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Complete List of Authors:	Zheng, Jianqiao; Sichuan University West China Hospital, Department of Anesthesiology Du, Li; Sichuan Cancer Hospital and Research Institute, Department of Anesthesiology Chen, Guo; Sichuan University West China Hospital, Department of Anesthesiology Zhang, Lu; Sichuan University West China Hospital, Department of Anesthesiology Deng, Xiaoqian; Sichuan University West China Hospital, Department of Anesthesiology Zhang, Weiyi; Sichuan University West China Hospital, Department of Anesthesiology
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TITLE PAGE

Efficacy of pericapsular nerve group (PENG) block on perioperative pain management in elderly patients undergoing hip surgical procedures: a protocol for a systematic review with meta-analysis and trial sequential analysis

Authors

Jianqiao Zheng[1] E-mail: zhjq1983@163.com

Li Du[2] E-mail: huaying-duli@163.com

Guo Chen[1] E-mail: Anesthesiology_SCU@163.com

Lu Zhang[1] E-mail: 304022514@qq.com

Xiaoqian Deng[1] E-mail: 50058837@qq.com

*Weiyi Zhang[1] E-mail: zhangweiyi@wchscu.cn

[1]Department of Anesthesiology, West China Hospital, Sichuan University No. 37th, Guoxue Alley, Wuhou District, Chengdu 610041, Sichuan, China.

[2]Department of Anesthesiology, Sichuan Cancer Hospital & Institute, Sichuan Cancer Center, School of Medicine, University of Electronic Science and Technology of China, No.55th, People's South Road, Chengdu 610041, Sichuan, China.

*Corresponding Author

Name: Weiyi Zhang

E-mail: zhangweiyi@wchscu.cn

Phone: +86-28-8542-3593

Address: Department of Anesthesiology, Sichuan University West China Hospital, No. 37th, Guoxue Alley, Wuhou District, Chengdu 610041, Sichuan, China.

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ABSTRACT

Introduction An increasing number of elderly patients suffer from hip diseases associated with moderate to severe perioperative pain during the global accelerating ageing process. Optimal analgesia can decrease perioperative complications and facilitate elderly patient's perioperative recovery. Pericapsular nerve group (PENG) block is a relatively new, analgesia adequate, and motor-sparing block technique for perioperative pain management of hip diseases. However, the efficacy of PENG block remains unclear as the limited clinical evidence. Then, we will perform a protocol for a systematic review and meta-analysis to identify the efficacy of PENG block for perioperative pain management.

Methods and analysis PubMed, Ovid Medline, Cochrane Library, Embase, Web of Science, China National Knowledge Infrastructure, Chinese BioMedical Literature, Wanfang and VIP databases will be searched from inception to August 2022 to identify randomized controlled trials of elderly patients accepting PENG block for hip diseases. Primary outcome will be the pain intensity after pain management. Secondary outcomes will be quadriceps strength, perioperative rescue analgesia information and perioperative complications. Assessment of heterogeneity will be primarily inspected by forest plots. if there is no indication of funnel plot asymmetry, a random-effects meta-analysis will be performed. The Cochrane risk-of-bias tool, GRADE (Grading of Recommendations

Assessment, Development and Evaluation) and trial sequential analysis will be conducted to evaluate the evidence quality and control the random errors. Funnel plots and Egger's regression test will be performed to evaluate publication bias.

Ethics and dissemination Ethical approval was not required for this systematic review protocol. The results will be disseminated through peer-reviewed publications.

Keywords pericapsular nerve group block, hip, elderly, meta-analysis, randomized controlled trial.

PROSPERO registration number CRD42022313895

Strengths and limitations of the study

►Application of Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines for better quality of meta-analytical results.

► Control of random errors with trial sequential analysis by calculating the diversity adjusted information size for the outcomes.

► Application of Funnel plots and Egger's regression test for Publication bias.

►Subgroup analysis based on patients' age, types of hip disease or surgery, perioperative period, type of anesthesia and perioperative pain management techniques for heterogeneity assessment.

INTRODUCTION

The global population greater than 60 years old is estimated to increase to 2.1 billion in 2050 (approximately 22% of the global population), and 3.1 billion by the year of 2100.[1] With this accelerating ageing process, an increasing number of elderly patients suffer from hip diseases such as hip fractures and hip osteoarthritis.[2-4] Hip surgery, including hip arthroplasty, hip fracture internal fixation and hip arthroscopy procedures are the main treatments for hip diseases.[5-8] Hip surgery is often associated with moderate to severe postoperative pain, particularly in hip fracture patients undergoing surgical treatment, and severe pain persists throughout the whole perioperative period.[9-11] As a minimally invasive approach, arthroscopic hip surgery is gaining popularity globally.[12] Despite being minimally invasive, patients undergoing arthroscopic hip surgery may still experience severe pain after the procedure. [13]

Perioperative pain, if inadequately controlled, can increase the risk of perioperative complications (including delirium, pulmonary complications and cardiovascular events), delay ambulation, decrease short-term mobility, interfere with rehabilitation, increase hospital length of stay, and even increase the mortality and morbidity, leading to poor functional prognosis.[14-19] Particularly in elderly patients, the risk of perioperative adverse events is higher due to the presence of polypharmacy and

multimorbidity.[20-22] In contrast, adequate pain management has been shown to facilitate postoperative mobilization, improve mobility and promote better functional recovery.[23-26] Early mobilization has been associated with a reduction in postoperative complications, including pneumonia, venous thromboembolism, pressure ulcers, and delirium.[27-29] Therefore, an optimal perioperative analgesia can facilitate elderly patients' perioperative recovery particularly.[30-33]

Traditionally, opioid analgesia is considered to be the basis of the perioperative pain management.[34-37] However, opioid-related complications such as delirium, urinary retention, nausea, constipation and respiratory depression may occur and can delay patient's recovery and discharge.[38-43] Considering these adverse events, especially the higher incidence of cognitive deficits in elderly patients suffering a hip fracture, opioid analgesics are often selected hesitantly.[44-48] In addition, in light of the current opioid crisis, strategies to minimize opioid use, including the use of multimodal perioperative pain management strategies with opioid-sparing oral and intravenous medications, regional anesthesia and analgesic techniques have become an increasing clinical focus in hip surgical procedures in elderly patients, as to decrease perioperative analgesic consumption.[49-53]

Peripheral nerve blocks, including lumbar plexus block, femoral nerve block, fascia iliac compartment block, 3-in-1 femoral nerve block,

sacral plexus block, obturator and sciatic nerve block and some inter-fascial plane blocks such as quadratus lumborum block, have also been suggested to decrease postoperative pain and opioid use during hip surgery.[54-61] However, peripheral nerve blocks may induce weakness of the quadriceps muscles, delay hospital discharge, and even predispose the patient to fall. [62-65] In some cases, it is difficult to position the patient as the extreme pain, particularly in hip fractures, accompanied by the deep depth of the block target, the lumbar plexus or quadratus lumborum block will become difficult.[66-68] In addition, another difficulty of adequate regional analgesia for hip pain is the complex innervation of the hip joint.[69] High branches of both the femoral and obturator nerves provide innervation to the anterior hip capsule. The accessory obturator nerve was also found to innervate the medial capsule.[70] [71] In this situation, the coverage of the articular nerve supply to the hip joint is critical for an effective analgesia. Hence, a simple, easy-to-perform, analgesia adequate and motor-sparing regional analgesia technique is the ideal regional analgesia technique for hip surgery.

Pericapsular nerve group (PENG) block is a relatively new peripheral nerve block technique, first described by Giron-Arango in patients with hip fractures, based on the complex innervation of the hip joint.[72] The targets of the PENG block are the musculofascial plane between the psoas tendon anteriorly and the pubic ramus posteriorly, so it can be easily performed in

the supine position, avoiding the additional pain from positioning the patient for perioperative nerve block.[73-76] In theory, PENG block has potential advantages over traditional forms of regional analgesia for pain originating from the hip, as local anesthetic deposits in this target could provide a wider and more complete block effect on the coverage area of sensory nerves innervating the hip.[77-87] Thus, it has the potential advantage of reducing postoperative pain without motor-blocking.[88-91] At present, PENG block has been described as an easy to perform in the supine position and as an effective and motor-sparing regional analgesia technique for hip surgery.[92-95]

The excellent analgesic benefit of PENG block for perioperative analgesia in hip surgery was highlighted in a significant number of publications of case reports, case series, reviews and retrospective studies [77-83, 92-95], but prospective and randomized controlled trials are rare.[84-87] Inadvertent quadriceps weakness was also reported in patients following the PENG block.[96-98] Due to the limited current clinical evidence, the efficacy and safety of the PENG block, particularly the efficacy of motor function preservation and the incidence of block-related adverse events remain controversial until now.[99-103]

Therefore, it is necessary to conduct a systematic review and meta-analysis to analyse the clinical efficacy of PENG block on perioperative pain management in elderly patients with hip diseases. The outcomes of

this systematic review will provide evidence for better clinical decision making and possible future directions for further clinical trials.

Objectives

We are performing this protocol of systematic review with meta-analysis and trial sequential analysis (TSA) of randomized clinical trials to evaluate the clinical efficacy and safety of PENG block on perioperative pain management in elderly patients with hip diseases.

METHODS AND ANALYSIS

Design and registration of the review

We devised this protocol according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines that has been registered with PROSPERO 2022 (registration number: CRD42022313895). [104] We will perform this systematic review and meta-analysis based on the Cochrane Handbook and report the results following the PRISMA statement.[105 106] This study is anticipated to begin searching in August 2022 and will be complete in January 2023.

Inclusion criteria for study selection

Types of studies

Only randomized controlled trials (RCTs) involving the clinical efficacy of PENG block on perioperative pain management in elderly patients with hip diseases will be included. There will be no language restrictions.

The exclusion criteria were as follows: (1) studies comparing PENG block versus PENG block combined with other analgesic techniques, or studies comparing PENG block under different guidance techniques (ultrasound guided or traditional landmark technique); (2) studies with data that could not be used for statistical analysis, or studies with incomplete data, or data that could not be extracted after contacting the original authors; and (3) studies that were duplicate publications, published as letters or editorials, abstracts from conferences, and reviews.

Types of participants

Elderly participants (≥65 years old) with any kind of hip disease (such as hip fracture, hip osteoarthritis) accepting PENG block for perioperative pain management (including preoperative analgesia, intraoperative anesthesia management and postoperative analgesia) will be included. There will be no limitations on participants' gender, ethnicity, body mass index (BMI) or American Society of Anesthesiologists (ASA) classification.

Types of interventions/controls

The intervention group will be the participants who received any kind of PENG block (including ultrasound-guided, X-ray-guided, CT-guided or traditional landmark-based techniques), alone or in combination with any other kind of analgesia technique for perioperative pain management, while the control group will receive any kind of analgesia technique other

than PENG block for perioperative pain management.

Types of outcome measures

Primary outcomes

The primary outcome will be the pain intensity after perioperative pain management by PENG block or other analgesia techniques. Pain intensity, including preoperative pain intensity and postoperative pain intensity, assessed by visual analog scale (VAS) scores or numeric rating scale (NRS) scores will be included. Perioperative static and dynamic pain intensity after pain management will also be included if possible.

Secondary outcomes

1. **Perioperative quadriceps strength**: will be evaluated as follows if possible.

- Incidence of quadriceps motor block (defined as paresis or paralysis of knee extension and hip adduction) [Knee extension was graded according to a 3-point scale: 0=normal strength (extension against gravity and against resistance)]; 1=paresis (extension against gravity but not against resistance); 2=paralysis (no extension possible).[107] Hip adduction scores of 0, 1, and 2 points indicated decreases in strength of 0%-20%, 21%-70%, and 71%-90% compared with baseline measurement, respectively. [108]
- Mobility of the quadriceps as defined by the Medical Research Council (MRC) scale.[109]

- Quadriceps strength was assessed by measuring of the force produced by voluntary isometric contractions with any type of reliable and valid stationary dynamometer (such as the Chatillon DPPH-250 force gauge, AMETEK, USA or Chatillon; AMETEK, Largo, Florida; Lafayette Instrument, Lafayette, Indiana; and MicroFET, Hoggan Health Industries, West Jordan, Utah).[110 111]

2. Perioperative rescue analgesia information

- Perioperative cumulative analgesic consumption: cumulative analgesic consumption for intraoperative anesthesia, and cumulative rescue analgesics for preoperative/postoperative analgesia will be included if possible. Any kind of analgesics, such as opioid analgesics and non-steroidal analgesics administered by different delivery methods, such as PCA (patient-controlled analgesia) devices, intravenous, oral, or intramuscular will be included if possible.
- Time to first analgesic request: time from end of preoperative pain management procedure to first analgesic request or time from end of surgery to first analgesic request will be included if possible.

3. Perioperative complications: if possible

- Block-related adverse events included vascular puncture, paresthesia, any local anesthetic toxicity, anaphylaxis, permanent nerve injury, bleeding or infection.

- Intraoperative adverse effects included hyoxemia(oxygen saturation less than 90% or oxygen partial arterial pressure≤60 mmHg); hypotension (defined as a decrease of >20% from preanesthetic patient baseline values or a systolic blood pressure less than 90 mmHg); arrhythmia [including bradycardia (defined as HR <55 beats/min); tachycardia (defined as HR>100 beats/min); any other types of arrhythmias]; and blood loss.
- Other adverse effects, including postoperative nausea/vomiting, pruritus, urinary retention, respiratory depression, sweating, dizziness, pruritus, urticaria, postoperative arrhythmia and postoperative pulmonary complications, were defined as the composite of any respiratory infection, respiratory failure, pleural effusion, atelectasis, or pneumothorax.

4. **Patients' recovery:** Length of stay, recovery time (defined as time until recovery room discharge criteria were met after surgery), the quality of postoperative recovery score (such as the Quality of Recovery-40 questionnaire) [112] and patients' ambulation (such as time-to-first ambulation and initial ambulation distance) will be included if possible.
5. **Patient satisfaction:**

Patient satisfaction with the performance of the perioperative pain management techniques or postoperative analgesia will be included if

possible. Satisfaction could be measured by a 5-point Likert scale (1=very dissatisfied; 2=dissatisfied; 3=neutral; 4=satisfied; 5= very satisfied), 10-point Likert scale (1= completely unsatisfied; 10=completely satisfied) or a postoperative questionnaire whether the patient would choose the same anesthetic or analgesia handling by the answer of "yes" or "no". [113]

Exploratory outcomes

1. **Perioperative sensory block:** Sensory block was evaluated using a 3-point scale [0=no block, 1=analgesia (patient can feel touch, not cold), 2=anesthesia (patient cannot feel touch)], which was assessed in the anterior, lateral and medial aspects of the mid-thigh. [107]
2. **Block ended time:** defined as the return of motor (if initially impaired) and/or sensory function, which was acquired from patients' recall.
3. **Perioperative mortality** was defined as all-cause death during the operation procedure, within 30 days after surgery, or death during hospitalization.

