vital organ functions as much as possible when meeting the needs of surgery. Previous lumbar and sacral plexus block depends on blind puncture technique and cannot ensure the clinical effectiveness. However, ultrasound visualization technology has promoted the wide application of lumbar and sacral plexus block. Combined lumbar and sacral plexus block with sedative anesthesia has gradually become alternative approach for hip fracture surgery in elderly patients, and this

anesthetic technique has been massively applied in our department and achieved satisfactory clinical results in recent years, but there is few reliable clinical evidence on whether it can be safely used for hip fracture surgery in elderly patients and improve the short-term or long-term outcomes. Thus, we have designed this trial protocol to illustrate the clinical value of combined lumbar and sacral plexus block with sedative anesthesia in elderly patients undergoing hip fracture surgery. In this study, we will observe the effect of the two anesthetic methods (general endotracheal anesthesia or combined lumbar and sacral plexus block plus sedation on the early prognostic indicators in elderly patients with hip fracture, including postoperative complications, postoperative analgesic effect, postoperative early mobility, postoperative delirium, patient's satisfaction to anesthesia and length of stay in ICU and hospital. This study will be the first prospective, multicenter, randomized controlled clinical trial to investigate the effect of the two anesthesia techniques on long-term prognostic indicators in elderly patients with hip fracture, including postoperative 1-year all-cause mortality and incidence of complications and adverse events. The results of this study will help elucidate whether ultrasound-guided combined lumbar and sacral plexus block with sedative anesthesia can be safely used in hip fracture surgery in elderly patients and can reduce the incidence of perioperative complications and improve long-term prognosis, so as to solve the troubling clinical problem and provide a theoretical basis for elderly patients undergoing hip fracture surgery to choose the optimal anesthetic method.

Abbreviations

ASA grade: American Society of Anesthesiologists grade; GA: General anesthesia; CLSB: Combined Lumbar and Sacral Plexus Block; PACU: Postanesthesia Care Unit; Hb: Hemoglobin Concentration; ICU: Intensive Care Unit; CCI: Comprehensive Complication Index; SOFA: Sequential Organ Failure Assessment; CAM: The Confusion Assessment method; MMSE: Mini-mental State Examination; ECG: Echocardiography; Pro-BNP: Pro Brain Natriuretic Peptide; hs-cTnT: High-sensitivity cardiac Troponin T; PONV: Postoperative Nausea and Vomiting; VAS: Visual Analog Scale

Contributors JZ and WJ designed the study and wrote the protocol. HZ and XW performed statistical analysis. HZ, XW and ZS were involved in protocol conception and design and manuscript revision. WJ is the principal investigator of this clinical trial. All authors read and approved the final version of the manuscript.

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Data sharing statement No additional data are available.

Patient consent Obtained.

Competing interests None declared.

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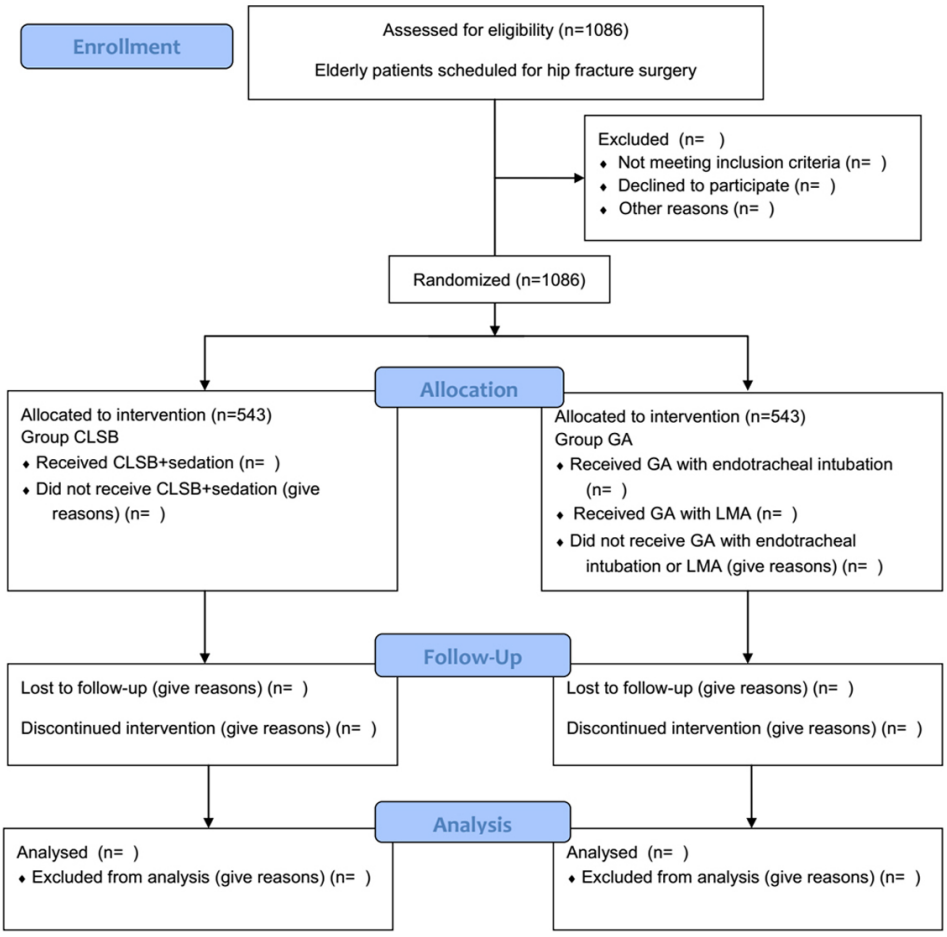
Figure legend

Fig. 1 CONSORT flowchart designed for subject enrollment



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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	3	Date and version identifier	3
Funding	4	Sources and types of financial, material, and other support	2-3
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	21
	5b	Name and contact information for the trial sponsor	n/a
	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
	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)	6

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	3-6
	6b	Explanation for choice of comparators	4-5
Objectives	7	Specific objectives or hypotheses	5-6
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, noninferiority, exploratory)	6
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	6
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)	7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-11
	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)	9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	n/a
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9-11
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	11-12
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)	10,12,24

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	12-13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6-7
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	13-14
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	13-14
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	13-14
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13-14
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	13-14
Methods: Data collection, management, and analysis			
Data collection methods	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	14-18
	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	n/a

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	17-18
Statistical methods	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	18
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	18
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	n/a
Methods: Monitoring			
Data monitoring	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	17-18
	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	n/a
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	17-18
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2-3
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)	2-3

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	18-19
	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	18-19
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	21
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18
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	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	3
	31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
	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	n/a
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

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Comparison of combined lumbar and sacral plexus block with sedation versus general anesthesia on postoperative outcomes in elderly patients undergoing hip fracture surgery(CLSB-HIPELD): study protocol for a prospective, multicenter, randomized controlled trial

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Comparison of combined lumbar and sacral plexus block with sedation versus general anesthesia on postoperative outcomes in elderly patients undergoing hip fracture surgery(CLSB-HIPELD): study protocol for a prospective, multicenter, randomized controlled trial

Junfeng Zhang[#], Xiaofeng Wang[#], Hui Zhang, Zhuolin Shu, Wei Jiang*

Department of Anesthesiology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai 200233, China

*Corresponding author: Wei Jiang MD, PhD. Address: 600 Yishan Road, Shanghai 200233, China. Tel: +86 21 64369181 ext. 58328; Fax: +86 21 64369181 ext. 58330. E-mail: jiangw@sjtu.edu.cn.

[#]These authors contributed equally to this work.

Email address of all authors:

JZ: Department of Anesthesiology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Email: zhangjunfeng@sjtu.edu.cn

XW: Department of Anesthesiology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Email: 240483680@qq.com

HZ: Department of Anesthesiology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Email: zhanghui12179@163.com

ZS: Department of Anesthesiology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Email:5883434@qq.com

WJ: Department of Anesthesiology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Email: jiangw@sjtu.edu.cn

ABSTRACT

Introduction Hip fracture in elderly people is a global public health problem, with substantial associated mortality and disability. Nearly all patients with hip fracture undergo surgical treatment, but optimal anesthesia for hip fracture surgery in elderly patients is still inconclusive. Ultrasound-guided combined lumbar and sacral plexus block has been widely used in hip fracture surgery in recent years, especially for some high-risk patients. However, it is not clear whether it can improve the postoperative outcomes of elderly patients with hip fracture.

Method and analysis This research project is a two-arm, parallel, multicenter, prospective randomized controlled trail. A total of 1086 patients aged 75 and older scheduled for hip fracture surgery in five clinical trial centers of China will be randomized in a 1:1 ratio to receive either combined lumbar and sacral plexus block plus sedation or general anesthesia. The primary outcome will be the postoperative 1-year all-cause mortality. The secondary outcomes will be the incidence of postoperative complications, high-sensitivity cardiac troponin T, early mobility after surgery, postoperative VAS pain scores, postoperative delirium, length of stay in ICU and hospital, cost-effective outcomes, Barthel Index and incidence of adverse events after discharge. Assessments will be conducted in four steps: preoperative, intraoperative and in-hospital data collection and post-discharge telephone follow-up.

Ethics and dissemination This study has been supported by Shanghai Municipal Commission of Health and Family Planning Foundation for Key Developing Disciplines (2015ZB0103) and approved by the Ethics Committee of Shanghai Sixth

People's Hospital [No: 2016-28-(2)]. At the time of manuscript submission, the protocol version is v1.6 (March 2nd, 2018) with one subsequent approved amendment. Results will be disseminated via an international peer-reviewed publication.

Trial registration number NCT03318133.

Key words Elderly; Hip fracture; Lumbar plexus block; Sacral plexus block; General anesthesia

Strengths and limitations of this study

- This study will be the first prospective, multicenter, randomized controlled clinical trial to investigate the effect of the two anesthesia techniques on long-term prognostic indicators in elderly patients with hip fracture.
- The results of this study will help elucidate whether CLSB plus sedation could be safely used in hip fracture surgery and reduce the incidence of perioperative complications and improve long-term outcome in elderly patients.
- Our study results will be limited to Chinese population, and further studies on other ethnic backgrounds will be required.

1.BACKGROUND

Hip fracture is a global public health problem with an incidence of more than 1.6 million worldwide each year [1]. Owing to the global increase of the population aged 65 years and over, the total number of hip fracture is expected to surpass 6 million by 2050 [2]. While early surgery is the most effective treatment method, the postoperative mortality and disability rates are still high [3]. The elderly patients with hip fracture frequently have multiple comorbidities, which put these patients at high risk of

morbidity and mortality after anesthesia [4, 5]. Seeking appropriate anesthesia technique is in urgent need to ensure that these patients can safely and effectively get through the perioperative period.

Most studies assessing the relationship between anesthesia technique and outcomes mainly focus on the comparisons between neuraxial anesthesia (including spinal and epidural anesthesia) and general anesthesia (with an endotracheal tube or a laryngeal mask airway). A recently updated systematic review and meta-analysis has found no difference between regional versus general anesthesia, but they also supposed that the number of participants included in the review was insufficient to eliminate a difference between the two techniques in the majority of outcomes studied[6]. Some other investigations have shown that neuraxial anesthesia for hip fracture can reduce postoperative morbidity[7, 8], but two recent large-sample size observational studies deemed that neuraxial anesthesia could not significantly improve the prognosis of patients [9, 10]. However, all of the above are retrospective observational studies, in which anesthesiologists might have selected the anesthesia technique based on their practice style and a variety of patient-related factors. For example, patients with coagulation dysfunction would have contraindication to neuraxial anesthesia and must receive general anesthesia. Neuraxial anesthesia is thought to be less postoperative complications, so elderly or critically ill patients might be more likely to receive neuraxial anesthesia[11], rather than being randomly assigned to different anesthesia groups. Therefore, there could be selection bias that affected the clinical significance of those results. In addition to general anesthesia and neuraxial anesthesia, ultrasound-

guided lumbar and sacral plexus block has been widely used in hip fracture surgeries in recent years, especially for some high-risk patients with cardiopulmonary dysfunction [12-14]. Compared with neuraxial anesthesia, combined lumbar and sacral plexus block is associated with less sympathetic block and better cardiovascular function stability. In addition, combined lumbar and sacral plexus block plus sedation could avoid endotracheal intubation or laryngeal mask airway(LMA) insertion and thereby might reduce the complications related to the general anesthesia. A recent small sample size retrospective study [14] compared the effect of general endotracheal anesthesia, neuraxial anesthesia and lumbar and sacral plexus block on the prognosis of patients with hip fracture, and the results showed that neuraxial anesthesia and combined lumbar and sacral plexus block could reduce the total mortality, and there was no significant difference between neuraxial anesthesia and combined lumbar and sacral plexus block. But the number of elderly and high-ASA-grade patients in the combined lumbar and sacral plexus block group was significantly greater than that in the neuraxial anesthesia group, suggesting that when comparing the effect of these two anesthetic methods in similar conditions, combined lumbar and sacral plexus block might have more advantages. However, it is not clear whether ultrasound-guided combined lumbar and sacral plexus block plus sedation could improve outcomes of elderly patients with hip fracture.

This paper describes the design of a prospective, multicenter, parallel, randomized controlled clinical trial to assess the effect of ultrasound-guided combined lumbar and sacral plexus block plus sedation versus general anesthesia on the postoperative

outcomes in elderly patients with hip fracture.

2. METHODS AND ANALYSIS

2.1. Patient and public involvement

Patients and public were not involved in the design or conduct of the study. We do not have any specific plans to disseminate our results to patients.

2.2. Study design

This will be a two-arm, parallel, multicenter, prospective, randomized controlled trial and the design of this study protocol has referred to the SPIRIT 2013 guideline [15, 16].

2.3. Study location

The study will be conducted in five teaching hospitals including Shang Sixth People's Hospital (Shanghai, China), Beijing Chaoyang Hospital (Beijing, China), Beijing Jishuitan Hospital (Beijing, China), First Affiliated Hospital of Wenzhou Medical University (Wenzhou, China), and Foshan Hospital of Traditional Chinese Medicine (Foshan, China).

2.4. Study population

Although elderly population was considered to be people older than 65 years in the present studies, introduction to aging population is latening owing to increasing life expectancy. As shown in a recent study[17], age is the primary risk factor on first year mortality in patients older than 75 years old with hip fractures. In addition, China wants to increase its citizens' average life expectancy to 77.3 by 2020 and 79 by 2030, up from 76.34 in 2015, according to "Plan of Health China 2030" published in 2015.

We thus used 75 years as an age cutoff for inclusion criteria in this study because optimal selection of anesthesia technique in this age group might have more clinical significance.

Elderly patients above 75 years scheduled for hip fracture surgery will be recruited voluntarily according to the inclusion and exclusion criteria below. All included patients are suitable for either general endotracheal anesthesia or combined lumbar and sacral plexus block plus sedation, which will not bring tendency to choose a specific type of anesthesia.

2.4.1. Inclusion criteria:

- Age ≥75 years old;
- First unilateral surgery for hip fracture including femoral neck, intertrochanteric or subtrochanteric fracture;
- Patient with planned hip fracture surgery within 24-72 h;
- Patient without peripheral nerve block within 24 h prior to surgery or patients with preoperative peripheral nerve blockade but its effect had faded away at the beginning of the operation.
- The ability to receive written informed consent from the patient or patient's legal representative.

2.4.2. Exclusion criteria:

- Refuse to participate;
- Unable to perform nerve block;
- Multiple trauma, multiple fractures or other fractures outside the inclusion criteria,

such as pathological fractures, pelvic fractures, femur fractures;

- Prosthetic fracture;
- Scheduled for bilateral hip fracture surgery;
- Usage of bone-cement fixation in the surgery;
- With recent cerebral stroke (<3 months);
- Concomitant active heart disease (unstable angina, acute myocardial infarction, recent myocardial infarction; decompensated heart failure; symptomatic arrhythmia; severe mitral or aortic stenotic heart disease);
- Patient with known severe lung and/or airway disease, acute respiratory failure, acute pulmonary infection, and acute attack of bronchial asthma;
- Current enrolment in another clinical trial;
- Contraindication for general endotracheal anesthesia (drug allergies to general anesthesia, difficult airway);
- Contraindication for lumbar and sacral plexus block (infection at the site of needle insertion, coagulopathy, allergy to local anesthetics).

2.5. Interventions

Eligible patients will be randomly assigned into either CLSB group receiving combined lumbar and sacral plexus block plus sedation or GA group receiving general anesthesia with endotracheal intubation or LMA (Figure 1). Standard anesthetic and surgical methods will be applied to ensure the consistency of treatment in the participating centers. Experienced and qualified anesthesiologists in every clinical centers will be specifically designated to perform combined lumbar-sacral plexus block

plus sedative anesthesia or GA in order to minimize the potential bias. To improve adherence to intervention protocols, study personnel are trained to follow the study protocol in accordance with the Good Clinical Practice (GCP) principles.

In the CLSB group (Combined lumbar-sacral plexus block with sedative anesthesia), the procedures will be performed as followed.