Search strategy

Two reviewers (Z-JQ and DL) will independently conduct the search and any disagreements will be resolved by consulting a third reviewer (Z-WY) as much as possible. English and Chinese electronic databases will be searched from inception to August 2022 for published literature. PubMed, Ovid Medline, Cochrane Library, Embase and Web of Science will be included in the English databases. The Chinese BioMedical

Literature (Sino-Med), China National Knowledge Infrastructure (CNKI), Wanfang database and VIP Database will be included in the Chinese databases. The trial registry database (Clinical Trials.gov and WHO International Clinical Trials Registry Platform) will also be scrutinized as to avoid missing ongoing or unpublished clinical trials. In addition, reference lists of each study will also be scanned for missing studies.

The following search terms will be used in the search strategy: pericapsular nerve group block, PENG block, elderly, hip, and randomized controlled trial. Related search terms will also be translated into Chinese for literature research and study identification in Chinese databases. The search strategies are listed in Supplementary Appendix file 1. Comprehensive updating of the literature search results will be performed prior to the final publication of systematic reviews to avoid missing published studies during the systematic review preparation.

Data collection and analysis

Selection of studies

At least two review authors (Z-JQ and DL) will be responsible for screening the potentially eligible studies by reading titles and abstracts. All identified and relevant full-text publications will be retrieved by screening the full text thoroughly, and the reasons for exclusion of the ineligible studies will be recorded. Any disagreement will be resolved through discussion or by consulting a third review author (Z-JQ and CG) as much

as possible. A fourth reviewer (Z-WY) will check out all procedures carefully prior to the final confirmation of the data extraction. Data extraction will be performed by at least two authors, and a third author will be consulted if there is any disagreement. Duplicate publications and companion papers of the same trial will be assessed by all review authors. The entire study selection process is displayed in the PRISMA flow diagram (figure 1).

Data extraction

Two review authors (Z-JQ and ZL) will use a standardized data collection form (Excel version 2013, Microsoft Inc, Washington DC, USA) for data extraction from each included study. The data extraction form included participants' demographic data, type of hip disease or hip surgery, type of anesthesia: local, spinal or general anesthesia, period of perioperative pain management (preoperative analgesia, intraoperative anesthesia and postoperative analgesia), inclusion and exclusion criteria, detailed information of analgesia techniques (type of perioperative analgesia techniques: PENG block or other analgesia techniques; type, concentration, dose, volume and adjuvant of local anesthetics), and any kind of outcomes including primary, secondary, and exploratory outcomes. Study design characteristics including: randomization method, allocation concealment, blinding (patients, treatment providers, outcome investigators), incomplete outcome data collection and statistical analysis,

and outcome reporting) will be recorded simultaneously. Continuous and dichotomous data will be recorded as the mean± SD and the percentages or the proportion. If necessary, a third review author (D-XQ) will cross-check the data to ensure precision. When the necessary information or data for analysis were missing or incomplete, we will contact the corresponding author of the research via email for the original data as much as possible. Necessary numerical data in the graphs will be extracted by Adobe Photoshop if necessary.[114] Extracted information and data are presented in table 1.

Table 1 Information and data extraction schedule

Subject	Content
Publication information	Title; author; Publish year; Country of origin; Corporate sponsorship; Contact email.
Participant	Sample size; Age; Sex; Height and weight or BMI; ASA physical status classification levels; Type of hip disease or hip surgery; Inclusion and exclusion criteria if necessary.
Intervention	Detail information of PENG block techniques (guidance techniques; target area of block; block needle; needle tracking techniques: in-plane and out-of-plane) Detail information of local anesthetics (type, concentration, dose, volume and adjuvant of local anesthetics).
Control	Detail information of block analgesia techniques (including guidance techniques; target area of block; block needle; needle tracking techniques: in-plane and out-of-plane; detail information of local anesthetics including type, concentration, dose, volume and adjuvant of local anesthetics) and non-block analgesia techniques (including type, dose, and administration method of analgesics).
Outcome	Primary outcome (pain intensity after perioperative pain management); Secondary outcome measurements (perioperative quadriceps strength; perioperative rescue analgesia information: perioperative cumulative analgesic consumption; time to first analgesic request; patients' recovery; perioperative complications; patients' satisfaction); Exploratory outcomes (perioperative sensory block; block ended time; perioperative mortality).
Study design	Randomization method; Blinding; Allocation concealment; Statistical analysis; Sample size calculation; Outcome reporting.
Other information	Type of anesthesia: local, spinal or general anesthesia; Period of perioperative pain management (preoperative analgesia, intraoperative anesthesia and postoperative

analgesia); Anesthesia time; Operation time; Assessment method or equipment of outcomes.

Quality assessment

The risk of bias in each included study will be assessed independently by two review authors (DL and ZL) under the guidance of the Cochrane risk of bias tool.[115] Methodology including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, other risks of bias and overall risk of bias will be evaluated. Each included study will be assessed by the risk of bias assessment tool from the Cochrane Handbook for Systematic Reviews of Interventions and then categorized into three levels (low risk of bias, unclear of bias and high risk of bias). [105,116, 117] Any discrepancies will be settled through discussions by all review authors or arbitration of third reviewer (Z-WY). Assessment of risk of bias is listed in Supplementary Appendix fie 2.

Measures of treatment effect

Mean differences (MDs) with 95% confidence intervals (CIs) will be used for continuous outcome data reported by the same scale, and standardized mean differences (SMDs) with 95% confidence intervals (CIs) will be used for continuous outcome data reported by different scales. The relative risks (RRs) with 95% CIs will be used for dichotomous outcome data.

Assessment of heterogeneity

Application of a fixed-effects model or random-effects models based on statistical heterogeneity is not recommended by the Cochrane guidelines.[105] Assessment of heterogeneity will be primarily inspected by forest plots. If there is no indication of funnel plot asymmetry, a random-effects meta-analysis will be performed. [105] If there is an indication of funnel plot asymmetry, then both a fixed-effect and a random-effect meta-analysis are problematic. In this situation, a sensitivity analysis will be performed by excluding small studies or meta-regression will be addressed directly. A P value <0.05 was assumed to be statistically significant.

Trial Sequential Analysis

The required information size (RIS) will be calculated to correct the risks of random errors by trial sequential analysis (TSA) using the TSA program version 0.9.5.10 Beta (Copenhagen Trial Unit, Copenhagen, Denmark). [118-120] TSA program version is available at http://www.ctu.dk/tsa.[121] Each outcome will be detected by RIS, the cumulative Z-curve and the TSA monitoring boundaries.[122 123]

For continuous outcomes, the observed SD, a mean difference of the observed SD/2 (clinically meaningful value), an alpha (type I error) of 2.5% and a beta (type II error) of 10% will be used in the TSA.[124] For dichotomous outcomes, the proportion or percentage from the control group, a relative risk variation of 20% (clinically meaningful value), an alpha (type I error) of 2.5% and a beta (type II error) of 10% will be used

in the TSA. [125]

Subgroup analysis

The results will be comprehensively interpreted through an analysis of subgroups or subsets as much as possible. If sufficient trials are available, data from different participants' ages, different types of hip disease or surgery, pain management during different perioperative periods, different pain management techniques in the control group, and different types of anesthesia will be analysed independently.

► Different participants' ages (PENG block for perioperative analgesia in elderly patients with different ages as follows: 65 years≤ Patients<75 years; 75 years≤ Patients<80 years; Patients≥80 years).

► Different types of hip disease or surgery (hip disease, such as hip fracture and hip osteoarthritis; hip surgery such as hip arthroplasty, hip fracture fixation and hip arthroscopy procedures).

► Pain management of different perioperative periods (PENG block for preoperative analgesia, intraoperative anesthesia and postoperative analgesia).

► Different pain management techniques in the control group (such as block analgesia techniques, including lumbar plexus block, femoral nerve block, fascia-iliac compartment block, 3-in-1 femoral nerve block, sacral plexus block, obturator and sciatic nerve block, and quadratus lumborum block. Non-block analgesia techniques such as opioid and no-opioid

analgesics).

► Different types of anesthesia (such as local anesthesia, spinal anesthesia or general anesthesia).

The interaction p value will be considered to test the statistically significant subgroup difference; if testing for interaction $p<0.05$ (a significant difference between subgroups exists), the results for individual subgroups will be reported separately. [105]

Sensitivity analysis

Sensitivity analysis will be applied after the analysis of subgroups or subsets as to evaluate the stability of the combined results, which could be affected by uncertain assumptions of data and usage. Significant changes in the pooled results may indicate significant heterogeneity in the included studies. Low-quality studies defined as high risk of bias studies according to the Cochrane risk of bias tool assessment will be excluded, and then re-analysis of the included studies will be performed to detect the existence of obvious differences between the combined effects. The stability of the pooled estimations will be detected by removing each included study one by one if necessary.

Assessment of publication biases

Egger's regression test and funnel plot analysis will be performed to estimate the potential publication bias, while more than 10 original studies involved an outcome.[126] [127] The symmetric pattern of the funnel plot by

trim-and-fill analysis will also be used to confirm the potential publication bias. The effect sizes of each included study will be normally symmetrically distributed around the center of a funnel plot in the absence of publication bias.[128] Publication biases will be detected by Stata/MP 16.0 (Stata Corp, College Station, TX, USA).

Grading the quality of evidence

The quality of evidence for each outcome will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria.[129] The quality of effect estimates will be classified as high, moderate, low or very low depending on the risk of bias, consistency, directness, precision and publication bias.[129] Data from randomized controlled trials are classified as high quality evidence according to GRADE, but it can be degraded according to risk of bias, imprecision, inconsistency, indirectness or publication bias.

Patient and public involvement statement

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

DISCUSSION

More and more elderly patients suffer from hip diseases in the global accelerating ageing process. As the main therapy for hip diseases, hip surgery is often associated with moderate to severe perioperative pain. An Optimal perioperative analgesia can decrease the risk of perioperative

complications and facilitate elderly patient perioperative recovery. Opioid analgesics are often selected hesitantly as opioid-related complications, which can delay patient recovery and discharge. Regional anesthesia and analgesic techniques for perioperative pain management have gradually become the clinical focus in elderly patients with hip diseases as to facilitate patient recovery. A simple, easy-to-perform, adequate analgesia and motor-sparing regional analgesia technique is the ideal regional analgesia technique for perioperative pain management of hip diseases.

The PENG block is a relatively new, easy-to-perform, analgesia adequate, and motor-sparing peripheral nerve block technique. The benefit of PENG block for perioperative analgesia in hip surgery was based on a significant number of publications of case reports, case series, reviews and retrospective studies, but prospective and randomized controlled trials are rare. Due to the limited current clinical evidence, the efficacy and safety of the PENG block remain unclear.

This systematic review will provide an overview of the current state of evidence on the clinical efficacy and safety of the PENG block for perioperative analgesia in the elderly patients with hip disease. We will examine the perioperative analgesia efficacy, the advantage of motor function preservation and the incidence of block-related adverse events of PENG block. The results of this systematic review will facilitate clinical decision making on better perioperative pain management of elderly

patients with hip disease.

This systematic review protocol was rigorously performed according to the Preferred Reporting Items for Systematic Review and Meta-Analyses Protocols (PRISMA-P) guidelines. The strengths of our systematic review are as follows: First, a comprehensive literature search of English and Chinese databases will be performed. Second, we will perform multivariable analysis (including subgroup analysis, trial sequential analysis for random errors; sensitivity analysis, study quality assessment, funnel plots and Egger's regression test for publication bias) to improve the quality of the evidence. Third, literature retrieval, data extraction, and study quality assessment will be performed independently according to the guidelines by at least two review authors. Any disagreement will be resolved through discussion or by consulting another review author as much as possible.

Limitations are as follows: First, studies with different perioperative periods, hip diseases or hip surgeries will be included, leading to potential heterogeneity. Second, PENG block is a relatively new peripheral nerve block technique, so the sample size of each included study may be limited, and the number of studies with available data for subgroup analyses may be small. Third, studies with high-level evidence such as well-designed randomized controlled trials with double-blind designs may be limited, as it is difficult to perform blinding for different block techniques in different

puncture positions. Fourth, PENG block is a relatively new peripheral nerve block technique, and it is difficult to define a significant clinical plausible value of mean difference and relative risk increase/decrease during literature research or the clinical experience. Therefore, a significant clinical plausible value will be defined according to TSA guidelines.

ETHICS AND DISSEMINATION

Ethical approval was not required for this systematic review protocol. The findings will be disseminated through peer-reviewed publications.

Timelines

Formal screening of search results will begin in August 2022. Data extraction will begin in November 2022. The project will be complete in January 2023.

Author Contributions

Z-JQ and DL conceived the idea for this systematic review. All authors (Z-JQ, DL, CG, ZL, D-XQ, Z-WY) developed the methodology for the systematic review. The manuscript was drafted by Z-JQ and DL, and revised by all authors. CG and Z-WY will screen potential studies, and perform duplicate independent data abstraction. Z-JQ and ZL will undertake risk of bias assessment and assess the evidence quality. Z-JQ and DL will conduct the data synthesis. All authors contributed to the research and agreed to be responsible for all aspects of the work.

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None.

Competing interests

None declared.

Data availability statement

Not applicable for this protocol.

Patient consent for publication

No patient was involved.

Provenance and peer review

Not commissioned; externally peer reviewed.