- Peripheral venous access for fluid infusion will be established;
- In the lateral decubitus position with the operated side uppermost, ultrasound-guided lumbar plexus block (L_{2-3} or/and L_{3-4} vertebral space level, 0.375% ropivacaine 25ml) will be performed, followed by sacral plexus block (0.375 % ropivacaine 20ml); We used the nerve stimulator to confirm the needle's correct position by a quadratus femoris twitch for lumbar plexus block and hamstring, leg, or foot twitches for sacral plexus block at a current within 0.4–0.6 mA, followed by relevant volume of 0.375% ropivacaine that was slowly injected in 5 ml increments to surround the target nerve under ultrasound monitoring.
- Radial arterial catheterization under local lidocaine anesthesia and arterial blood pressure monitoring will be performed. Blockade effectiveness will be evaluated 30 minutes after nerve block; The intervention will be discontinued for a given patient and convert to general anesthesia with endotracheal intubation or LMA if the satisfactory blockade is not acquired. These patient are still followed up for further statistical analysis according to the formal protocol because they have been randomly allocated.
- After confirmation of satisfactory blockade, target-controlled infusion of propofol

will be used to maintain Ramsay sedation score between 3-4 points. $P_{ET}CO_2$ will be monitored through nasopharyngeal airway. Small-dose sufentanil (1-2μg each time) will be titrated to maintain spontaneous breathing.

In the GA group, the procedures will be performed as followed.

- Peripheral venous access for fluid infusion will be established;
- Radial arterial catheterization under local lidocaine anesthesia and arterial blood pressure monitoring will be conducted;
- Anesthesia will be induced with propofol (1.5-3mg/kg), rocuronium(0.3-0.9mg/kg), and sufentanil (0.2-0.6μg/kg) for tracheal intubation or LMA insertion. Mechanical ventilation will be performed to maintain normal $P_{ET}CO_2$.
- Sevoflurane, propofol and sufentanil will be used to maintain anesthesia during surgery, while rocuronium will be added as needed.

During surgery, fluid infusion and blood transfusion will be used to maintain stable hemodynamics. Perioperative arterial pressure lower than 30% of the baseline will be defined as hypotension, upon which ephedrine or phenylephrine will be administrated. The type and dosage of infusion depends on anesthesiologist's experience. Blood transfusion will be given according to blood loss and hemoglobin concentration(Hb) level (80-100g/L)[18]. Following surgery, patients will be sent to the postanesthesia care unit (PACU) and then transferred to orthopedic ward or intensive care unit(ICU) according to the local procedures of each clinical center. Postoperative analgesia can be administrated with regard to the routine clinical practice of each trial site, aiming to maintain a Visual Analogue Scale (VAS) pain score ≤3.

2.6. Outcomes and measurements

2.6.1. Primary outcome

Postoperative 1-year all-cause mortality (follow-up time points are set as 1 month, 3 months, 6 months and 1 year after surgery);

2.6.2. Secondary outcomes

2.6.2.1. Occurrence of intraoperative complications, including:

- Intraoperative hypotension and vasopressor dosage;
- Intraoperative arrhythmia, myocardial ischemia, myocardial infarction, massive hemorrhage, pulmonary embolism and hypoxemia;
- Intraoperative blood loss and blood transfusion volume;

2.6.2.2. High-sensitivity cardiac troponin T(hs-cTnT), measured on the 1 and 3 days after surgery;

2.6.2.3. Early mobility after surgery;

2.6.2.4. Incidence of various complications and Comprehensive Complication Index (CCI) [19] during hospitalization after surgery;

2.6.2.5. Postoperative analgesic effectiveness within three days after the surgery;

2.6.2.6. Incidence of delirium on the 1, 2 and 3 days after surgery, diagnosed with Confusion Assessment Method(CAM)[20];

2.6.2.7. Sequential Organ Failure Assessment(SOFA) [21], assessed on the 1 and 3 days after surgery;

2.6.2.8. Bauer Patient Satisfaction Questionnaire[22], assessed on the 3 days after surgery;

2.6.2.9. Length of stay in ICU and hospital;

2.6.3. Other observational variables:

2.6.3.1. Economic parameters including total cost in hospital and expenditure for anesthesia;

2.6.3.2. Functional recovery on the 30 days after surgery, evaluated by Barthel Activities of Daily Living Index (Barthel Index);

2.6.3.3. Post-discharge destination, and incidence of complications and adverse events after discharge.

2.7. Participant timeline

For a given participant, assessment will be performed one day prior to surgery and again on the day of surgery to confirm whether qualified for enrollment. Randomization will perform on the day of surgery. And then intervention will be performed. The accrual period of this trial is expected to be about 1 year. The patients will be followed up on the 1, 2 and 3 days after surgery and on the day of discharge. The total follow-up period will be set as 1 year and the telephone follow-up will be conducted at the 1, 3, 6 and 12 months after surgery.

2.8. Power and Sample Size Calculation

We estimate the sample size using the formula by Schoendeld under the assumption of the validity of the proportional-hazards regression model [23, 24]. We take significance level 0.05 (two-sided) and power 0.80. Patients will be randomly assigned to one of the two anesthesia groups in five different clinical centers. A retrospective study included patients over 65 years old showed that the one-year mortality was 41.7% for GA group and 28.3% for combined peripheral nerve block (CPNB) group [14]. In

this study, only patients with age 75 years or older will be included, so we expect the actual mortality of the GA group will be higher than that in the previous study. Therefore, we assume the mortality to be 55% for GA group and 46.75% for CLSB group (15% relative reduction compared with GA group). Then the sample size needed for this study is 868 (with 434 in each of the two groups). When the mortality of the GA group is only 45%, the above calculated sample size can still detect a 20% improvement in the CLSB group with the power of at least 0.80. In consideration of the possible lost to follow up, we add an additional 20% to the above calculated sample size. So the total number of patients needed for this study is 1086.

2.9. Randomization and blinding

Upon the receipt of informed consents, patients will be randomly assigned to the two groups in any one of the five centers. Sequentially numbered sealed opaque envelops with group allocation inside altered anesthetist to use CLSB or GA. The R program will be used to generate randomization block allocation for each of the five centers with randomly selected block sizes of four, six, and eight. The envelopes will be placed in the patient's chart before the start of each procedure by a doctor of the research team. The research staff who will interview patients postoperatively are blinded for the allocated treatment. The statistician will be blinded. A spreadsheet linking the patient number and name will be password protected and kept on a research computer. The recruitment will stop when the total number of patients reaches 1086. The subjects and intervention performers (anesthesiologists) know the randomized allocation, but the follow-up personnel and statistician was blinded to the randomized

allocation and intervention.

2.10. Data collection and management

Data will be collected in four steps: preoperative, intraoperative and in-hospital data collection and post-discharge telephone follow-up.

2.10.1. Preoperative data:

2.10.1.1. Basic information including name, admission number, height, weight, gender, age, blood pressure, heart rate and ASA grade (American Society of Anesthesiologists grade).

2.10.1.2. Preoperative information including diagnosis, type of surgery, type and dosage of anticoagulants, and days passed until surgery.

2.10.1.3. Preoperative complications and medication related to cardiovascular disease, stroke, respiratory disease, kidney disease, diabetes, Parkinson's disease, and deep venous thrombosis of lower extremity if any.

2.10.1.4. Preoperative examination results including blood gas analysis, ECG, echocardiography, blood routine testing, liver and kidney function testing, coagulation testing (D-dimer), Pro-BNP, hs-cTnT, and lower extremity vascular ultrasonography.

2.10.1.5. Preoperative evaluation results including MMSE (Mini-mental State Examination), SOFA and Barthel Index, all of which might be associated with the postoperative complications.

2.10.2. Intraoperative data

2.10.2.1. Duration of surgery, incidence of intraoperative hypotension or hypertension, and vasoactive drug dosage.

2.10.2.2. Intraoperative blood loss, blood transfusion volume, and intraoperative fluid infusion volume.

2.10.2.3. Intraoperative arrhythmia (sinus bradycardia, sinus tachycardia, ventricular arrhythmia, atrial arrhythmia, etc.), myocardial ischemia, and myocardial infarction.

2.10.2.4. Intraoperative complications: massive hemorrhage, pulmonary embolism, allergic reaction, hypoxemia, bronchospasm, gastric reflux and aspiration.

2.10.2.5. Intraoperative conversion of anesthesia and the relevant causes.

2.10.3. In-hospital data

2.10.3.1. High-sensitivity cardiac troponin T(hs-cTnT), measured on the 1 and 3 days after surgery;

2.10.3.2. Earlier mobilization and postoperative hip rehabilitation: the daily degree of maximal hip flexion and abduction will be recorded [25]. The day after surgery, all 2 groups will start an identical physical therapy regimen. The patients will perform passive and active hip flexion and abduction exercises twice daily. Patients will be encouraged to get out of bed as soon as possible and try ambulation with a walker. The maximal degree of hip flexion and abduction tolerated by each patient will be recorded for three days. The day of first ambulation will be also recorded for each group.