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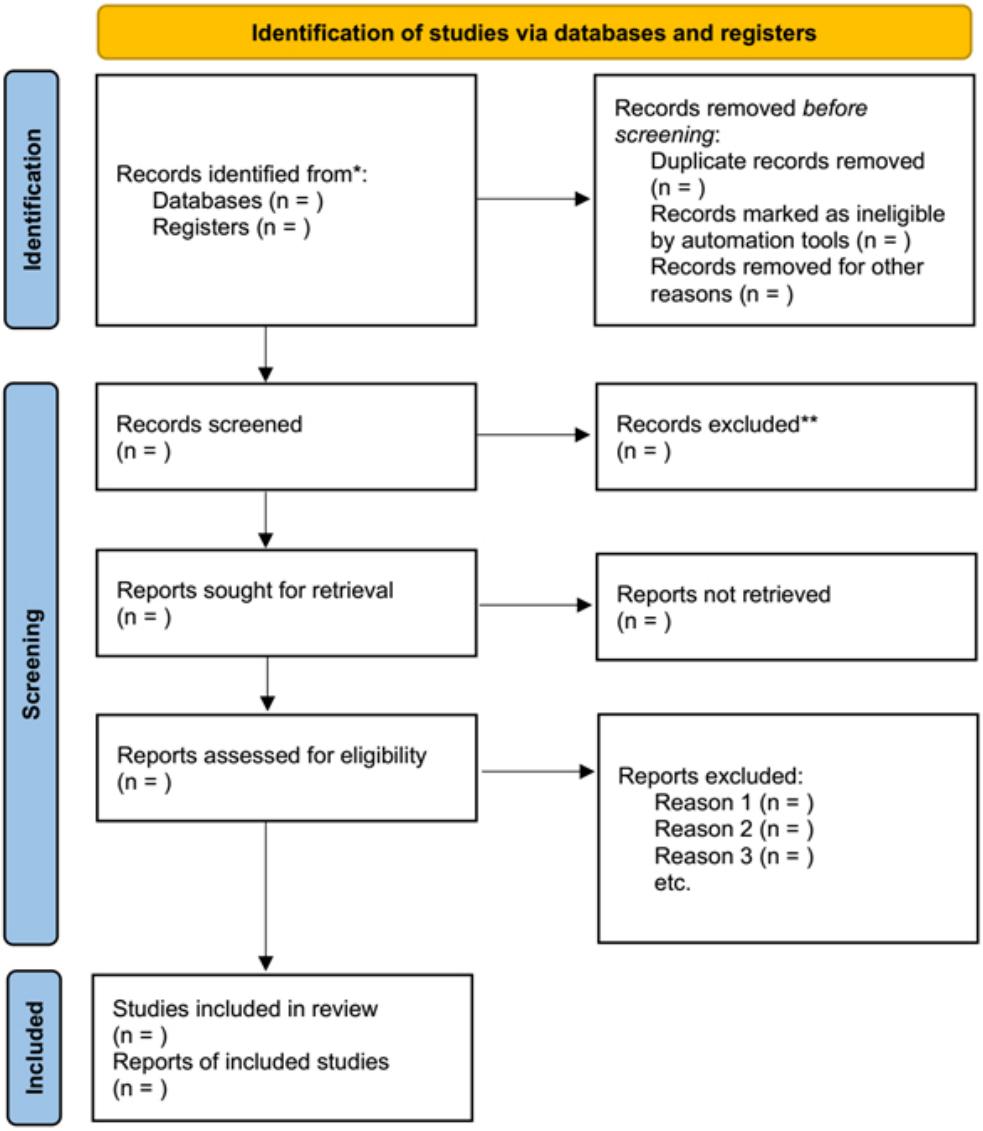
Figure Legends

Figure 1. The PRISMA flow diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analysis.



The PRISMA flow diagram

Supplementary Appendix file 1: Search strategy

Search strategy of PubMed as follows:

#1 “Hip "[MeSH Terms] OR Hips [tiab] OR Coxa [tiab] OR Coxas [tiab]

#2 “arthroscopy” [Mesh] or Arthroscopies[af] or Arthroscopic Surgical Procedures [af] or Arthroscopic Surgical Procedure[af] or Procedure, Arthroscopic Surgical[af] or Procedures, Arthroscopic Surgical[af] or Surgical Procedure, Arthroscopic[af] or Surgery, Arthroscopic [af] or Surgical Procedures, Arthroscopic[af] or Arthroscopic Surgery [af] or Arthroscopic Surgeries[af] or Surgeries, Arthroscopic[af]

#3 #1 AND #2

#4 “Hip Fracture” [Mesh] OR “Femoral Neck Fractures” [Mesh] OR Femoral Neck Fracture [tiab] OR Femur Neck Fractures[tiab] OR Femur Neck Fracture [tiab] OR Fractures, Hip [af] OR Trochanteric Fractures [af] OR Fractures, Trochanteric [af] OR Intertrochanteric Fractures [af] OR Fractures, Intertrochanteric [af] OR Subtrochanteric Fractures [af] OR Fractures, Subtrochanteric [af] Femoral Fracture[af] OR Fracture, Femoral [af] OR Fractures, Femoral [af] (hip* or intertrochanteric or subtrochanteric or trochanteric or pertrochanteric or peritrochanteric or femur or femoral or acetabul*) AND fracture*

#5 “Osteoarthritis, Hip” [Mesh] OR Hip Osteoarthritis[af] OR Osteoarthritis Of Hip [af] OR Osteoarthritis Of Hips[af] OR Coxarthrosis [af] OR Coxarthroses [af] OR Osteoarthritis of the Hip[af]

#6 Hip Injuries [Mesh] OR Hip Dislocation [Mesh] OR Injuries, Hip [af] OR Dislocation, Hip [af] OR Dislocations, Hip[af] OR Hip Dislocations[af] OR Hip Displacement[af] OR Displacement, Hip[af] OR Displacements, Hip[af] OR Hip Displacements[af] OR Hip Dysplasia[af] OR Dysplasia, Hip[af] OR Dysplasias, Hip[af] OR Hip Dysplasias [af]

#7 “Hip Prosthesis” [Mesh] OR “Arthroplasty, Replacement, Hip” [Mesh] OR Hip Prostheses [af] OR Prostheses, Hip[af] OR Prosthesis, Hip[af] OR Femoral Head Prosthesis[af] OR Femoral Head Prostheses[af] OR Prostheses, Femoral Head [af] OR Prosthesis, Femoral Head [af] OR Arthroplasties, Replacement, Hip [af] OR Arthroplasty, Hip Replacement [af] OR Hip Prosthesis Implantation [af] OR Hip Prosthesis Implantations [af] OR Implantation, Hip Prosthesis [af] OR Prosthesis Implantation, Hip [af] OR Hip Replacement Arthroplasty [af] OR Replacement Arthroplasties, Hip [af] OR Replacement Arthroplasty, Hip [af] OR Arthroplasties, Hip

Replacement [af] OR Hip Replacement Arthroplasties [af] OR Hip Replacement, Total [af] OR Total Hip Replacement [af] OR Total Hip Arthroplasty [af] OR Arthroplasty, Total Hip [af] OR Hip Arthroplasty, Total [af] OR Total Hip Arthroplasties [af] OR Replacement, Total Hip [af] OR Total Hip Replacements [af]

#8 #3 OR #4 OR #5 OR #6 OR #7

#9 “Aged” [Mesh] or "Aged, 80 and over"[Mesh] or "Aged, 65 and over"[Mesh] or Centenarians [Mesh] or Nonagenarians [Mesh]or Octogenarians [Mesh] or Geriatrics [Mesh] or Elderly [af] or Centenarian [af] or Nonagenarian [af] or Oldest Old [af] or Octogenarian [af] or aging [af] or aged [af] or elderly[af] or senior [af] or old [af] or old-age[af].

#10 “pericapsular nerve group block” [af] OR PENG [af]

#11 #8 AND #9 AND #10

#12 “controlled clinical trial” [Publication Type] OR “randomized controlled trial” [Publication Type] OR “randomized” [Title/Abstract] OR “randomized” [Title/Abstract] OR “Placebo” [Title/Abstract] OR “randomly” [Title/Abstract] OR “Clinical trial” [Title]

#13 (animals [MeSH Terms]) NOT ((human [MeSH Terms]) AND (animals [MeSH Terms]))

#14 #11 and #12 not #13

Search strategy of Cochrane library as follows:

#1 MeSH descriptor: [Hip] explode all trees.

#2 (Hips OR Coxa OR Coxas): ti,ab,kw

#3 #1 or # 2

#4 MeSH descriptor: [arthroscopy] explode all trees

#5 (arthroscop*): ti,ab,kw

#6 #4 or # 5

#7 #3 and # 6

#8 MeSH descriptor: [Hip Fracture] explode all trees

#9 (hip surgery OR hip prosthes* OR hip replacement* OR hip arthroplast* OR femoral head prosthes* OR joint prosthes*): ti,ab,kw

#10 ((hip* or fem?r* or intertrochant* or trochant* or pertrochant* or intertrochant* or peritrochant* or subtrochant* or intracapsular* or extracapsular* or acetabul*) and fracture*)

#11 MeSH descriptor: [Osteoarthritis, Hip] explode all trees

#12 (Hip Osteoarthritis OR Osteoarthritis Of Hip OR Osteoarthritis Of Hips OR Coxarthrosis OR Coxarthroses OR Osteoarthritis of the Hip): ti,ab,kw

#13 MeSH descriptor: [Hip Injuries] explode all trees

#14 ((disloca* or displace* or dysplas*) and hip*)

#15 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14

#16 MeSH descriptor: [Aged] explode all trees

#17 MeSH descriptor: [Aged, 80 and over] explode all trees

#18 MeSH descriptor: [Aged, 65 and over] explode all trees

#19 MeSH descriptor: [Geriatrics] explode all trees

#20 MeSH descriptor: [Nonagenarians] explode all trees

#21 MeSH descriptor: [Octogenarians] explode all trees

#22((Geriatric* or Elder* or old-age or pensioner*or aging or aged or elderly or senior or old or Oldest Old or old-age or Nonagenarian* or Octogenarian*)

#23 #16 or #17 or #18 or #19 or #20 or #21 or #22

#24 (pericapsular nerve group block or PENG): ti,ab,kw

#25 (controlled clinical trial):pt or (randomized controlled trial):pt or (random*): ti,ab,kw or (Clinical trial):ti,ab,kw

#26 #15 and #23 and #24 and #25

Search strategy of Web of Science as follows:

#1 TS= (Hip or Hips or Coxa or Coxas)

#2 TS= (arthroscop*)

#3 #1 and #2

#4 TS= (Hip* or femu* or femo* or intertrochant* or trochant* or pertrochant* or intertrochant* or peritrochant* or subtrochant* or intracapsular* or extracapsular* or acetabul*)

#5 TS= (fracture*)

#6 #4 and #5

#7 TS= (Hip Osteoarthritis or Osteoarthritis of Hip or Osteoarthritis of Hips or Coxarthrosis or Coxarthroses or Osteoarthritis of the Hip)

#8 TS= (Hip Injuries or Hip disloca* or Hip displace* or Hip dysplas*)

#9 #3 OR #6 OR #7 OR #8

#10 TS= (Geriatric* or Elder* or old-age or pensioner*or aging or aged or elderly or senior or old or Oldest Old or old-age or Nonagenarian* or Octogenarian*)

#11 TS= (pericapsular nerve group block or PENG)

#12 TS= (random* or Clinical trial)

#13 #9 and #10 and #11 and #12

Search strategy for Ovid Medline as follows:

#1 exp Hip/

#2 (Hips OR Coxa OR Coxas) .mp.

#3 #1 or # 2

#4 exp arthroscopy/

#5 (arthroscop*).mp.

#6 #4 or # 5

#7 #3 and # 6

#8 exp Hip Fracture/

#9 (hip surgery OR hip prosthes* OR hip replacement* OR hip arthroplast* OR femoral head prosthes* OR joint prosthes*).mp.

#10 ((hip* or fem?r* or intertrochant* or trochant* or pertrochant* or intertrochant* or peritrochant* or subtrochant* or intracapsular* or extracapsular* or acetabul*) and fracture*).mp.

#11 exp Osteoarthritis, Hip/

#12 (Hip Osteoarthritis or Osteoarthritis of Hip or Osteoarthritis of Hips or Coxarthrosis or Coxarthroses or Osteoarthritis of the Hip) .mp.

#13 exp Hip Injuries/

#14 ((disloca* or displace* or dysplas*) and hip*).mp.

#15 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14

#16 exp Aged/

#17 exp Aged, 80 and over/

#18 exp Aged, 65 and over/

#19 exp Geriatrics/

#20 exp Nonagenarians/

#21 exp Octogenarians/

#22((Geriatric* or Elder* or old-age or pensioner*or aging or aged or elderly or senior or old or Oldest Old or old-age or Nonagenarian* or Octogenarian*).mp.

#23 #16 or #17 or #18 or #19 or #20 or #21 or #22

#24 (pericapsular nerve group block or PENG) .mp.

#25 #15 and #23 and #24

#26 randomized controlled trial.pt.

#27controlled clinical trial.pt.

#28 randomized.ab.

#29 placebo.ab.

#30 clinical trials as topic.sh.

#31 randomly.ab.

#32 trial.ti.

#33 #26 or #27 or #28 or #29 or #30 or #31 or #32

#34 (animals not (humans and animals)).sh.

#35 #25 and #33 not #34

Search strategy for Embase as follows:

#1 exp Hip/

#2 (Hips OR Coxa OR Coxas) .mp.

#3 #1 or # 2

#4 exp arthroscopy/

#5 (arthroscop*).mp.

#6 #4 or # 5

#7 #3 and # 6

#8 exp Hip Fracture/

#9 (hip surgery OR hip prosthes* OR hip replacement* OR hip arthroplast* OR femoral head prosthes* OR joint prosthes*).mp.

#10 ((hip* or fem?r* or intertrochant* or trochant* or pertrochant* or intertrochant* or peritrochant* or subtrochant* or intracapsular* or extracapsular* or acetabul*) and fracture*).mp.

#11 exp Osteoarthritis, Hip/

#12 (Hip Osteoarthritis or Osteoarthritis of Hip or Osteoarthritis of Hips or Coxarthrosis or

Coxarthroses or Osteoarthritis of the Hip) .mp.

#13 exp Hip Injuries/

#14 ((disloca* or displace* or dysplas*) and hip*).mp.

#15 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14

#16 exp Aged/

#17 exp Aged, 80 and over/

#18 exp Aged, 65 and over/

#19 exp Geriatrics/

#20 exp Nonagenarians/

#21 exp Octogenarians/

#22((Geriatric* or Elder* or old-age or pensioner*or aging or aged or elderly or senior or old or Oldest Old or old-age or Nonagenarian* or Octogenarian*).mp.

#23 #16 or #17 or #18 or #19 or #20 or #21 or #22

#24 (pericapsular nerve group block or PENG) .mp.

#25 #15 and #23 and #24

#26 exp randomized controlled trial/

#27(random*).mp.

#28 (placebo*).mp.

#29 Clinical trial.mp.

#30 clinical trials as topic.sh.

#31 #26 or #27 or #28 or #29 or #30

#32 (exp animal/ or nonhuman/ or exp animal experiment/) not human/

#33 #25 and #31 not #32

WHO ICTRP Trial registry

http://apps.who.int/trialsearch (WHO ICTRP register) will be searched via the advanced search page. Search terms were: (Hips OR Coxa OR Coxas or fem?r* or intertrochant* or trochant* or pertrochant* or intertrochant* or peritrochant* or subtrochant* or intracapsular* or extracapsular* or acetabul*) AND (Geriatric* or Elder* or old-age or pensioner*or aging or aged or elderly or senior or old or Oldest Old or old-age or Nonagenarian* or Octogenarian*) AND (pericapsular nerve group block or PENG).