2.10.3.3. Postoperative complications including incidence and severity of various complications and the CCI [19] value at discharge. Complications were assessed and graded using the Clavien-Dindo classification. CCI will be derived from these features at discharge, using the CCI calculator available online (www.assessurgery.com). Complications include:

- Myocardial ischemia, myocardial infarction, heart failure, arrhythmia;
- Pulmonary infection, respiratory failure, pulmonary embolism;
- Postoperative delirium;
- Cerebral ischemia, cerebrovascular accident;
- Renal failure, urinary retention;
- Regurgitation and pulmonary aspiration;
- Postoperative nausea and vomiting (PONV);
- Postoperative bleeding and 24h postoperative drainage volume;
- Reoperation.

2.10.3.4. The intensity of postoperative pain at rest and on movement will be assessed with Visual Analogue Scale (VAS) (0 no pain, and 10 worst possible pain) at the 24, 48, and 72 hours after surgery.

2.10.3.6. CAM will be evaluated on the 1, 2 and 3 days after surgery.

2.10.3.7. SOFA [21] will be evaluated on the 1 and 3 days after surgery.

2.10.3.8. Bauer Patient Satisfaction Questionnaire will be assessed on the 3 days after surgery.

2.10.3.9. Length of ICU stay, length of hospital stay, total hospitalization cost, and expenditure for anesthesia.

2.10.4. Post-discharge follow-up data

2.10.4.1. Telephone follow-up will be performed on the 1, 3, 6 and 12 months after surgery to collect the following information.

- Discharge destinations. Disposition status after discharge will be classified as follows: dead, nursing home (e.g., skilled nursing facility, intermediate care facility,

extended care facility, nursing home), community dwelling (e.g., home alone, home with others), or other.

- Dead or not, specific cause and time.
- Incidence of complications and adverse events: heart, lungs, brain, liver, kidney, four limbs, and hospitalization, etc.

2.10.4.2. Barthel Index for evaluation of functional recovery will be collected on the 30 days after surgery.

2.11. Data and safety monitoring

Preoperative, intraoperative and in-hospital data will be collected from the electronic medical record, monitor machines and relevant manual records by one of the research staff. Telephone follow-up will be conducted by the research team. Data will be securely managed by an independent contract research organization (Shanghai Ruihui Biotech Co., Ltd, Shanghai). All serious adverse events, as well as all non-serious adverse events that are unexpected and judged to be related to the study treatment, will be recorded in the study database and reported as required to local IRBs and to the Shanghai Jiao Tong University Affiliated Sixth People's Hospital IRB. Data and safety monitoring will be the responsibility of the study director/principle investigator(PI), the study biostatistician, site clinical directors and an independent Data and Safety Monitoring Board(DSMB) selected by the study PI. The DSMB will be composed of 5-7 independent, multidisciplinary experts who are not have subordinate relationships with the PI or any member of the study team. The DSMB will review study implementation and the occurrence of adverse events.

2.12. Statistical analysis

The data will be analyzed using intention-to-treat approach. Demographics information will be compared for patients of the two groups to ensure the data are balanced. Student t-test will be used for quantitative variables such as age, and heart rate, blood pressure. Chi-square test will be used for categorical variables such as Sex, ASA classification grades. The VAS pain scores will be analyzed using repeated measure ANOVA to test the effects of treatment, time, and the interaction effect. The effects of different covariates on the mortality measured at 1 month, 3 months, 6 months and 12 months will be assessed using a logistic regression model. The primary analysis model will be Cox regression model with covariates. Either logistic regression or ordinary multiple regression method will also be used to assess the effects of the covariate on the secondary and other outcomes as well depending on the type of dependent variable. The proportional-hazards regression model will be used to compare the survival times of the patients in the two groups and to assess the effects of the covariates. All tests will be two-sided and a value of $P<0.05$ will be considered statistically significant.

2.13. Access to data

During the study, data will be stored in a password-protected system and can be accessed by the research staff who sign the confidential disclosure agreements. Data without patient identification will be publicly accessible after the study.

2.14. Confidentiality

Each participant will be given an identification number and referred by the

identification number throughout the study and in all study-related information. This information will be securely stored in a password-protected access system provided by a local supplier. Relevant paper records will be stored in a locked cabinet in an access-controlled room. All records containing any patients' personal identifiers will be separately stored similarly as above.

2.15. Trial status

At the time of manuscript submission, the study is in the preparation phase for recruitment.

3. DISCUSSION

Choice of anesthesia for hip fracture surgery in elderly patients is still inconclusive. General anesthesia with endotracheal intubation or LMA is a common procedure for hip fracture surgery, with advantages of wide indications and maintaining relatively stable hemodynamics. Compared with general anesthesia, neuraxial anesthesia avoids endotracheal intubation or LMA insertion. But vertebral degeneration and anatomical abnormalities in elderly patients often make neuraxial anesthesia puncture difficult, and most of these patients are taking anticoagulants, which are the contraindication of neuraxial anesthesia. So the neuraxial anesthesia has limitations in application for the elderly patient. The principle for anesthesia selection is to reduce or avoid the effect of anesthesia on systemic and vital organ functions as much as possible when meeting the needs of surgery. Previous lumbar and sacral plexus block depends on blind puncture technique and cannot ensure the clinical effectiveness. However, ultrasound visualization technology has promoted the wide application of lumbar and sacral plexus

block. Combined lumbar and sacral plexus block with sedative anesthesia has gradually become alternative approach for hip fracture surgery in elderly patients, and this anesthetic technique has been massively applied in our department and achieved satisfactory clinical results in recent years, but there is few reliable clinical evidence on whether it can be safely used for hip fracture surgery in elderly patients and improve the short-term or long-term outcomes. Thus, we have designed this trial protocol to illustrate the clinical value of combined lumbar and sacral plexus block with sedative anesthesia in elderly patients undergoing hip fracture surgery. In this study, we will observe the effect of the two anesthetic methods (general endotracheal anesthesia or combined lumbar and sacral plexus block plus sedation on the early prognostic indicators in elderly patients with hip fracture, including postoperative complications, postoperative analgesic effect, postoperative early mobility, postoperative delirium, patient's satisfaction to anesthesia and length of stay in ICU and hospital. This study will be the first prospective, multicenter, randomized controlled clinical trial to investigate the effect of the two anesthesia techniques on long-term prognostic indicators in elderly patients with hip fracture, including postoperative 1-year all-cause mortality and incidence of complications and adverse events. The results of this study will help elucidate whether ultrasound-guided combined lumbar and sacral plexus block with sedative anesthesia can be safely used in hip fracture surgery in elderly patients and can reduce the incidence of perioperative complications and improve long-term prognosis, so as to solve the troubling clinical problem and provide a theoretical basis for elderly patients undergoing hip fracture surgery to choose the optimal

anesthetic method.

Abbreviations

ASA grade: American Society of Anesthesiologists grade; GA: General anesthesia; CLSB: Combined Lumbar and Sacral Plexus Block; PACU: Postanesthesia Care Unit; Hb: Hemoglobin Concentration; ICU: Intensive Care Unit; CCI: Comprehensive Complication Index; SOFA: Sequential Organ Failure Assessment; CAM: The Confusion Assessment method; MMSE: Mini-mental State Examination; ECG: Echocardiography; Pro-BNP: Pro Brain Natriuretic Peptide; hs-cTnT: High-sensitivity cardiac Troponin T; PONV: Postoperative Nausea and Vomiting; VAS: Visual Analog Scale

Contributors JZ and WJ designed the study and wrote the protocol. HZ and XW performed statistical analysis. HZ, XW and ZS were involved in protocol conception and design and manuscript revision. WJ is the principal investigator of this clinical trial. All authors read and approved the final version of the manuscript.

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Data sharing statement No additional data are available.

Patient consent Obtained.

Competing interests None declared.