Clinicaltrials.gov search strategy

http://clinicaltrials.gov (NIH register) will be searched via advanced search page. Search terms were: Condition or disease: (Hips OR Coxa OR Coxas or fem?r* or intertrochant* or trochant* or pertrochant* or intertrochant* or peritrochant* or subtrochant* or intracapsular* or extracapsular* or acetabul*) AND (Geriatric* or Elder* or old-age or pensioner*or aging or aged or elderly or senior or old or Oldest Old or old-age or Nonagenarian* or Octogenarian*).

Study type: Interventional Studies.

Intervention/treatment: (pericapsular nerve group block or PENG)

Chinese database

China National Knowledge Infrastructure (CNKI) search strategy

(髋[全部字段]or 关节[全部字段] or 股骨头[全部字段]or 关节唇[全部字段] or 股骨颈 [全部字段] or 转子 [全部字段] or 骨盆 [全部字段] or 关节炎[全部字段] or 骨折[全部字段]or 损伤[全部字段] or 脱位[全部字段] or 撞击[全部字段] or 关节镜[全部字段] or 微创[全部字段] or 保守[全部字段]or 置换[全部字段] or 成形[全部字段] or 假体[全部字段] or 固定[全部字段] or 外伤[全部字段]) and (关节囊周[全部字段] or PENG[全部字段] or 阻滞 [全部字段]) and (老年[全部字段] or 高龄[全部字段] or 老龄 or 80 岁以上[全部字段]) and (随机[全部字段] or 对照[全部字段])

Chinese BioMedical Literature (CBM)

(髋[全部字段] or 关节[全部字段] or 股骨头[全部字段]or 关节唇[全部字段] or 股骨颈 [全部字段] or 转子 [全部字段] or 骨盆 [全部字段] or 关节炎[全部字段] or 骨折[全部字段]or 损伤[全部字段] or 脱位[全部字段] or 撞击[全部字段] or 关节镜[全部字段] or 微创[全部字段] or 保守[全部字段]or 置换[全部字段] or 成形[全部字段] or 假体[全部字段] or 固定[全部字段] or 外伤[全部字段]) and (关节囊周[全部字段] or PENG[全部字段] or 阻滞 [全部字段]) and (老年[全部字段] or 高龄[全部字段] or 老龄 or 80 岁以上[全部字段]) and (随机[全部字段] or 对照[全部字段])

VIP database

关键词=(髋 or 关节 or 股骨头 or 关节唇 or 股骨颈 or 转子 or 骨盆 or 关节炎 or 骨折 or 损伤 or 脱位 or 撞击 or 关节镜 or 微创 or 保守 or 置换 or 成形 or 假体 or 固定 or 外伤) AND 关键词= (老年 or 高龄 or 老龄 or 80 岁以上) AND 关键词= (关节囊周 or PENG or 阻滞) AND

关键词= (随机 or 对照)

Wan fang database.

(髋[全部字段]or 关节[全部字段]股骨头[全部字段]or 关节唇[全部字段] or 股骨颈 [全部字段] or 转子 [全部字段] or 骨盆 [全部字段] or 关节炎[全部字段] or 骨折[全部字段]or 损伤[全部字段] or 脱位[全部字段] or 撞击[全部字段] or 关节镜[全部字段] or 微创[全部字段] or 保守[全部字段]or 置换[全部字段] or 成形[全部字段] or 假体[全部字段] or 固定[全部字段] or 外伤[全部字段]) and (关节囊周[全部字段] or PENG[全部字段] or 阻滞 [全部字段]) and (老年[全部字段] or 高龄[全部字段] or 老龄 or 80 岁以上[全部字段]) and (随机[全部字段] or 对照[全部字段])

Supplementary Appendix file 2 : Assessment of risk of bias

Random sequence generation

- ***Low risk:*** If sequence generation was achieved using computer random number generator or a random number table. Drawing lots, tossing a coin, shuffling cards, and throwing dice were also considered adequate if performed by an independent adjudicator.
- ***Unclear risk:*** If the method of randomisation was not specified, but the trial was still presented as being randomised.
- ***High risk:*** If the allocation sequence is not randomised or only quasi-randomised. These trials will be excluded.

Allocation concealment

- ***Low risk:*** If the allocation of patients was performed by a central independent unit, onsite locked computer or identical-looking numbered sealed envelopes.
- ***Uncertain risk:*** If the trial was classified as randomised but the allocation concealment process was not described.
- ***High risk:*** If the allocation sequence was familiar to the investigators who assigned participants.

Blinding of participants and treatment providers

- ***Low risk:*** If the participants and the treatment providers were blinded to intervention allocation and this was described.
- ***Uncertain risk:*** If the procedure of blinding was insufficiently described.
- ***High risk:*** If blinding of participants and the treatment providers was not performed.

Blinding of outcome assessment

- ***Low risk of bias:*** If it was mentioned that outcome assessors were blinded and this was described.
- ***Uncertain risk of bias:*** If it was not mentioned if the outcome assessors in the trial were blinded or the extent of blinding was insufficiently described.
- ***High risk of bias:*** If no blinding or incomplete blinding of outcome assessors was performed.

Incomplete outcome data

- ***Low risk of bias:*** If missing data were unlikely to make treatment effects depart from plausible

values. This could be either (1) there were no drop-outs or withdrawals for all outcomes, or (2) the numbers and reasons for the withdrawals and drop-outs for all outcomes were clearly stated and could be described as being similar to both groups. Generally, the trial is judged as at a low risk of bias due to incomplete outcome data if drop-outs are less than 5%. However, the 5% cut-off is not definitive.

- ***Uncertain risk of bias:*** If there was insufficient information to assess whether missing data were likely to induce bias on the results.
- ***High risk of bias:*** If the results were likely to be biased due to missing data either because the pattern of drop-outs could be described as being different in the two intervention groups or the trial used improper methods in dealing with the missing data (e.g. last observation carried forward).

Selective outcome reporting

- ***Low risk of bias:*** If a protocol was published before or at the time the trial was begun and the outcomes specified in the protocol were reported on. If there is no protocol or the protocol was published after the trial has begun, reporting of serious adverse events will grant the trial a grade of low risk of bias.
- ***Uncertain risk of bias:*** If no protocol was published and the outcome of serious adverse events were not reported on.
- ***High risk of bias:*** If the outcomes in the protocol were not reported on.

Other risks of bias

- ***Low risk of bias:*** If the trial appears to be free of other components that could put it at risk of bias.
- ***Unclear risk of bias:*** If the trial may or may not be free of other components that could put it at risk of bias.
- ***High risk of bias:*** If there are other factors in the trial that could put it at risk of bias (including, Design-specific risk of bias, stopped early due to some data-dependent process including a formal-stopping rule, baseline imbalance, claimed fraudulent, blocked randomization in unblinded trials, differential diagnostic activity, contamination, inappropriate measurement instrument for outcomes, deviation from the study protocol unrelated to the clinical practice, authors conducted trials on the same topic, academic bias, for-profit bias, inappropriate

financial conflict of interest).

Overall risk of bias

- ***Low risk of bias:*** The trial will be classified as overall 'low risk of bias' only if all of the bias domains described in the above paragraphs are classified as 'low risk of bias'.
- ***High risk of bias:*** The trial will be classified as 'high risk of bias' if any of the bias risk domains described in the above are classified as 'unclear' or 'high risk of bias'.
- We will assess the domains 'blinding of outcome assessment', 'incomplete outcome data', and 'selective out- come reporting' for each outcome result. Thus, we can assess the bias risk for each outcome assessed in addition to each trial. Our primary conclusions will be based on the results of our primary outcome results with overall low risk of bias. Both our primary and secondary conclusions will be presented in the summary of findings tables.

Criteria classification

- If all risk of bias domains were scored as having a low risk of bias, the trial was defined as having a low overall risk of bias.
- If one or more of the bias domains were scored as unclear or high risk of bias, the trial was defined as having a high overall risk of bias.
- Trials with a low risk of bias in all domains (including sequence generation, allocation concealment, blinding, incomplete data, selective outcome reporting, and other risks of bias) will be classified as having a low overall risk of bias.
- Trials with one or more of these domains scored as unclear or high risk of bias will be defined as having a high overall risk of bias.

PRISMA-P checklist

Table PRISMA-P (preferred reporting items for systematic review and meta-analysis protocols) 2015 checklist: recommended items to address in a systematic review protocol

Section and topic	Item No	Checklist item	Reported on page #
Administrative information			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	None
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3,8
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	24
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	None
Support:			
Sponsor	5b	Provide name for the review funder and/or sponsor	None
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	None
Introduction			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-7
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	7-13
Methods			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	8-13 ; 14-15

Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	13-16
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	13-14, S1
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	14-16
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	14-15
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	14-16
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	16
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	10-13
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	16-20
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	17
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	17
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	18-21
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	17
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	20
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	18-20

BMJ Open

Efficacy of pericapsular nerve group (PENG) block on perioperative pain management in elderly patients undergoing hip surgical procedures: a protocol for a systematic review with meta-analysis and trial sequential analysis

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TITLE PAGE

Efficacy of pericapsular nerve group (PENG) block on perioperative pain management in elderly patients undergoing hip surgical procedures: a protocol for a systematic review with meta-analysis and trial sequential analysis

Authors

Jianqiao Zheng[1] E-mail: zhjq1983@163.com

Li Du[2] E-mail: huaying-duli@163.com

Guo Chen[1] E-mail: Anesthesiology_SCU@163.com

Lu Zhang[1] E-mail: 304022514@qq.com

Xiaoqian Deng[1] E-mail: 50058837@qq.com

*Weiyi Zhang[1] E-mail: zhangweiyi@wchscu.cn

[1]Department of Anesthesiology, West China Hospital, Sichuan University No. 37th, Guoxue Alley, Wuhou District, Chengdu 610041, Sichuan, China.

[2]Department of Anesthesiology, Sichuan Cancer Hospital & Institute, Sichuan Cancer Center, School of Medicine, University of Electronic Science and Technology of China, No.55th, People's South Road, Chengdu 610041, Sichuan, China.

*Corresponding Author

Name: Weiyi Zhang

E-mail: zhangweiyi@wchscu.cn

Phone: +86-28-8542-3593

Address: Department of Anesthesiology, Sichuan University West China Hospital, No. 37th, Guoxue Alley, Wuhou District, Chengdu 610041, Sichuan, China.

Words: 4100

ABSTRACT

Introduction An increasing number of elderly patients suffer from hip diseases associated with moderate to severe perioperative pain during the accelerating global aging process. Optimal analgesia can decrease perioperative complications and facilitate elderly patients' perioperative recovery. Pericapsular nerve group (PENG) block is a relatively new, analgesia adequate, and motor-sparing block technique for perioperative pain management of hip diseases. However, the efficacy of PENG block remains unclear as the limited clinical evidence. Then, we will perform a protocol for a systematic review and meta-analysis to identify the efficacy of PENG block for perioperative pain management.

Methods and analysis PubMed, Ovid Medline, Cochrane Library, Embase, Web of Science, China National Knowledge Infrastructure, Chinese BioMedical Literature, Wanfang, and VIP databases will be searched from inception to August 2022 to identify randomized controlled trials of elderly patients accepting PENG block for hip diseases. The primary outcome will be the pain intensity after pain management. Secondary outcomes will be quadriceps strength, perioperative rescue analgesia information and perioperative complications. Assessment of heterogeneity will be primarily inspected by forest plots. If there is no indication of funnel plot asymmetry, a random-effects meta-analysis will be performed. The Cochrane risk-of-bias tool, GRADE (Grading of

Recommendations Assessment, Development, and Evaluation) and trial sequential analysis will be conducted to evaluate the evidence quality and control the random errors. Funnel plots and Egger's regression test will be performed to evaluate publication bias.

Ethics and dissemination Ethical approval was not required for this systematic review protocol. The results will be disseminated through peer-reviewed publications.

Keywords pericapsular nerve group block, hip, elderly, meta-analysis, randomized controlled trial.

PROSPERO registration number CRD42022313895

Strengths and limitations of the study

►Application of Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines for a better quality of meta-analytical results.

► Control of random errors with trial sequential analysis by calculating the diversity adjusted information size for the outcomes.

► Application of Funnel plots and Egger's regression test for publication bias.

►Subgroup analysis based on patients' age, types of hip disease or surgery, perioperative period, type of anesthesia, and perioperative pain management techniques for heterogeneity assessment.

INTRODUCTION

The global population over 60 years old is estimated to increase to 2.1 billion in 2050 (approximately 22% of the global population) and 3.1 billion by 2100.[1] With this accelerating aging process, an increasing number of elderly patients suffer from hip diseases such as hip fractures, and hip osteoarthritis.[2-4] Hip surgery, including hip arthroplasty, hip fracture internal fixation and hip arthroscopy procedures are the main treatments for hip diseases.[5-8] Hip surgery is often associated with moderate to severe postoperative pain, particularly in hip fracture patients undergoing surgical treatment, and severe pain persists throughout the perioperative period.[9-11] As a minimally invasive approach, arthroscopic hip surgery is gaining popularity globally.[12] Despite being minimally invasive, patients undergoing arthroscopic hip surgery may still experience severe pain after the procedure. [13]

Perioperative pain, if inadequately controlled, can increase the risk of perioperative complications (including delirium, pulmonary complications, and cardiovascular events), delay ambulation, decrease short-term mobility, interfere with rehabilitation, increase hospital length of stay, and even increase the mortality and morbidity, leading to poor functional prognosis.[14-19] In elderly patients, the risk of perioperative adverse events is higher due to polypharmacy and multimorbidity.[20-22] In contrast, adequate pain management has been shown to facilitate postoperative

mobilization, improve mobility and promote better functional recovery.[23-26] Early mobilization has been associated with reducing postoperative complications, including pneumonia, venous thromboembolism, pressure ulcers, and delirium.[27-29] Therefore, optimal perioperative analgesia can facilitate elderly patients' perioperative recovery.[30-33]

Traditionally, opioid analgesia is considered the basis of perioperative pain management.[34-37] However, opioid-related complications such as delirium, urinary retention, nausea, constipation and respiratory depression may occur and can delay patients' recovery and discharge.[38-43] Considering these adverse events, especially the higher incidence of cognitive deficits in elderly patients suffering a hip fracture, opioid analgesics are often selected hesitantly.[44-48] In addition, in light of the current opioid crisis, strategies to minimize opioid use, including the use of multimodal perioperative pain management strategies with opioid-sparing oral and intravenous medications, regional anesthesia and analgesic techniques have become an increasing clinical focus in hip surgical procedures in elderly patients.[49-53]

Peripheral nerve blocks (including lumbar plexus block, femoral nerve block, fascia iliac compartment block, 3-in-1 femoral nerve block, sacral plexus block, obturator block, and sciatic nerve block) and some inter-fascial plane blocks (such as quadratus lumborum block) have also been suggested to decrease postoperative pain and opioid use during hip

surgery.[54-61] However, peripheral nerve blocks may induce weakness of the quadriceps muscles, delay hospital discharge, and even predispose the patient to fall. [62-65] In some cases, it is difficult to position the patient as the extreme pain, particularly in hip fractures, accompanied by the deep depth of the block target, the lumbar plexus or quadratus lumborum block will become difficult.[66-68] In addition, another difficulty of adequate regional analgesia for hip pain is the complex innervation of the hip joint.[69] High branches of the femoral and obturator nerves provide innervation to the anterior hip capsule. The accessory obturator nerve was also found to innervate the medial capsule.[70] [71] In this situation, the coverage of the articular nerve supply to the hip joint is critical for adequate analgesia. Hence, a simple, easy-to-perform, analgesia adequate, and motor-sparing regional analgesia technique is the ideal regional analgesia technique for hip surgery.