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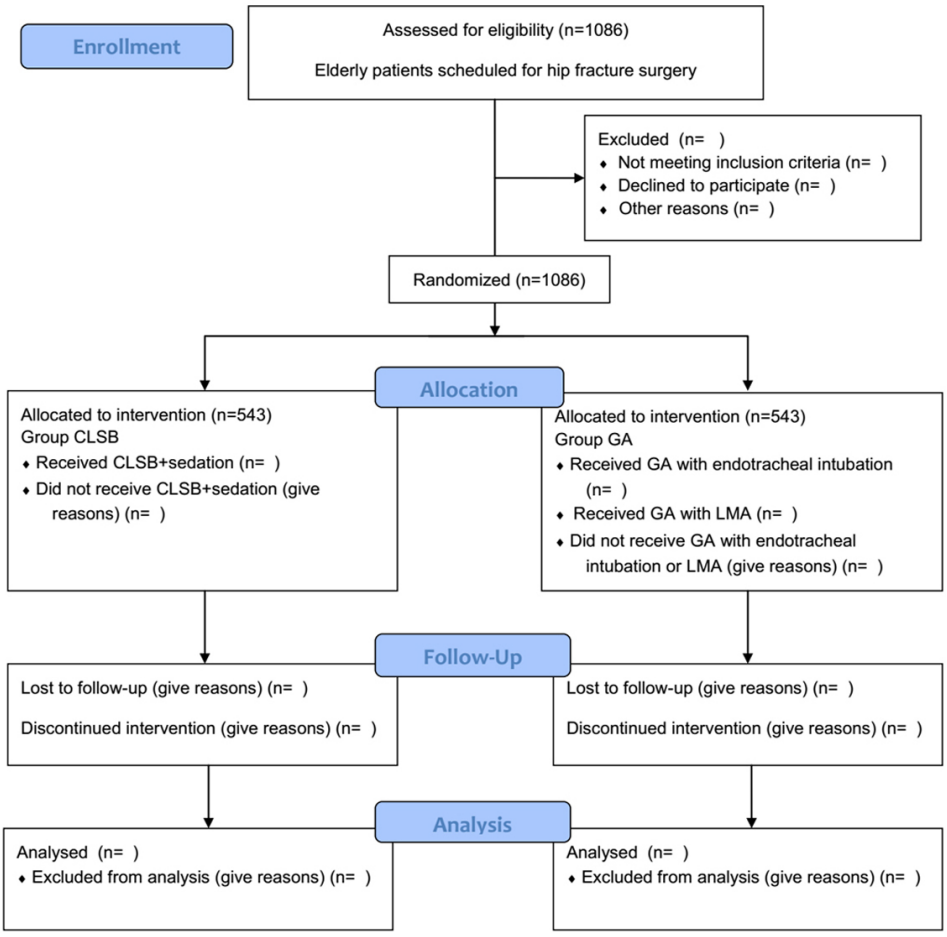
Figure legend

Fig. 1 CONSORT flowchart designed for subject enrollment



100x99mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	3	Date and version identifier	3
Funding	4	Sources and types of financial, material, and other support	2-3
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	21
	5b	Name and contact information for the trial sponsor	n/a
	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
	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)	6

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	3-6
	6b	Explanation for choice of comparators	4-5
Objectives	7	Specific objectives or hypotheses	5-6
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, noninferiority, exploratory)	6
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	6
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)	7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-11
	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)	9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	n/a
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9-11
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	11-12
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)	10,12,24

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	12-13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6-7
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	13-14
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	13-14
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	13-14
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13-14
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	13-14
Methods: Data collection, management, and analysis			
Data collection methods	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	14-18
	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	n/a

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	17-18
Statistical methods	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	18
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	18
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	n/a
Methods: Monitoring			
Data monitoring	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	17-18
	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	n/a
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	17-18
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2-3
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)	2-3

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	18-19
	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	18-19
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	21
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18
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	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	3
	31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
	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	n/a
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

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Comparison of combined lumbar and sacral plexus block with sedation versus general anesthesia on postoperative outcomes in elderly patients undergoing hip fracture surgery(CLSB-HIPELD): study protocol for a prospective, multicenter, randomized controlled trial

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Primary Subject Heading:	Anaesthesia
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Keywords:	Hip fracture, Elderly, Lumbar plexus block, Sacral plexus block, General anesthesia

Comparison of combined lumbar and sacral plexus block with sedation versus general anesthesia on postoperative outcomes in elderly patients undergoing hip fracture surgery(CLSB-HIPELD): study protocol for a prospective, multicenter, randomized controlled trial

Junfeng Zhang[#], Xiaofeng Wang[#], Hui Zhang, Zhuolin Shu, Wei Jiang*

Department of Anesthesiology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai 200233, China

*Corresponding author: Wei Jiang MD, PhD. Address: 600 Yishan Road, Shanghai 200233, China. Tel: +86 21 64369181 ext. 58328; Fax: +86 21 64369181 ext. 58330. E-mail: jiangw@sjtu.edu.cn.

[#]These authors contributed equally to this work.

Email address of all authors:

JZ: Department of Anesthesiology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Email: zhangjunfeng@sjtu.edu.cn

XW: Department of Anesthesiology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Email: 240483680@qq.com

HZ: Department of Anesthesiology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Email: zhanghui12179@163.com

ZS: Department of Anesthesiology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Email:5883434@qq.com

WJ: Department of Anesthesiology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Email: jiangw@sjtu.edu.cn

ABSTRACT

Introduction Hip fracture in elderly people is a global public health problem, with substantial associated mortality and disability. Nearly all patients with hip fracture undergo surgical treatment, but optimal anesthesia for hip fracture surgery in elderly patients is still inconclusive. Ultrasound-guided combined lumbar and sacral plexus block has been widely used in hip fracture surgery in recent years, especially for some high-risk patients. However, it is not clear whether it can improve the postoperative outcomes of elderly patients with hip fracture.

Method and analysis This research project is a two-arm, parallel, multicenter, prospective randomized controlled trail. A total of 1086 patients aged 75 and older scheduled for hip fracture surgery in five clinical trial centers of China will be randomized in a 1:1 ratio to receive either combined lumbar and sacral plexus block plus sedation or general anesthesia. The primary outcome will be the postoperative 1-year all-cause mortality. The secondary outcomes will be the incidence of postoperative complications, high-sensitivity cardiac troponin T, early mobility after surgery, postoperative VAS pain scores, postoperative delirium, length of stay in ICU and hospital, cost-effective outcomes, Barthel Index and incidence of adverse events after discharge. Assessments will be conducted in four steps: preoperative, intraoperative and in-hospital data collection and post-discharge telephone follow-up.

Ethics and dissemination This study has been supported by Shanghai Municipal Commission of Health and Family Planning Foundation for Key Developing Disciplines (2015ZB0103) and approved by the Ethics Committee of Shanghai Sixth

People's Hospital [No: 2016-28-(2)]. At the time of manuscript submission, the protocol version is v1.6 (March 2nd, 2018) with one subsequent approved amendment. Results will be disseminated via an international peer-reviewed publication.

Trial registration number NCT03318133.

Key words Elderly; Hip fracture; Lumbar plexus block; Sacral plexus block; General anesthesia

Strengths and limitations of this study

- This study will be the first prospective, multicenter, randomized controlled clinical trial to investigate the effect of the two anesthesia techniques on long-term prognostic indicators in elderly patients with hip fracture.
- The results of this study will help elucidate whether CLSB plus sedation could be safely used in hip fracture surgery and reduce the incidence of perioperative complications and improve long-term outcome in elderly patients.
- Our study results will be limited to Chinese population, and further studies on other ethnic backgrounds will be required.

1.BACKGROUND

Hip fracture is a global public health problem with an incidence of more than 1.6 million worldwide each year [1]. Owing to the global increase of the population aged 65 years and over, the total number of hip fracture is expected to surpass 6 million by 2050 [2]. While early surgery is the most effective treatment method, the postoperative mortality and disability rates are still high [3]. The elderly patients with hip fracture frequently have multiple comorbidities, which put these patients at high risk of

morbidity and mortality after anesthesia [4, 5]. Seeking appropriate anesthesia technique is in urgent need to ensure that these patients can safely and effectively get through the perioperative period.

Most studies assessing the relationship between anesthesia technique and outcomes mainly focus on the comparisons between neuraxial anesthesia (including spinal and epidural anesthesia) and general anesthesia (with an endotracheal tube or a laryngeal mask airway). A recently updated systematic review and meta-analysis has found no difference between regional versus general anesthesia, but they also supposed that the number of participants included in the review was insufficient to eliminate a difference between the two techniques in the majority of outcomes studied[6]. Some other investigations have shown that neuraxial anesthesia for hip fracture can reduce postoperative morbidity[7, 8], but two recent large-sample size observational studies deemed that neuraxial anesthesia could not significantly improve the prognosis of patients [9, 10]. However, all of the above are retrospective observational studies, in which anesthesiologists might have selected the anesthesia technique based on their practice style and a variety of patient-related factors. For example, patients with coagulation dysfunction would have contraindication to neuraxial anesthesia and must receive general anesthesia. Neuraxial anesthesia is thought to be less postoperative complications, so elderly or critically ill patients might be more likely to receive neuraxial anesthesia[11], rather than being randomly assigned to different anesthesia groups. Therefore, there could be selection bias that affected the clinical significance of those results. In addition to general anesthesia and neuraxial anesthesia, ultrasound-

guided lumbar and sacral plexus block has been widely used in hip fracture surgeries in recent years, especially for some high-risk patients with cardiopulmonary dysfunction [12-14]. Compared with neuraxial anesthesia, combined lumbar and sacral plexus block is associated with less sympathetic block and better cardiovascular function stability. In addition, combined lumbar and sacral plexus block plus sedation could avoid endotracheal intubation or laryngeal mask airway(LMA) insertion and thereby might reduce the complications related to the general anesthesia. A recent small sample size retrospective study [14] compared the effect of general endotracheal anesthesia, neuraxial anesthesia and lumbar and sacral plexus block on the prognosis of patients with hip fracture, and the results showed that neuraxial anesthesia and combined lumbar and sacral plexus block could reduce the total mortality, and there was no significant difference between neuraxial anesthesia and combined lumbar and sacral plexus block. But the number of elderly and high-ASA-grade patients in the combined lumbar and sacral plexus block group was significantly greater than that in the neuraxial anesthesia group, suggesting that when comparing the effect of these two anesthetic methods in similar conditions, combined lumbar and sacral plexus block might have more advantages. However, it is not clear whether ultrasound-guided combined lumbar and sacral plexus block plus sedation could improve outcomes of elderly patients with hip fracture.

This paper describes the design of a prospective, multicenter, parallel, randomized controlled clinical trial to assess the effect of ultrasound-guided combined lumbar and sacral plexus block plus sedation versus general anesthesia on the postoperative

outcomes in elderly patients with hip fracture.

2. METHODS AND ANALYSIS

2.1. Patient and public involvement

Patients and public were not involved in the design or conduct of the study. We do not have any specific plans to disseminate our results to patients.

2.2. Study design

This will be a two-arm, parallel, multicenter, prospective, randomized controlled trial and the design of this study protocol has referred to the SPIRIT 2013 guideline [15, 16].

2.3. Study location

The study will be conducted in five teaching hospitals including Shang Sixth People's Hospital (Shanghai, China), Beijing Chaoyang Hospital (Beijing, China), Beijing Jishuitan Hospital (Beijing, China), First Affiliated Hospital of Wenzhou Medical University (Wenzhou, China), and Foshan Hospital of Traditional Chinese Medicine (Foshan, China).

2.4. Study population

Although elderly population was considered to be people older than 65 years in the present studies, introduction to aging population is latening owing to increasing life expectancy. As shown in a recent study[17], age is the primary risk factor on first year mortality in patients older than 75 years old with hip fractures. In addition, China wants to increase its citizens' average life expectancy to 77.3 by 2020 and 79 by 2030, up from 76.34 in 2015, according to "Plan of Health China 2030" published in 2015.

We thus used 75 years as an age cutoff for inclusion criteria in this study because optimal selection of anesthesia technique in this age group might have more clinical significance.

Elderly patients above 75 years scheduled for hip fracture surgery will be recruited voluntarily according to the inclusion and exclusion criteria below. All included patients are suitable for either general endotracheal anesthesia or combined lumbar and sacral plexus block plus sedation, which will not bring tendency to choose a specific type of anesthesia.

2.4.1. Inclusion criteria:

- Age ≥75 years old;
- First unilateral surgery for hip fracture including femoral neck, intertrochanteric or subtrochanteric fracture;
- Patient with planned hip fracture surgery within 24-72 h;
- Patient without peripheral nerve block within 24 h prior to surgery or patients with preoperative peripheral nerve blockade but its effect had faded away at the beginning of the operation.
- The ability to receive written informed consent from the patient or patient's legal representative.

2.4.2. Exclusion criteria:

- Refuse to participate;
- Unable to perform nerve block;
- Multiple trauma, multiple fractures or other fractures outside the inclusion criteria,

such as pathological fractures, pelvic fractures, femur fractures;

- Prosthetic fracture;
- Scheduled for bilateral hip fracture surgery;
- Usage of bone-cement fixation in the surgery;
- With recent cerebral stroke (<3 months);
- Concomitant active heart disease (unstable angina, acute myocardial infarction, recent myocardial infarction; decompensated heart failure; symptomatic arrhythmia; severe mitral or aortic stenotic heart disease);
- Patient with known severe lung and/or airway disease, acute respiratory failure, acute pulmonary infection, and acute attack of bronchial asthma;
- Current enrolment in another clinical trial;
- Contraindication for general endotracheal anesthesia (drug allergies to general anesthesia, difficult airway);
- Contraindication for lumbar and sacral plexus block (infection at the site of needle insertion, coagulopathy, allergy to local anesthetics).

2.5. Interventions

Eligible patients will be randomly assigned into either CLSB group receiving combined lumbar and sacral plexus block plus sedation or GA group receiving general anesthesia with endotracheal intubation or LMA (Figure 1). Standard anesthetic and surgical methods will be applied to ensure the consistency of treatment in the participating centers. Experienced and qualified anesthesiologists in every clinical centers will be specifically designated to perform combined lumbar-sacral plexus block

plus sedative anesthesia or GA in order to minimize the potential bias. To improve adherence to intervention protocols, study personnel are trained to follow the study protocol in accordance with the Good Clinical Practice (GCP) principles.

In the CLSB group (Combined lumbar-sacral plexus block with sedative anesthesia), the procedures will be performed as followed.

- Peripheral venous access for fluid infusion will be established;
- In the lateral decubitus position with the operated side uppermost, ultrasound-guided lumbar plexus block (L_{2-3} or/and L_{3-4} vertebral space level, 0.375% ropivacaine 25ml) will be performed, followed by sacral plexus block (0.375 % ropivacaine 20ml); We used the nerve stimulator to confirm the needle's correct position by a quadratus femoris twitch for lumbar plexus block and hamstring, leg, or foot twitches for sacral plexus block at a current within 0.4–0.6 mA, followed by relevant volume of 0.375% ropivacaine that was slowly injected in 5 ml increments to surround the target nerve under ultrasound monitoring.
- Radial arterial catheterization under local lidocaine anesthesia and arterial blood pressure monitoring will be performed. Blockade effectiveness will be evaluated 30 minutes after nerve block; The intervention will be discontinued for a given patient and convert to general anesthesia with endotracheal intubation or LMA if the satisfactory blockade is not acquired. These patient are still followed up for further statistical analysis according to the formal protocol because they have been randomly allocated.
- After confirmation of satisfactory blockade, target-controlled infusion of propofol

will be used to maintain Ramsay sedation score between 3-4 points. $P_{ET}CO_2$ will be monitored through nasopharyngeal airway. Small-dose sufentanil (1-2μg each time) will be titrated to maintain spontaneous breathing.

In the GA group, the procedures will be performed as followed.

- Peripheral venous access for fluid infusion will be established;
- Radial arterial catheterization under local lidocaine anesthesia and arterial blood pressure monitoring will be conducted;
- Anesthesia will be induced with propofol (1.5-3mg/kg), rocuronium(0.3-0.9mg/kg), and sufentanil (0.2-0.6μg/kg) for tracheal intubation or LMA insertion. Mechanical ventilation will be performed to maintain normal $P_{ET}CO_2$.
- Sevoflurane, propofol and sufentanil will be used to maintain anesthesia during surgery, while rocuronium will be added as needed.

During surgery, fluid infusion and blood transfusion will be used to maintain stable hemodynamics. Perioperative arterial pressure lower than 30% of the baseline will be defined as hypotension, upon which ephedrine or phenylephrine will be administrated. The type and dosage of infusion depends on anesthesiologist's experience. Blood transfusion will be given according to blood loss and hemoglobin concentration(Hb) level (80-100g/L)[18]. Following surgery, patients will be sent to the postanesthesia care unit (PACU) and then transferred to orthopedic ward or intensive care unit(ICU) according to the local procedures of each clinical center. Postoperative analgesia can be administrated with regard to the routine clinical practice of each trial site, aiming to maintain a Visual Analogue Scale (VAS) pain score ≤3.