Pericapsular nerve group (PENG) block is a relatively new peripheral nerve block technique, first described by Giron-Arango in patients with hip fractures, which was based on the complex innervation of the hip joint.[72] The target of the PENG block is the musculofascial plane between the psoas tendon anteriorly and the pubic ramus posteriorly. It can be easily performed in the supine position, avoiding the additional pain from positioning the patient for peripheral nerve block.[73-76] In theory, PENG block has potential advantages over traditional forms of regional analgesia

for pain originating from the hip, as local anesthetic deposits in this target could provide a broader and more complete block effect on the coverage area of sensory nerves innervating the hip.[77-87] Thus, it has the potential advantage of reducing postoperative pain without motor-blocking.[88-91] PENG block has been described as easy to perform in the supine position and as an effective and motor-sparing regional analgesia technique for hip surgery.[92-95]

The excellent analgesic benefit of PENG block for perioperative analgesia in hip surgery was highlighted in a significant number of publications of case reports, case series, reviews and retrospective studies [77-83, 92-95], but prospective and randomized controlled trials are rare.[84-87] Inadvertent quadriceps weakness was also reported in patients following the PENG block.[96-98] Due to limited clinical evidence, the efficacy and safety of the PENG block, particularly the efficacy of motor function preservation and the incidence of block-related adverse events remain controversial until now.[99-103]

Therefore, it is necessary to conduct a systematic review and meta-analysis to analyze the clinical efficacy of PENG block on perioperative pain management in elderly patients with hip diseases. The outcomes of this systematic review will provide evidence for better clinical decision-making and possible future directions for further clinical trials.

Objectives

We are performing this protocol of systematic review with meta-analysis and trial sequential analysis (TSA) of randomized clinical trials to evaluate the clinical efficacy and safety of PENG block on perioperative pain management in elderly patients with hip diseases.

METHODS AND ANALYSIS

Design and registration of the review

We devised this protocol according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines registered with PROSPERO 2022 (registration number: CRD42022313895). [104] We will perform this systematic review and meta-analysis based on the Cochrane Handbook and report the results following the PRISMA statement.[105 106] This study is anticipated to begin searching in August 2022 and will be completed in January 2023.

Inclusion criteria for study selection

Types of studies

Only randomized controlled trials (RCTs) involving the clinical efficacy of PENG block on perioperative pain management in elderly patients with hip diseases will be included. There will be no language restrictions.

The exclusion criteria were as follows: (1) studies comparing PENG block versus PENG block combined with other analgesic techniques, or studies comparing PENG block under different guidance techniques

(ultrasound guided or traditional landmark technique); (2) studies with data that could not be used for statistical analysis, or studies with incomplete data, or data that could not be extracted after contacting the original authors; and (3) studies that were duplicate publications, published as letters or editorials, abstracts from conferences, and reviews.

Types of participants

Elderly participants (≥65 years old) with any hip disease (such as hip fracture, or hip osteoarthritis) accepting PENG block for perioperative pain management (including preoperative analgesia, intraoperative anesthesia management, and postoperative analgesia) will be included. There will be no limitations on participants' gender, ethnicity, body mass index (BMI), or American Society of Anesthesiologists (ASA) classification.

Types of interventions/controls

The intervention group will be the participants who received any kind of PENG block (including ultrasound-guided, X-ray-guided, CT-guided or traditional landmark-based techniques), alone or in combination with any other kind of analgesia technique for perioperative pain management, while the control group will receive any kind of analgesia technique other than PENG block for perioperative pain management.

Types of outcome measures

Primary outcomes

The primary outcome will be the pain intensity after perioperative

pain management by PENG block or other analgesia techniques. Pain intensity, including preoperative and postoperative pain intensity will be included and assessed by visual analog scale (VAS) scores, numeric rating scale (NRS) scores or other scale scores. Perioperative static and dynamic pain intensity after pain management will also be included if possible.

Secondary outcomes

1. **Unexpected perioperative femoral nerve block** will be evaluated as follows if possible.

- Incidence of quadriceps motor block (defined as paresis or paralysis of knee extension and hip adduction) [Knee extension was graded according to a 3-point scale: 0=normal strength (extension against gravity and resistance)]; 1=paresis (extension against gravity but not against resistance); 2=paralysis (no extension possible).[107] Hip adduction scores of 0, 1, and 2 points indicated decreases in strength of 0%-20%, 21%-70%, and 71%-90% compared with baseline measurement, respectively. [108]
- Mobility of the quadriceps as defined by the Medical Research Council (MRC) scale.[109]
- Quadriceps strength was assessed by measuring the force produced by voluntary isometric contractions with any type of reliable and valid stationary dynamometer (such as the Chatillon DPPH-250 force gauge, AMETEK, USA or Chatillon; AMETEK, Largo, Florida; Lafayette

Instrument, Lafayette, Indiana; and MicroFET, Hoggan Health Industries, West Jordan, Utah).[110 111]

2. Perioperative rescue analgesia information

- Perioperative cumulative analgesic consumption: cumulative analgesic consumption for intraoperative anesthesia and cumulative rescue analgesics for preoperative/postoperative analgesia will be included if possible. Any kind of analgesics, such as opioid analgesics and non-steroidal analgesics administered by different delivery methods, such as PCA (patient-controlled analgesia) devices, intravenous, oral, or intramuscular will be included if possible.
- Time to first analgesic request: time from the end of the preoperative pain management procedure to the first analgesic request or time from the end of surgery to the first analgesic request will be included if possible.

3. Perioperative complications: if possible

- Block-related adverse events included vascular puncture, paresthesia, local anesthetic toxicity, anaphylaxis, permanent nerve injury, bleeding, or infection.
- Intraoperative adverse effects included hyoxemia(oxygen saturation less than 90% or oxygen partial arterial pressure≤60 mmHg); hypotension (defined as a decrease of >20% from preanesthetic patient baseline values or a systolic blood pressure less than 90 mmHg);

arrhythmia [including bradycardia (defined as HR <55 beats/min); tachycardia (defined as HR>100 beats/min); any other types of arrhythmias]; and blood loss.

- Other adverse effects: including postoperative nausea/vomiting, pruritus, urinary retention, respiratory depression, sweating, dizziness, pruritus, urticaria, postoperative arrhythmia, and postoperative pulmonary complications, were defined as the composite of any respiratory infection, respiratory failure, pleural effusion, atelectasis, or pneumothorax.

4. **Patients' recovery:** Length of stay, recovery time (defined as the time until recovery room discharge criteria were met after surgery), the quality of postoperative recovery score (such as the Quality of Recovery-40 questionnaire) [112] and patients' ambulation (such as time-to-first ambulation and initial ambulation distance) will be included if possible.

5. **Patient satisfaction:**

If possible, patient satisfaction with performing the perioperative pain management techniques or postoperative analgesia will be included. Satisfaction could be measured by a 5-point Likert scale (1=very dissatisfied; 2=dissatisfied; 3=neutral; 4=satisfied; 5= very satisfied), 10-point Likert scale (1= completely unsatisfied; 10=completely satisfied) or

a postoperative questionnaire whether the patient would choose the same anesthetic or analgesia handling by the answer of "yes" or "no". [113]

Exploratory outcomes

1. **Perioperative sensory block:** Sensory block was evaluated using a 3-point scale [0=no block, 1=analgesia (patient can feel touch, not cold), 2=anesthesia (patient cannot feel touch)], which was assessed in the anterior, lateral and medial aspects of the mid-thigh. [107]
2. **Block ended time:** defined as the return of motor (if initially impaired) and/or sensory function, which was acquired from patients' recall.
3. **Perioperative mortality** was defined as all-cause death during the operation procedure, within 30 days after surgery, or death during hospitalization.

Search strategy

Two reviewers (Z-JQ and DL) will independently conduct the search, and any disagreements will be resolved by consulting a third reviewer (Z-WY) as much as possible. English and Chinese electronic databases will be searched for published literature from inception to August 2022. PubMed, Ovid Medline, Cochrane Library, Embase, and Web of Science will be included in the English databases. The Chinese BioMedical Literature (Sino-Med), China National Knowledge Infrastructure (CNKI), Wanfang database and VIP Database will be included in the Chinese databases. The trial registry database (Clinical Trials.gov and WHO

International Clinical Trials Registry Platform) will also be scrutinized to avoid missing ongoing or unpublished clinical trials. In addition, reference lists of each study will also be scanned for missing studies.

The search strategy will use the following search terms: pericapsular nerve group block, PENG block, elderly, hip, and randomized controlled trial. Related search terms will also be translated into Chinese for literature research and study identification in Chinese databases. The search strategies are listed in Supplementary Appendix file 1. Comprehensive updating of the literature search results will be performed prior to the final publication of systematic reviews to avoid missing published studies during the systematic review preparation.

Data collection and analysis

Selection of studies

At least two review authors (Z-JQ and DL) will be responsible for screening the potentially eligible studies by reading titles and abstracts. All identified and relevant full-text publications will be retrieved by screening the full text thoroughly, and the reasons for excluding the ineligible studies will be recorded. Any disagreement will be resolved through discussion or by consulting a third review author (Z-JQ and CG) as much as possible. A fourth reviewer (Z-WY) will carefully check out all procedures before the final confirmation of the data extraction. Data extraction will be performed by at least two authors, and a third author will be consulted if there is any

disagreement. Duplicate publications and companion papers of the same trial will be assessed by all review authors. The study selection process is displayed in the PRISMA flow diagram (figure 1).

Data extraction

Two review authors (Z-JQ and ZL) will use a standardized data collection form (Excel version 2013, Microsoft Inc, Washington DC, USA) for data extraction from each included study. The data extraction form included participants' demographic data, type of hip disease or hip surgery, type of anesthesia: local, spinal or general anesthesia, period of perioperative pain management (preoperative analgesia, intraoperative anesthesia and postoperative analgesia), inclusion and exclusion criteria, detailed information of analgesia techniques (type of perioperative analgesia techniques: PENG block or other analgesia techniques; type, concentration, dose, volume and adjuvant of local anesthetics), and any outcomes including primary, secondary, and exploratory outcomes. Study design characteristics including randomization method, allocation concealment, blinding (patients, treatment providers, outcome investigators), incomplete outcome data collection and statistical analysis, and outcome reporting) will be recorded simultaneously. Continuous and dichotomous data will be recorded as the mean± SD and the percentages or the proportion. If necessary, a third review author (D-XQ) will cross-check the data to ensure precision. When the necessary information or data

for analysis is missing or incomplete, we will contact the corresponding author of the research via email for the original data as much as possible. Necessary numerical data in the graphs will be extracted by Adobe Photoshop if necessary. [114] Extracted information and data are presented in table 1.

Table 1 Information and data extraction schedule

Subject	Content
Publication information	Title; author; Publish year; Country of origin; Corporate sponsorship; Contact email.
Participant	Sample size; Age; Sex; Height and weight or BMI; ASA physical status classification levels; Type of hip disease or hip surgery; Inclusion and exclusion criteria if necessary.
Intervention	Detail information of PENG block techniques (guidance techniques; target area of block; block needle; needle tracking techniques: in-plane and out-of-plane) Detail information of local anesthetics (type, concentration, dose, volume and adjuvant of local anesthetics).
Control	Detail information of block analgesia techniques (including guidance techniques; target area of block; block needle; needle tracking techniques: in-plane and out-of-plane; detail information of local anesthetics including type, concentration, dose, volume and adjuvant of local anesthetics) and non-block analgesia techniques (including type, dose, and administration method of analgesics).
Outcome	Primary outcome (pain intensity after perioperative pain management); Secondary outcome measurements (perioperative quadriceps strength; perioperative rescue analgesia information: perioperative cumulative analgesic consumption; time to first analgesic request; patients' recovery; perioperative complications; patients' satisfaction); Exploratory outcomes (perioperative sensory block; block ended time; perioperative mortality).
Study design	Randomization method; Blinding; Allocation concealment; Statistical analysis; Sample size calculation; Outcome reporting.
Other information	Type of anesthesia: local, spinal or general anesthesia; Period of perioperative pain management (preoperative analgesia, intraoperative anesthesia and postoperative analgesia); Anesthesia time; Operation time; Assessment method or equipment of outcomes.

Quality assessment

The risk of bias in each included study will be assessed independently by two review authors (DL and ZL) under the guidance of the Cochrane

risk of bias tool.[115] Methodology (including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, other risks of bias, and overall risk of bias) will be evaluated. Each included study will be assessed by the risk of bias assessment tool from the Cochrane Handbook for Systematic Reviews of Interventions and then categorized into three levels (low risk of bias, unclear of bias, and high risk of bias). [105,116, 117] Any discrepancies will be settled through discussions by all review authors or arbitration of a third reviewer (Z-WY). Assessment of risk of bias is listed in Supplementary Appendix fie 2.

Measures of treatment effect

Mean differences (MDs) with 95% confidence intervals (CIs) will be used for continuous outcome data reported by the same scale, and standardized mean differences (SMDs) with 95% confidence intervals (CIs) will be used for continuous outcome data reported by different scales. The relative risks (RRs) with 95% CIs will be used for dichotomous outcome data.

Assessment of heterogeneity

The application of a fixed-effects model or random-effects model based on statistical heterogeneity is not recommended by the Cochrane guidelines.[105] Assessment of heterogeneity will be primarily inspected by forest plots. If there is no indication of funnel plot asymmetry, a random-

effects meta-analysis will be performed. [105] If there is an indication of funnel plot asymmetry, then both a fixed-effect and a random-effect meta-analysis are problematic. In this situation, a sensitivity analysis will be performed by excluding small studies or meta-regression will be addressed directly. A P value <0.05 was assumed to be statistically significant.