2.6. Outcomes and measurements

2.6.1. Primary outcome

Postoperative 1-year all-cause mortality (follow-up time points are set as 1 month, 3 months, 6 months and 1 year after surgery);

2.6.2. Secondary outcomes

2.6.2.1. Occurrence of intraoperative complications, including:

- Intraoperative hypotension and vasopressor dosage;
- Intraoperative arrhythmia, myocardial ischemia, myocardial infarction, massive hemorrhage, pulmonary embolism and hypoxemia;
- Intraoperative blood loss and blood transfusion volume;

2.6.2.2. High-sensitivity cardiac troponin T(hs-cTnT), measured on the 1 and 3 days after surgery;

2.6.2.3. Early mobility after surgery;

2.6.2.4. Incidence of various complications and Comprehensive Complication Index (CCI) [19] during hospitalization after surgery;

2.6.2.5. Postoperative analgesic effectiveness within three days after the surgery;

2.6.2.6. Incidence of delirium on the 1, 2 and 3 days after surgery, diagnosed with Confusion Assessment Method(CAM)[20];

2.6.2.7. Sequential Organ Failure Assessment(SOFA) [21], assessed on the 1 and 3 days after surgery;

2.6.2.8. Bauer Patient Satisfaction Questionnaire[22], assessed on the 3 days after surgery;

2.6.2.9. Length of stay in ICU and hospital;

2.6.3. Other observational variables:

2.6.3.1. Economic parameters including total cost in hospital and expenditure for anesthesia;

2.6.3.2. Functional recovery on the 30 days after surgery, evaluated by Barthel Activities of Daily Living Index (Barthel Index);

2.6.3.3. Post-discharge destination, and incidence of complications and adverse events after discharge.

2.7. Participant timeline

For a given participant, assessment will be performed one day prior to surgery and again on the day of surgery to confirm whether qualified for enrollment. Randomization will perform on the day of surgery. And then intervention will be performed. The accrual period of this trial is expected to be about 1 year. The patients will be followed up on the 1, 2 and 3 days after surgery and on the day of discharge. The total follow-up period will be set as 1 year and the telephone follow-up will be conducted at the 1, 3, 6 and 12 months after surgery.

2.8. Power and Sample Size Calculation

We estimate the sample size using the formula by Schoendeld under the assumption of the validity of the proportional-hazards regression model [23, 24]. We take significance level 0.05 (one-sided) and power 0.80. Patients will be randomly assigned to one of the two anesthesia groups in five different clinical centers. A retrospective study included patients over 65 years old showed that the one-year mortality was 41.7% for GA group and 28.3% for combined peripheral nerve block (CPNB) group [14]. In

this study, only patients with age 75 years or older will be included, so we expect the actual mortality of the GA group will be higher than that in the previous study. Therefore, we assume the mortality to be 55% for GA group and 46.75% for CLSB group (15% relative reduction compared with GA group). Then the sample size needed for this study is 868 (with 434 in each of the two groups). When the mortality of the GA group is only 45%, the above calculated sample size can still detect a 20% improvement in the CLSB group with the power of at least 0.80. In consideration of the possible lost to follow up, we add an additional 20% to the above calculated sample size. So the total number of patients needed for this study is 1086.

2.9. Randomization and blinding

Upon the receipt of informed consents, patients will be randomly assigned to the two groups in any one of the five centers. Sequentially numbered sealed opaque envelops with group allocation inside altered anesthetist to use CLSB or GA. The R program will be used to generate randomization block allocation for each of the five centers with randomly selected block sizes of four, six, and eight. The envelopes will be placed in the patient's chart before the start of each procedure by a doctor of the research team. The research staff who will interview patients postoperatively are blinded for the allocated treatment. The statistician will be blinded. A spreadsheet linking the patient number and name will be password protected and kept on a research computer. The recruitment will stop when the total number of patients reaches 1086. The subjects and intervention performers (anesthesiologists) know the randomized allocation, but the follow-up personnel and statistician was blinded to the randomized

allocation and intervention.

2.10. Data collection and management

Data will be collected in four steps: preoperative, intraoperative and in-hospital data collection and post-discharge telephone follow-up.

2.10.1. Preoperative data:

2.10.1.1. Basic information including name, admission number, height, weight, gender, age, blood pressure, heart rate and ASA grade (American Society of Anesthesiologists grade).

2.10.1.2. Preoperative information including diagnosis, type of surgery, type and dosage of anticoagulants, and days passed until surgery.

2.10.1.3. Preoperative complications and medication related to cardiovascular disease, stroke, respiratory disease, kidney disease, diabetes, Parkinson's disease, and deep venous thrombosis of lower extremity if any.

2.10.1.4. Preoperative examination results including blood gas analysis, ECG, echocardiography, blood routine testing, liver and kidney function testing, coagulation testing (D-dimer), Pro-BNP, hs-cTnT, and lower extremity vascular ultrasonography.

2.10.1.5. Preoperative evaluation results including MMSE (Mini-mental State Examination), SOFA and Barthel Index, all of which might be associated with the postoperative complications.

2.10.2. Intraoperative data

2.10.2.1. Duration of surgery, incidence of intraoperative hypotension or hypertension, and vasoactive drug dosage.

2.10.2.2. Intraoperative blood loss, blood transfusion volume, and intraoperative fluid infusion volume.

2.10.2.3. Intraoperative arrhythmia (sinus bradycardia, sinus tachycardia, ventricular arrhythmia, atrial arrhythmia, etc.), myocardial ischemia, and myocardial infarction.

2.10.2.4. Intraoperative complications: massive hemorrhage, pulmonary embolism, allergic reaction, hypoxemia, bronchospasm, gastric reflux and aspiration.

2.10.2.5. Intraoperative conversion of anesthesia and the relevant causes.

2.10.3. In-hospital data

2.10.3.1. High-sensitivity cardiac troponin T(hs-cTnT), measured on the 1 and 3 days after surgery;

2.10.3.2. Earlier mobilization and postoperative hip rehabilitation: the daily degree of maximal hip flexion and abduction will be recorded [25]. The day after surgery, all 2 groups will start an identical physical therapy regimen. The patients will perform passive and active hip flexion and abduction exercises twice daily. Patients will be encouraged to get out of bed as soon as possible and try ambulation with a walker. The maximal degree of hip flexion and abduction tolerated by each patient will be recorded for three days. The day of first ambulation will be also recorded for each group.

2.10.3.3. Postoperative complications including incidence and severity of various complications and the CCI [19] value at discharge. Complications were assessed and graded using the Clavien-Dindo classification. CCI will be derived from these features at discharge, using the CCI calculator available online (www.assessurgery.com). Complications include:

- Myocardial ischemia, myocardial infarction, heart failure, arrhythmia;
- Pulmonary infection, respiratory failure, pulmonary embolism;
- Postoperative delirium;
- Cerebral ischemia, cerebrovascular accident;
- Renal failure, urinary retention;
- Regurgitation and pulmonary aspiration;
- Postoperative nausea and vomiting (PONV);
- Postoperative bleeding and 24h postoperative drainage volume;
- Reoperation.

2.10.3.4. The intensity of postoperative pain at rest and on movement will be assessed with Visual Analogue Scale (VAS) (0 no pain, and 10 worst possible pain) at the 24, 48, and 72 hours after surgery.

2.10.3.6. CAM will be evaluated on the 1, 2 and 3 days after surgery.

2.10.3.7. SOFA [21] will be evaluated on the 1 and 3 days after surgery.

2.10.3.8. Bauer Patient Satisfaction Questionnaire will be assessed on the 3 days after surgery.

2.10.3.9. Length of ICU stay, length of hospital stay, total hospitalization cost, and expenditure for anesthesia.

2.10.4. Post-discharge follow-up data

2.10.4.1. Telephone follow-up will be performed on the 1, 3, 6 and 12 months after surgery to collect the following information.

- Discharge destinations. Disposition status after discharge will be classified as follows: dead, nursing home (e.g., skilled nursing facility, intermediate care facility,

extended care facility, nursing home), community dwelling (e.g., home alone, home with others), or other.

- Dead or not, specific cause and time.
- Incidence of complications and adverse events: heart, lungs, brain, liver, kidney, four limbs, and hospitalization, etc.

2.10.4.2. Barthel Index for evaluation of functional recovery will be collected on the 30 days after surgery.

2.11. Data and safety monitoring

Preoperative, intraoperative and in-hospital data will be collected from the electronic medical record, monitor machines and relevant manual records by one of the research staff. Telephone follow-up will be conducted by the research team. Data will be securely managed by an independent contract research organization (Shanghai Ruihui Biotech Co., Ltd, Shanghai). All serious adverse events, as well as all non-serious adverse events that are unexpected and judged to be related to the study treatment, will be recorded in the study database and reported as required to local IRBs and to the Shanghai Jiao Tong University Affiliated Sixth People's Hospital IRB. Data and safety monitoring will be the responsibility of the study director/principle investigator(PI), the study biostatistician, site clinical directors and an independent Data and Safety Monitoring Board(DSMB) selected by the study PI. The DSMB will be composed of 5-7 independent, multidisciplinary experts who are not have subordinate relationships with the PI or any member of the study team. The DSMB will review study implementation and the occurrence of adverse events.

2.12. Statistical analysis

The data will be analyzed using intention-to-treat approach. Demographics information will be compared for patients of the two groups to ensure the data are balanced. Student t-test will be used for quantitative variables such as age, and heart rate, blood pressure. Chi-square test will be used for categorical variables such as Sex, ASA classification grades. The VAS pain scores will be analyzed using repeated measure ANOVA to test the effects of treatment, time, and the interaction effect. The effects of different covariates on the mortality measured at 1 month, 3 months, 6 months and 12 months will be assessed using a logistic regression model. The primary analysis model will be Cox regression model with covariates. Either logistic regression or ordinary multiple regression method will also be used to assess the effects of the covariate on the secondary and other outcomes as well depending on the type of dependent variable. The proportional-hazards regression model will be used to compare the survival times of the patients in the two groups and to assess the effects of the covariates. The statistical analysis will be performed using statistical software SPSS 24.0 (IBM Corporation, Armonk, NY, USA) with a significance level of 0.05.

2.13. Access to data

During the study, data will be stored in a password-protected system and can be accessed by the research staff who sign the confidential disclosure agreements. Data without patient identification will be publicly accessible after the study.

2.14. Confidentiality

Each participant will be given an identification number and referred by the

identification number throughout the study and in all study-related information. This information will be securely stored in a password-protected access system provided by a local supplier. Relevant paper records will be stored in a locked cabinet in an access-controlled room. All records containing any patients' personal identifiers will be separately stored similarly as above.

2.15. Trial status

At the time of manuscript submission, the study is in the preparation phase for recruitment.

3. DISCUSSION

Choice of anesthesia for hip fracture surgery in elderly patients is still inconclusive. General anesthesia with endotracheal intubation or LMA is a common procedure for hip fracture surgery, with advantages of wide indications and maintaining relatively stable hemodynamics. Compared with general anesthesia, neuraxial anesthesia avoids endotracheal intubation or LMA insertion. But vertebral degeneration and anatomical abnormalities in elderly patients often make neuraxial anesthesia puncture difficult, and most of these patients are taking anticoagulants, which are the contraindication of neuraxial anesthesia. So the neuraxial anesthesia has limitations in application for the elderly patient. The principle for anesthesia selection is to reduce or avoid the effect of anesthesia on systemic and vital organ functions as much as possible when meeting the needs of surgery. Previous lumbar and sacral plexus block depends on blind puncture technique and cannot ensure the clinical effectiveness. However, ultrasound visualization technology has promoted the wide application of lumbar and sacral plexus

block. Combined lumbar and sacral plexus block with sedative anesthesia has gradually become alternative approach for hip fracture surgery in elderly patients, and this anesthetic technique has been massively applied in our department and achieved satisfactory clinical results in recent years, but there is few reliable clinical evidence on whether it can be safely used for hip fracture surgery in elderly patients and improve the short-term or long-term outcomes. Thus, we have designed this trial protocol to illustrate the clinical value of combined lumbar and sacral plexus block with sedative anesthesia in elderly patients undergoing hip fracture surgery. In this study, we will observe the effect of the two anesthetic methods (general endotracheal anesthesia or combined lumbar and sacral plexus block plus sedation on the early prognostic indicators in elderly patients with hip fracture, including postoperative complications, postoperative analgesic effect, postoperative early mobility, postoperative delirium, patient's satisfaction to anesthesia and length of stay in ICU and hospital. This study will be the first prospective, multicenter, randomized controlled clinical trial to investigate the effect of the two anesthesia techniques on long-term prognostic indicators in elderly patients with hip fracture, including postoperative 1-year all-cause mortality and incidence of complications and adverse events. The results of this study will help elucidate whether ultrasound-guided combined lumbar and sacral plexus block with sedative anesthesia can be safely used in hip fracture surgery in elderly patients and can reduce the incidence of perioperative complications and improve long-term prognosis, so as to solve the troubling clinical problem and provide a theoretical basis for elderly patients undergoing hip fracture surgery to choose the optimal

anesthetic method.

Abbreviations

ASA grade: American Society of Anesthesiologists grade; GA: General anesthesia; CLSB: Combined Lumbar and Sacral Plexus Block; PACU: Postanesthesia Care Unit; Hb: Hemoglobin Concentration; ICU: Intensive Care Unit; CCI: Comprehensive Complication Index; SOFA: Sequential Organ Failure Assessment; CAM: The Confusion Assessment method; MMSE: Mini-mental State Examination; ECG: Echocardiography; Pro-BNP: Pro Brain Natriuretic Peptide; hs-cTnT: High-sensitivity cardiac Troponin T; PONV: Postoperative Nausea and Vomiting; VAS: Visual Analog Scale

Contributors JZ and WJ designed the study and wrote the protocol. HZ and XW performed statistical analysis. HZ, XW and ZS were involved in protocol conception and design and manuscript revision. WJ is the principal investigator of this clinical trial. All authors read and approved the final version of the manuscript.

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Data sharing statement No additional data are available.

Patient consent Obtained.

Competing interests None declared.

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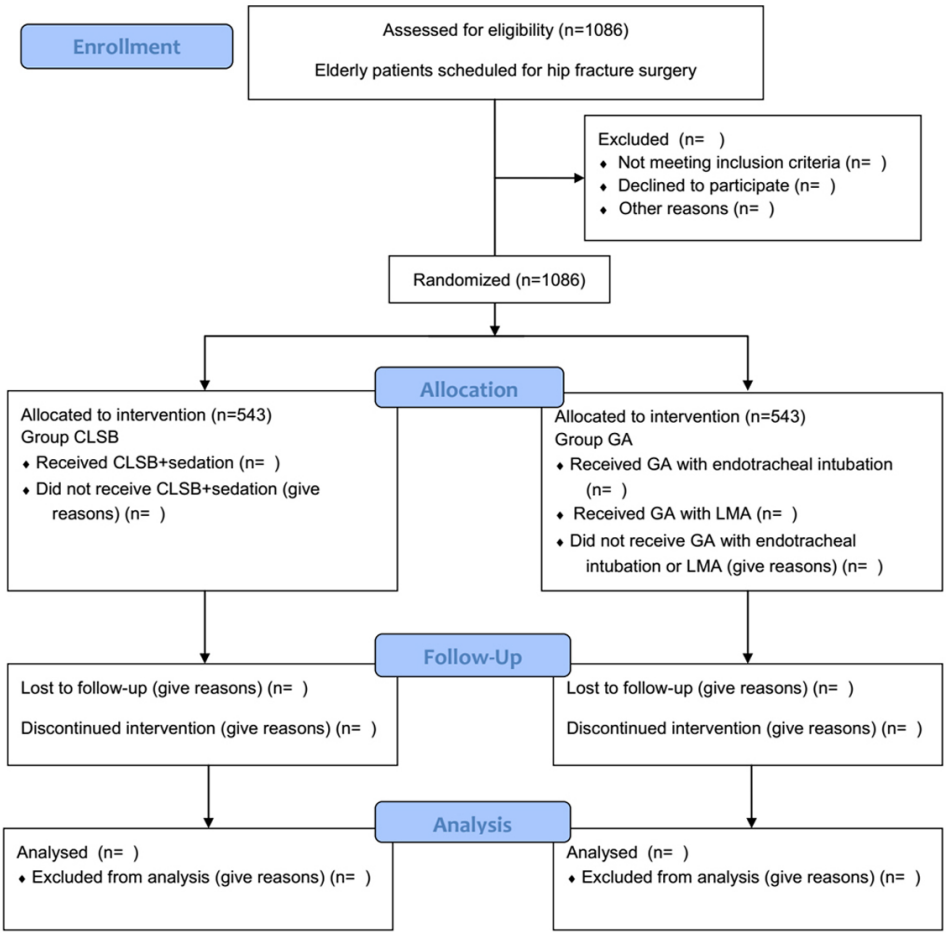
Figure legend

Fig. 1 CONSORT flowchart designed for subject enrollment



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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	3	Date and version identifier	3
Funding	4	Sources and types of financial, material, and other support	2-3
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	21
	5b	Name and contact information for the trial sponsor	n/a
	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
	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)	6

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	3-6
	6b	Explanation for choice of comparators	4-5
Objectives	7	Specific objectives or hypotheses	5-6
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, noninferiority, exploratory)	6
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	6
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)	7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-11
	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)	9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	n/a
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9-11
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	11-12
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)	10,12,24

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	12-13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6-7
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	13-14
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	13-14
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	13-14
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13-14
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	13-14
Methods: Data collection, management, and analysis			
Data collection methods	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	14-18
	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	n/a

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	17-18
Statistical methods	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	18
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	18
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	n/a
Methods: Monitoring			
Data monitoring	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	17-18
	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	n/a
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	17-18
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2-3
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)	2-3

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	18-19
	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	18-19
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	21
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18
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	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	3
	31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
	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	n/a
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

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.