Trial Sequential Analysis

The required information size (RIS) will be calculated to correct the risks of random errors by trial sequential analysis (TSA) using the TSA program version 0.9.5.10 Beta (Copenhagen Trial Unit, Copenhagen, Denmark). [118-120] TSA program version is available at http://www.ctu.dk/tsa.[121] Each outcome will be detected by RIS, the cumulative Z-curve, and the TSA monitoring boundaries.[122 123]

For continuous outcomes, the observed SD, a mean difference of the observed SD/2 (clinically meaningful value), an alpha (type I error) of 2.5%, and a beta (type II error) of 10% will be used in the TSA.[124] For dichotomous outcomes, the proportion or percentage from the control group, a relative risk variation of 20% (clinically meaningful value), an alpha (type I error) of 2.5%, and a beta (type II error) of 10% will be used in the TSA. [125]

Subgroup analysis

The results will be comprehensively interpreted through an analysis of subgroups or subsets as much as possible. If sufficient trials are available,

data from different participants' ages, different types of hip disease or different kinds of surgical techniques of hip surgery, pain management during different perioperative periods, different pain management techniques in the control group, different types of anesthesia, and different types, concentrations, doses, volumes, and adjuvants of local anesthetics for PENG block will be analyzed independently.

► Different participants' ages (PENG block for perioperative analgesia in elderly patients with different ages as follows: 65 years≤ Patients<75 years; 75 years≤ Patients<80 years; Patients≥80 years).

► Different types of hip disease or different kinds of surgical techniques of hip surgery (hip disease, such as hip fracture and hip osteoarthritis; hip surgery, such as different kinds of surgical techniques of hip arthroplasty, hip fracture fixation, and hip arthroscopy procedures).

► Pain management of different perioperative periods (PENG block for preoperative analgesia, intraoperative anesthesia, and postoperative analgesia).

► Different pain management techniques in the control group (such as block analgesia techniques, including lumbar plexus block, femoral nerve block, fascia-iliac compartment block, 3-in-1 femoral nerve block, sacral plexus block, obturator and sciatic nerve block, and quadratus lumborum block. Non-block analgesia techniques such as opioid and no-opioid analgesics).

► Different types of anesthesia (such as local anesthesia, spinal anesthesia or general anesthesia).

► Different volumes, concentrations, doses, and adjuvants of local anesthetics for PENG block.

The interaction p value will be considered to test the statistically significant subgroup difference; if testing for interaction $p<0.05$ (a significant difference between subgroups exists), the results for individual subgroups will be reported separately. [105]

Sensitivity analysis

Sensitivity analysis will be applied after the analysis of subgroups or subsets to evaluate the stability of the combined results, which could be affected by uncertain assumptions of data and usage. Significant changes in the pooled results may indicate significant heterogeneity in the included studies. Low-quality studies, defined as high-risk bias studies according to the Cochrane risk of bias tool assessment, will be excluded. Then, the included studies will be re-analyzed to detect obvious differences between the combined effects. The stability of the pooled estimations will be detected by removing each included study if necessary.

Assessment of publication biases

Egger's regression test and funnel plot analysis will be performed to estimate the potential publication bias, while more than ten original studies involved an outcome.[126] [127] The symmetric pattern of the funnel plot by

trim-and-fill analysis will also be used to confirm the potential publication bias. The effect sizes of each included study will normally be symmetrically distributed around the center of a funnel plot in the absence of publication bias.[128] Publication biases will be detected by Stata/MP 16.0 (Stata Corp, College Station, TX, USA).

Grading the quality of evidence

The quality of evidence for each outcome will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria.[129] The quality of effect estimates will be classified as high, moderate, low or very low depending on the risk of bias, consistency, directness, precision and publication bias.[129] Data from randomized controlled trials are classified as high-quality evidence according to GRADE. However, it can be degraded according to the risk of bias, imprecision, inconsistency, indirectness, or publication bias.

Patient and public involvement statement

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

DISCUSSION

More and more elderly patients suffer from hip diseases in the global accelerating aging process. As the main therapy for hip diseases, hip surgery is often associated with moderate to severe perioperative pain. Optimal perioperative analgesia can decrease the risk of perioperative

complications and facilitate elderly patient perioperative recovery. Opioid analgesics are often selected hesitantly as opioid-related complications, which can delay patient recovery and discharge. Regional anesthesia and analgesic techniques for perioperative pain management have gradually become the clinical focus in elderly patients with hip diseases to facilitate patient recovery. A simple, easy-to-perform, adequate analgesia and motor-sparing regional analgesia technique is ideal for perioperative pain management of hip diseases.

The PENG block is a relatively new, easy-to-perform, analgesia adequate, and motor-sparing peripheral nerve block technique. The benefit of PENG block for perioperative analgesia in hip surgery was based on many publications of case reports, case series, reviews, and retrospective studies. However, prospective and randomized controlled trials are rare. Due to the limited clinical evidence, the efficacy and safety of the PENG block remain unclear.

This systematic review will provide an overview of the current state of evidence on the clinical efficacy and safety of the PENG block for perioperative analgesia in elderly patients with hip disease. We will examine the perioperative analgesia efficacy, the advantage of motor function preservation and the incidence of block-related adverse events of PENG block. The results of this systematic review will facilitate clinical decision-making on better perioperative pain management of elderly

patients with hip disease.

This systematic review protocol was rigorously performed according to the Preferred Reporting Items for Systematic Review and Meta-Analyses Protocols (PRISMA-P) guidelines. The strengths of our systematic review are as follows: First, a comprehensive literature search of English and Chinese databases will be performed. Second, we will perform multivariable analysis (including subgroup analysis, trial sequential analysis for random errors, sensitivity analysis, study quality assessment, funnel plots, and Egger's regression test for publication bias) to improve the quality of the evidence. Third, literature retrieval, data extraction, and study quality assessment will be performed independently according to the guidelines by at least two review authors. Any disagreement will be resolved through discussion or by consulting another review author as much as possible.

Limitations are as follows: First, studies with different perioperative periods, hip diseases, or hip surgeries will be included, leading to potential heterogeneity. Second, PENG block is a relatively new peripheral nerve block technique, so the sample size of each included study may be limited, and the number of studies with available data for subgroup analyses may be small. Third, studies with high-level evidence such as well-designed randomized controlled trials with double-blind designs may be limited, as it is difficult to perform blinding for different block techniques in different

puncture positions. Fourth, PENG block is a relatively new peripheral nerve block technique. It is difficult to define a significant clinical plausible value of mean difference and relative risk increase/decrease during literature research or clinical experience. Therefore, a significant clinical plausible value will be defined according to TSA guidelines.

ETHICS AND DISSEMINATION

Ethical approval was not required for this systematic review protocol. The findings will be disseminated through peer-reviewed publications.

Timelines

Formal screening of search results will begin in August 2022. Data extraction will begin in November 2022. The project will be complete in January 2023.

Author Contributions

Z-JQ and DL conceived the idea for this systematic review. All authors (Z-JQ, DL, CG, ZL, D-XQ, Z-WY) developed the methodology for the systematic review. The manuscript was drafted by Z-JQ and DL, and revised by all authors. CG and Z-WY will screen potential studies, and perform duplicate independent data abstraction. Z-JQ and ZL will undertake a risk of bias assessment and assess the evidence quality. Z-JQ and DL will conduct the data synthesis. All authors contributed to the research and agreed to be responsible for all aspects of the work.

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Competing interests

None declared.

Data availability statement

Not applicable for this protocol.

Patient consent for publication

No patient was involved.

Provenance and peer review

Not commissioned; externally peer reviewed.

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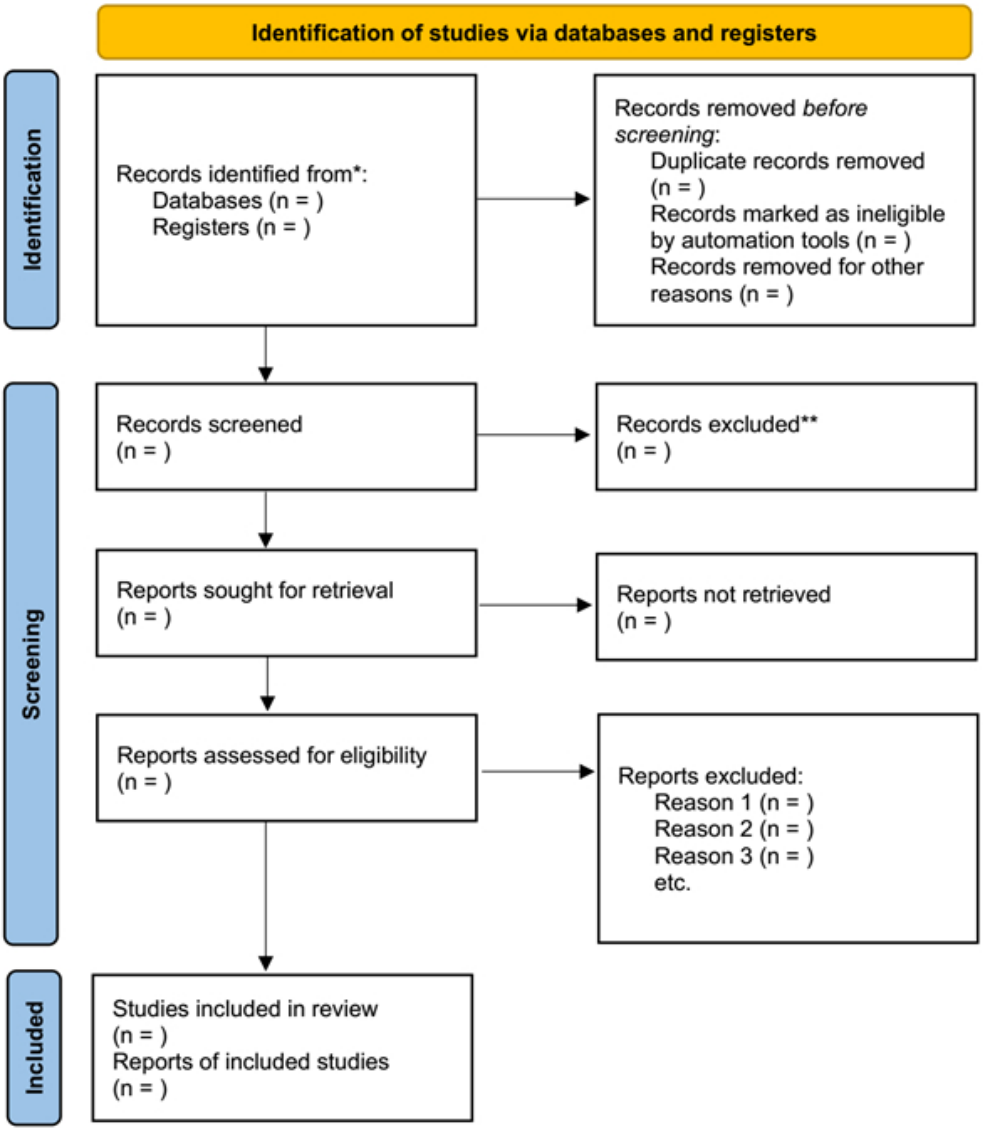
Figure Legends

Figure 1. The PRISMA flow diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analysis.



The PRISMA flow diagram

Supplementary Appendix file 1: Search strategy

Search strategy of PubMed as follows:

#1 “Hip "[MeSH Terms] OR Hips [tiab] OR Coxa [tiab] OR Coxas [tiab]

#2 “arthroscopy” [Mesh] or Arthroscopies[af] or Arthroscopic Surgical Procedures [af] or Arthroscopic Surgical Procedure[af] or Procedure, Arthroscopic Surgical[af] or Procedures, Arthroscopic Surgical[af] or Surgical Procedure, Arthroscopic[af] or Surgery, Arthroscopic [af] or Surgical Procedures, Arthroscopic[af] or Arthroscopic Surgery [af] or Arthroscopic Surgeries[af] or Surgeries, Arthroscopic[af]

#3 #1 AND #2

#4 “Hip Fracture” [Mesh] OR “Femoral Neck Fractures” [Mesh] OR Femoral Neck Fracture [tiab] OR Femur Neck Fractures[tiab] OR Femur Neck Fracture [tiab] OR Fractures, Hip [af] OR Trochanteric Fractures [af] OR Fractures, Trochanteric [af] OR Intertrochanteric Fractures [af] OR Fractures, Intertrochanteric [af] OR Subtrochanteric Fractures [af] OR Fractures, Subtrochanteric [af] Femoral Fracture[af] OR Fracture, Femoral [af] OR Fractures, Femoral [af] (hip* or intertrochanteric or subtrochanteric or trochanteric or pertrochanteric or peritrochanteric or femur or femoral or acetabul*) AND fracture*

#5 “Osteoarthritis, Hip” [Mesh] OR Hip Osteoarthritis[af] OR Osteoarthritis Of Hip [af] OR Osteoarthritis Of Hips[af] OR Coxarthrosis [af] OR Coxarthroses [af] OR Osteoarthritis of the Hip[af]

#6 Hip Injuries [Mesh] OR Hip Dislocation [Mesh] OR Injuries, Hip [af] OR Dislocation, Hip [af] OR Dislocations, Hip[af] OR Hip Dislocations[af] OR Hip Displacement[af] OR Displacement, Hip[af] OR Displacements, Hip[af] OR Hip Displacements[af] OR Hip Dysplasia[af] OR Dysplasia, Hip[af] OR Dysplasias, Hip[af] OR Hip Dysplasias [af]

#7 “Hip Prosthesis” [Mesh] OR “Arthroplasty, Replacement, Hip” [Mesh] OR Hip Prostheses [af] OR Prostheses, Hip[af] OR Prosthesis, Hip[af] OR Femoral Head Prosthesis[af] OR Femoral Head Prostheses[af] OR Prostheses, Femoral Head [af] OR Prosthesis, Femoral Head [af] OR Arthroplasties, Replacement, Hip [af] OR Arthroplasty, Hip Replacement [af] OR Hip Prosthesis Implantation [af] OR Hip Prosthesis Implantations [af] OR Implantation, Hip Prosthesis [af] OR Prosthesis Implantation, Hip [af] OR Hip Replacement Arthroplasty [af] OR Replacement Arthroplasties, Hip [af] OR Replacement Arthroplasty, Hip [af] OR Arthroplasties, Hip

Replacement [af] OR Hip Replacement Arthroplasties [af] OR Hip Replacement, Total [af] OR Total Hip Replacement [af] OR Total Hip Arthroplasty [af] OR Arthroplasty, Total Hip [af] OR Hip Arthroplasty, Total [af] OR Total Hip Arthroplasties [af] OR Replacement, Total Hip [af] OR Total Hip Replacements [af]

#8 #3 OR #4 OR #5 OR #6 OR #7

#9 “Aged” [Mesh] or "Aged, 80 and over"[Mesh] or "Aged, 65 and over"[Mesh] or Centenarians [Mesh] or Nonagenarians [Mesh]or Octogenarians [Mesh] or Geriatrics [Mesh] or Elderly [af] or Centenarian [af] or Nonagenarian [af] or Oldest Old [af] or Octogenarian [af] or aging [af] or aged [af] or elderly[af] or senior [af] or old [af] or old-age[af].

#10 “pericapsular nerve group block” [af] OR PENG [af]

#11 #8 AND #9 AND #10

#12 “controlled clinical trial” [Publication Type] OR “randomized controlled trial” [Publication Type] OR “randomized” [Title/Abstract] OR “randomized” [Title/Abstract] OR “Placebo” [Title/Abstract] OR “randomly” [Title/Abstract] OR “Clinical trial” [Title]

#13 (animals [MeSH Terms]) NOT ((human [MeSH Terms]) AND (animals [MeSH Terms]))

#14 #11 and #12 not #13

Search strategy of Cochrane library as follows:

#1 MeSH descriptor: [Hip] explode all trees.

#2 (Hips OR Coxa OR Coxas): ti,ab,kw

#3 #1 or # 2

#4 MeSH descriptor: [arthroscopy] explode all trees

#5 (arthroscop*): ti,ab,kw

#6 #4 or # 5

#7 #3 and # 6

#8 MeSH descriptor: [Hip Fracture] explode all trees

#9 (hip surgery OR hip prosthes* OR hip replacement* OR hip arthroplast* OR femoral head prosthes* OR joint prosthes*): ti,ab,kw

#10 ((hip* or fem?r* or intertrochant* or trochant* or pertrochant* or intertrochant* or peritrochant* or subtrochant* or intracapsular* or extracapsular* or acetabul*) and fracture*)

#11 MeSH descriptor: [Osteoarthritis, Hip] explode all trees

#12 (Hip Osteoarthritis OR Osteoarthritis Of Hip OR Osteoarthritis Of Hips OR Coxarthrosis OR Coxarthroses OR Osteoarthritis of the Hip): ti,ab,kw

#13 MeSH descriptor: [Hip Injuries] explode all trees

#14 ((disloca* or displace* or dysplas*) and hip*)

#15 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14

#16 MeSH descriptor: [Aged] explode all trees

#17 MeSH descriptor: [Aged, 80 and over] explode all trees

#18 MeSH descriptor: [Aged, 65 and over] explode all trees

#19 MeSH descriptor: [Geriatrics] explode all trees

#20 MeSH descriptor: [Nonagenarians] explode all trees

#21 MeSH descriptor: [Octogenarians] explode all trees

#22((Geriatric* or Elder* or old-age or pensioner*or aging or aged or elderly or senior or old or Oldest Old or old-age or Nonagenarian* or Octogenarian*)

#23 #16 or #17 or #18 or #19 or #20 or #21 or #22

#24 (pericapsular nerve group block or PENG): ti,ab,kw

#25 (controlled clinical trial):pt or (randomized controlled trial):pt or (random*): ti,ab,kw or (Clinical trial):ti,ab,kw

#26 #15 and #23 and #24 and #25

Search strategy of Web of Science as follows:

#1 TS= (Hip or Hips or Coxa or Coxas)

#2 TS= (arthroscop*)

#3 #1 and #2

#4 TS= (Hip* or femu* or femo* or intertrochant* or trochant* or pertrochant* or intertrochant* or peritrochant* or subtrochant* or intracapsular* or extracapsular* or acetabul*)

#5 TS= (fracture*)

#6 #4 and #5

#7 TS= (Hip Osteoarthritis or Osteoarthritis of Hip or Osteoarthritis of Hips or Coxarthrosis or Coxarthroses or Osteoarthritis of the Hip)

#8 TS= (Hip Injuries or Hip disloca* or Hip displace* or Hip dysplas*)

#9 #3 OR #6 OR #7 OR #8

#10 TS= (Geriatric* or Elder* or old-age or pensioner*or aging or aged or elderly or senior or old or Oldest Old or old-age or Nonagenarian* or Octogenarian*)

#11 TS= (pericapsular nerve group block or PENG)

#12 TS= (random* or Clinical trial)

#13 #9 and #10 and #11 and #12

Search strategy for Ovid Medline as follows:

#1 exp Hip/

#2 (Hips OR Coxa OR Coxas) .mp.

#3 #1 or # 2

#4 exp arthroscopy/

#5 (arthroscop*).mp.

#6 #4 or # 5

#7 #3 and # 6

#8 exp Hip Fracture/

#9 (hip surgery OR hip prosthes* OR hip replacement* OR hip arthroplast* OR femoral head prosthes* OR joint prosthes*).mp.

#10 ((hip* or fem?r* or intertrochant* or trochant* or pertrochant* or intertrochant* or peritrochant* or subtrochant* or intracapsular* or extracapsular* or acetabul*) and fracture*).mp.

#11 exp Osteoarthritis, Hip/

#12 (Hip Osteoarthritis or Osteoarthritis of Hip or Osteoarthritis of Hips or Coxarthrosis or Coxarthroses or Osteoarthritis of the Hip) .mp.

#13 exp Hip Injuries/

#14 ((disloca* or displace* or dysplas*) and hip*).mp.

#15 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14

#16 exp Aged/

#17 exp Aged, 80 and over/

#18 exp Aged, 65 and over/

#19 exp Geriatrics/

#20 exp Nonagenarians/

#21 exp Octogenarians/

#22((Geriatric* or Elder* or old-age or pensioner*or aging or aged or elderly or senior or old or Oldest Old or old-age or Nonagenarian* or Octogenarian*).mp.

#23 #16 or #17 or #18 or #19 or #20 or #21 or #22

#24 (pericapsular nerve group block or PENG) .mp.

#25 #15 and #23 and #24

#26 randomized controlled trial.pt.

#27controlled clinical trial.pt.

#28 randomized.ab.

#29 placebo.ab.

#30 clinical trials as topic.sh.

#31 randomly.ab.

#32 trial.ti.

#33 #26 or #27 or #28 or #29 or #30 or #31 or #32

#34 (animals not (humans and animals)).sh.

#35 #25 and #33 not #34

Search strategy for Embase as follows:

#1 exp Hip/

#2 (Hips OR Coxa OR Coxas) .mp.

#3 #1 or # 2

#4 exp arthroscopy/

#5 (arthroscop*).mp.

#6 #4 or # 5

#7 #3 and # 6

#8 exp Hip Fracture/

#9 (hip surgery OR hip prosthes* OR hip replacement* OR hip arthroplast* OR femoral head prosthes* OR joint prosthes*).mp.

#10 ((hip* or fem?r* or intertrochant* or trochant* or pertrochant* or intertrochant* or peritrochant* or subtrochant* or intracapsular* or extracapsular* or acetabul*) and fracture*).mp.

#11 exp Osteoarthritis, Hip/

#12 (Hip Osteoarthritis or Osteoarthritis of Hip or Osteoarthritis of Hips or Coxarthrosis or

Coxarthroses or Osteoarthritis of the Hip) .mp.

#13 exp Hip Injuries/

#14 ((disloca* or displace* or dysplas*) and hip*).mp.

#15 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14

#16 exp Aged/

#17 exp Aged, 80 and over/

#18 exp Aged, 65 and over/

#19 exp Geriatrics/

#20 exp Nonagenarians/

#21 exp Octogenarians/

#22((Geriatric* or Elder* or old-age or pensioner*or aging or aged or elderly or senior or old or Oldest Old or old-age or Nonagenarian* or Octogenarian*).mp.

#23 #16 or #17 or #18 or #19 or #20 or #21 or #22

#24 (pericapsular nerve group block or PENG) .mp.

#25 #15 and #23 and #24

#26 exp randomized controlled trial/

#27(random*).mp.

#28 (placebo*).mp.

#29 Clinical trial.mp.

#30 clinical trials as topic.sh.

#31 #26 or #27 or #28 or #29 or #30

#32 (exp animal/ or nonhuman/ or exp animal experiment/) not human/

#33 #25 and #31 not #32

WHO ICTRP Trial registry

http://apps.who.int/trialsearch (WHO ICTRP register) will be searched via the advanced search page. Search terms were: (Hips OR Coxa OR Coxas or fem?r* or intertrochant* or trochant* or pertrochant* or intertrochant* or peritrochant* or subtrochant* or intracapsular* or extracapsular* or acetabul*) AND (Geriatric* or Elder* or old-age or pensioner*or aging or aged or elderly or senior or old or Oldest Old or old-age or Nonagenarian* or Octogenarian*) AND (pericapsular nerve group block or PENG).

Clinicaltrials.gov search strategy

http://clinicaltrials.gov (NIH register) will be searched via advanced search page. Search terms were: Condition or disease: (Hips OR Coxa OR Coxas or fem?r* or intertrochant* or trochant* or pertrochant* or intertrochant* or peritrochant* or subtrochant* or intracapsular* or extracapsular* or acetabul*) AND (Geriatric* or Elder* or old-age or pensioner*or aging or aged or elderly or senior or old or Oldest Old or old-age or Nonagenarian* or Octogenarian*).

Study type: Interventional Studies.

Intervention/treatment: (pericapsular nerve group block or PENG)

Chinese database

China National Knowledge Infrastructure (CNKI) search strategy

(髋[全部字段]or 关节[全部字段] or 股骨头[全部字段]or 关节唇[全部字段] or 股骨颈 [全部字段] or 转子 [全部字段] or 骨盆 [全部字段] or 关节炎[全部字段] or 骨折[全部字段]or 损伤[全部字段] or 脱位[全部字段] or 撞击[全部字段] or 关节镜[全部字段] or 微创[全部字段] or 保守[全部字段]or 置换[全部字段] or 成形[全部字段] or 假体[全部字段] or 固定[全部字段] or 外伤[全部字段]) and (关节囊周[全部字段] or PENG[全部字段] or 阻滞 [全部字段]) and (老年[全部字段] or 高龄[全部字段] or 老龄 or 80 岁以上[全部字段]) and (随机[全部字段] or 对照[全部字段])

Chinese BioMedical Literature (CBM)

(髋[全部字段] or 关节[全部字段] or 股骨头[全部字段]or 关节唇[全部字段] or 股骨颈 [全部字段] or 转子 [全部字段] or 骨盆 [全部字段] or 关节炎[全部字段] or 骨折[全部字段]or 损伤[全部字段] or 脱位[全部字段] or 撞击[全部字段] or 关节镜[全部字段] or 微创[全部字段] or 保守[全部字段]or 置换[全部字段] or 成形[全部字段] or 假体[全部字段] or 固定[全部字段] or 外伤[全部字段]) and (关节囊周[全部字段] or PENG[全部字段] or 阻滞 [全部字段]) and (老年[全部字段] or 高龄[全部字段] or 老龄 or 80 岁以上[全部字段]) and (随机[全部字段] or 对照[全部字段])

VIP database

关键词=(髋 or 关节 or 股骨头 or 关节唇 or 股骨颈 or 转子 or 骨盆 or 关节炎 or 骨折 or 损伤 or 脱位 or 撞击 or 关节镜 or 微创 or 保守 or 置换 or 成形 or 假体 or 固定 or 外伤) AND 关键词= (老年 or 高龄 or 老龄 or 80 岁以上) AND 关键词= (关节囊周 or PENG or 阻滞) AND

关键词= (随机 or 对照)

Wan fang database.

(髋[全部字段]or 关节[全部字段]股骨头[全部字段]or 关节唇[全部字段] or 股骨颈 [全部字段] or 转子 [全部字段] or 骨盆 [全部字段] or 关节炎[全部字段] or 骨折[全部字段]or 损伤[全部字段] or 脱位[全部字段] or 撞击[全部字段] or 关节镜[全部字段] or 微创[全部字段] or 保守[全部字段]or 置换[全部字段] or 成形[全部字段] or 假体[全部字段] or 固定[全部字段] or 外伤[全部字段]) and (关节囊周[全部字段] or PENG[全部字段] or 阻滞 [全部字段]) and (老年[全部字段] or 高龄[全部字段] or 老龄 or 80 岁以上[全部字段]) and (随机[全部字段] or 对照[全部字段])

Supplementary Appendix file 2 : Assessment of risk of bias

Random sequence generation

- ***Low risk:*** If sequence generation was achieved using computer random number generator or a random number table. Drawing lots, tossing a coin, shuffling cards, and throwing dice were also considered adequate if performed by an independent adjudicator.
- ***Unclear risk:*** If the method of randomisation was not specified, but the trial was still presented as being randomised.
- ***High risk:*** If the allocation sequence is not randomised or only quasi-randomised. These trials will be excluded.

Allocation concealment

- ***Low risk:*** If the allocation of patients was performed by a central independent unit, onsite locked computer or identical-looking numbered sealed envelopes.
- ***Uncertain risk:*** If the trial was classified as randomised but the allocation concealment process was not described.
- ***High risk:*** If the allocation sequence was familiar to the investigators who assigned participants.

Blinding of participants and treatment providers

- ***Low risk:*** If the participants and the treatment providers were blinded to intervention allocation and this was described.
- ***Uncertain risk:*** If the procedure of blinding was insufficiently described.
- ***High risk:*** If blinding of participants and the treatment providers was not performed.

Blinding of outcome assessment

- ***Low risk of bias:*** If it was mentioned that outcome assessors were blinded and this was described.
- ***Uncertain risk of bias:*** If it was not mentioned if the outcome assessors in the trial were blinded or the extent of blinding was insufficiently described.
- ***High risk of bias:*** If no blinding or incomplete blinding of outcome assessors was performed.

Incomplete outcome data

- ***Low risk of bias:*** If missing data were unlikely to make treatment effects depart from plausible

values. This could be either (1) there were no drop-outs or withdrawals for all outcomes, or (2) the numbers and reasons for the withdrawals and drop-outs for all outcomes were clearly stated and could be described as being similar to both groups. Generally, the trial is judged as at a low risk of bias due to incomplete outcome data if drop-outs are less than 5%. However, the 5% cut-off is not definitive.

- ***Uncertain risk of bias:*** If there was insufficient information to assess whether missing data were likely to induce bias on the results.
- ***High risk of bias:*** If the results were likely to be biased due to missing data either because the pattern of drop-outs could be described as being different in the two intervention groups or the trial used improper methods in dealing with the missing data (e.g. last observation carried forward).

Selective outcome reporting

- ***Low risk of bias:*** If a protocol was published before or at the time the trial was begun and the outcomes specified in the protocol were reported on. If there is no protocol or the protocol was published after the trial has begun, reporting of serious adverse events will grant the trial a grade of low risk of bias.
- ***Uncertain risk of bias:*** If no protocol was published and the outcome of serious adverse events were not reported on.
- ***High risk of bias:*** If the outcomes in the protocol were not reported on.

Other risks of bias

- ***Low risk of bias:*** If the trial appears to be free of other components that could put it at risk of bias.
- ***Unclear risk of bias:*** If the trial may or may not be free of other components that could put it at risk of bias.
- ***High risk of bias:*** If there are other factors in the trial that could put it at risk of bias (including, Design-specific risk of bias, stopped early due to some data-dependent process including a formal-stopping rule, baseline imbalance, claimed fraudulent, blocked randomization in unblinded trials, differential diagnostic activity, contamination, inappropriate measurement instrument for outcomes, deviation from the study protocol unrelated to the clinical practice, authors conducted trials on the same topic, academic bias, for-profit bias, inappropriate

financial conflict of interest).

Overall risk of bias

- ***Low risk of bias:*** The trial will be classified as overall 'low risk of bias' only if all of the bias domains described in the above paragraphs are classified as 'low risk of bias'.
- ***High risk of bias:*** The trial will be classified as 'high risk of bias' if any of the bias risk domains described in the above are classified as 'unclear' or 'high risk of bias'.
- We will assess the domains 'blinding of outcome assessment', 'incomplete outcome data', and 'selective out- come reporting' for each outcome result. Thus, we can assess the bias risk for each outcome assessed in addition to each trial. Our primary conclusions will be based on the results of our primary outcome results with overall low risk of bias. Both our primary and secondary conclusions will be presented in the summary of findings tables.

Criteria classification

- If all risk of bias domains were scored as having a low risk of bias, the trial was defined as having a low overall risk of bias.
- If one or more of the bias domains were scored as unclear or high risk of bias, the trial was defined as having a high overall risk of bias.
- Trials with a low risk of bias in all domains (including sequence generation, allocation concealment, blinding, incomplete data, selective outcome reporting, and other risks of bias) will be classified as having a low overall risk of bias.
- Trials with one or more of these domains scored as unclear or high risk of bias will be defined as having a high overall risk of bias.

PRISMA-P checklist

Table PRISMA-P (preferred reporting items for systematic review and meta-analysis protocols) 2015 checklist: recommended items to address in a systematic review protocol

Section and topic	Item No	Checklist item	Reported on page #
Administrative information			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	None
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3,8
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	24
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	None
Support:			
Sponsor	5b	Provide name for the review funder and/or sponsor	None
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	None
Introduction			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-7
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	7-13
Methods			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	8-13 ; 14-15

Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	13-16
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	13-14, S1
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	14-16
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	14-15
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	14-16
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	16
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	10-13
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	16-20
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	17
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	17
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	18-21
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	17
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	20
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	18-20

BMJ Open

Efficacy of pericapsular nerve group (PENG) block on perioperative pain management in elderly patients undergoing hip surgical procedures: a protocol for a systematic review with meta-analysis and trial sequential analysis

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TITLE PAGE

Efficacy of pericapsular nerve group (PENG) block on perioperative pain management in elderly patients undergoing hip surgical procedures: a protocol for a systematic review with meta-analysis and trial sequential analysis

Authors

Jianqiao Zheng[1] E-mail: zhjq1983@163.com

Li Du[2] E-mail: huaying-duli@163.com

Guo Chen[1] E-mail: Anesthesiology_SCU@163.com

Lu Zhang[1] E-mail: 304022514@qq.com

Xiaoqian Deng[1] E-mail: 50058837@qq.com

*Weiyi Zhang[1] E-mail: zhangweiyi@wchscu.cn

[1]Department of Anesthesiology, West China Hospital, Sichuan University No. 37th, Guoxue Alley, Wuhou District, Chengdu 610041, Sichuan, China.

[2]Department of Anesthesiology, Sichuan Cancer Hospital & Institute, Sichuan Cancer Center, School of Medicine, University of Electronic Science and Technology of China, No.55th, People's South Road, Chengdu 610041, Sichuan, China.

*Corresponding Author

Name: Weiyi Zhang

E-mail: zhangweiyi@wchscu.cn

Phone: +86-28-8542-3593

Address: Department of Anesthesiology, Sichuan University West China Hospital, No. 37th, Guoxue Alley, Wuhou District, Chengdu 610041, Sichuan, China.

Words: 4100

ABSTRACT

Introduction An increasing number of elderly patients suffer from hip diseases associated with moderate to severe perioperative pain during the accelerating global aging process. Optimal analgesia can decrease perioperative complications and facilitate elderly patients' perioperative recovery. Pericapsular nerve group (PENG) block is a relatively new, analgesia adequate, and motor-sparing block technique for perioperative pain management of hip diseases. However, the efficacy of PENG block remains unclear as the limited clinical evidence. Then, we will perform a protocol for a systematic review and meta-analysis to identify the efficacy of PENG block for perioperative pain management.

Methods and analysis PubMed, Ovid Medline, Cochrane Library, Embase, Web of Science, China National Knowledge Infrastructure, Chinese BioMedical Literature, Wanfang, and VIP databases will be searched from inception to August 2022 to identify randomized controlled trials of elderly patients accepting PENG block for hip diseases. The primary outcome will be the pain intensity after pain management. Secondary outcomes will be quadriceps strength, perioperative rescue analgesia information and perioperative complications. Assessment of heterogeneity will be primarily inspected by forest plots. If there is no indication of funnel plot asymmetry, a random-effects meta-analysis will be performed. The Cochrane risk-of-bias tool, GRADE (Grading of

Recommendations Assessment, Development, and Evaluation) and trial sequential analysis will be conducted to evaluate the evidence quality and control the random errors. Funnel plots and Egger's regression test will be performed to evaluate publication bias.

Ethics and dissemination Ethical approval was not required for this systematic review protocol. The results will be disseminated through peer-reviewed publications.

Keywords pericapsular nerve group block, hip, elderly, meta-analysis, randomized controlled trial.

PROSPERO registration number CRD42022313895

Strengths and limitations of the study

►Application of Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines for a better quality of meta-analytical results.

► Control of random errors with trial sequential analysis by calculating the diversity adjusted information size for the outcomes.

► Application of Funnel plots and Egger's regression test for publication bias.

►Subgroup analysis based on patients' age, types of hip disease or surgery, perioperative period, type of anesthesia, and perioperative pain management techniques for heterogeneity assessment.

INTRODUCTION

The global population over 60 years old is estimated to increase to 2.1 billion in 2050 (approximately 22% of the global population) and 3.1 billion by 2100.[1] With this accelerating aging process, an increasing number of elderly patients suffer from hip diseases such as hip fractures, and hip osteoarthritis.[2-4] Hip surgery, including hip arthroplasty, hip fracture internal fixation and hip arthroscopy procedures are the main treatments for hip diseases.[5-8] Hip surgery is often associated with moderate to severe postoperative pain, particularly in hip fracture patients undergoing surgical treatment, and severe pain persists throughout the perioperative period.[9-11] As a minimally invasive approach, arthroscopic hip surgery is gaining popularity globally.[12] Despite being minimally invasive, patients undergoing arthroscopic hip surgery may still experience severe pain after the procedure. [13]

Perioperative pain, if inadequately controlled, can increase the risk of perioperative complications (including delirium, pulmonary complications, and cardiovascular events), delay ambulation, decrease short-term mobility, interfere with rehabilitation, increase hospital length of stay, and even increase the mortality and morbidity, leading to poor functional prognosis.[14-19] In elderly patients, the risk of perioperative adverse events is higher due to polypharmacy and multimorbidity.[20-22] In contrast, adequate pain management has been shown to facilitate postoperative

mobilization, improve mobility and promote better functional recovery.[23-26] Early mobilization has been associated with reducing postoperative complications, including pneumonia, venous thromboembolism, pressure ulcers, and delirium.[27-29] Therefore, optimal perioperative analgesia can facilitate elderly patients' perioperative recovery.[30-33]

Traditionally, opioid analgesia is considered the basis of perioperative pain management.[34-37] However, opioid-related complications such as delirium, urinary retention, nausea, constipation and respiratory depression may occur and can delay patients' recovery and discharge.[38-43] Considering these adverse events, especially the higher incidence of cognitive deficits in elderly patients suffering a hip fracture, opioid analgesics are often selected hesitantly.[44-48] In addition, in light of the current opioid crisis, strategies to minimize opioid use, including the use of multimodal perioperative pain management strategies with opioid-sparing oral and intravenous medications, regional anesthesia and analgesic techniques have become an increasing clinical focus in hip surgical procedures in elderly patients.[49-53]

Peripheral nerve blocks (including lumbar plexus block, femoral nerve block, fascia iliac compartment block, 3-in-1 femoral nerve block, sacral plexus block, obturator block, and sciatic nerve block) and some inter-fascial plane blocks (such as quadratus lumborum block) have also been suggested to decrease postoperative pain and opioid use during hip

surgery.[54-61] However, peripheral nerve blocks may induce weakness of the quadriceps muscles, delay hospital discharge, and even predispose the patient to fall. [62-65] In some cases, it is difficult to position the patient as the extreme pain, particularly in hip fractures, accompanied by the deep depth of the block target, the lumbar plexus or quadratus lumborum block will become difficult.[66-68] In addition, another difficulty of adequate regional analgesia for hip pain is the complex innervation of the hip joint.[69] High branches of the femoral and obturator nerves provide innervation to the anterior hip capsule. The accessory obturator nerve was also found to innervate the medial capsule.[70] [71] In this situation, the coverage of the articular nerve supply to the hip joint is critical for adequate analgesia. Hence, a simple, easy-to-perform, analgesia adequate, and motor-sparing regional analgesia technique is the ideal regional analgesia technique for hip surgery.

Pericapsular nerve group (PENG) block is a relatively new peripheral nerve block technique, first described by Giron-Arango in patients with hip fractures, which was based on the complex innervation of the hip joint.[72] The target of the PENG block is the musculofascial plane between the psoas tendon anteriorly and the pubic ramus posteriorly. It can be easily performed in the supine position, avoiding the additional pain from positioning the patient for peripheral nerve block.[73-76] In theory, PENG block has potential advantages over traditional forms of regional analgesia

for pain originating from the hip, as local anesthetic deposits in this target could provide a broader and more complete block effect on the coverage area of sensory nerves innervating the hip.[77-87] Thus, it has the potential advantage of reducing postoperative pain without motor-blocking.[88-91] PENG block has been described as easy to perform in the supine position and as an effective and motor-sparing regional analgesia technique for hip surgery.[92-95]

The excellent analgesic benefit of PENG block for perioperative analgesia in hip surgery was highlighted in a significant number of publications of case reports, case series, reviews and retrospective studies [77-83, 92-95], but prospective and randomized controlled trials are scarce.[84-87] Inadvertent quadriceps weakness was also reported in patients following the PENG block.[96-98] Due to limited clinical evidence, the efficacy and safety of the PENG block, particularly the efficacy of motor function preservation and the incidence of block-related adverse events remain controversial until now.[99-103]

Therefore, it is necessary to conduct a systematic review and meta-analysis to analyze the clinical efficacy of PENG block on perioperative pain management in elderly patients with hip diseases. The outcomes of this systematic review will provide evidence for better clinical decision-making and possible future directions for further clinical trials.

Objectives

We are performing this protocol of systematic review with meta-analysis and trial sequential analysis (TSA) of randomized clinical trials to evaluate the clinical efficacy and safety of PENG block on perioperative pain management in elderly patients with hip diseases.

METHODS AND ANALYSIS

Design and registration of the review

We devised this protocol according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines registered with PROSPERO 2022 (registration number: CRD42022313895). [104] We will perform this systematic review and meta-analysis based on the Cochrane Handbook and report the results following the PRISMA statement.[105 106] This study is anticipated to begin searching in August 2022 and will be completed in January 2023.

Inclusion criteria for study selection

Types of studies

Only randomized controlled trials (RCTs) involving the clinical efficacy of PENG block on perioperative pain management in elderly patients with hip diseases will be included. There will be no language restrictions.

The exclusion criteria were as follows: (1) studies comparing PENG block versus PENG block combined with other analgesic techniques, or studies comparing PENG block under different guidance techniques

(ultrasound guided or traditional landmark technique); (2) studies with data that could not be used for statistical analysis, or studies with incomplete data, or data that could not be extracted after contacting the original authors; and (3) studies that were duplicate publications, published as letters or editorials, abstracts from conferences, and reviews.

Types of participants

Elderly participants (≥65 years old) with any hip disease (such as hip fracture, or hip osteoarthritis) accepting PENG block for perioperative pain management (including preoperative analgesia, intraoperative anesthesia management, and postoperative analgesia) will be included. There will be no limitations on participants' gender, ethnicity, body mass index (BMI), or American Society of Anesthesiologists (ASA) classification.

Types of interventions/controls

The intervention group will be the participants who received any kind of PENG block (including ultrasound-guided, X-ray-guided, CT-guided or traditional landmark-based techniques), alone or in combination with any other kind of analgesia technique for perioperative pain management, while the control group will receive any kind of analgesia technique other than PENG block for perioperative pain management.

Types of outcome measures

Primary outcomes

The primary outcome will be the pain intensity after perioperative

pain management by PENG block or other analgesia techniques. Pain intensity, including preoperative and postoperative pain intensity will be included and assessed by visual analog scale (VAS) scores, numeric rating scale (NRS) scores or other scale scores. Perioperative static and dynamic pain intensity after pain management will also be included if possible.

Secondary outcomes

1. **Unexpected perioperative femoral nerve block** will be evaluated as follows if possible.

- Incidence of quadriceps motor block (defined as paresis or paralysis of knee extension and hip adduction) [Knee extension was graded according to a 3-point scale: 0=normal strength (extension against gravity and resistance)]; 1=paresis (extension against gravity but not against resistance); 2=paralysis (no extension possible).[107] Hip adduction scores of 0, 1, and 2 points indicated decreases in strength of 0%-20%, 21%-70%, and 71%-90% compared with baseline measurement, respectively. [108]
- Mobility of the quadriceps as defined by the Medical Research Council (MRC) scale.[109]
- Quadriceps strength was assessed by measuring the force produced by voluntary isometric contractions with any type of reliable and valid stationary dynamometer (such as the Chatillon DPPH-250 force gauge, AMETEK, USA or Chatillon; AMETEK, Largo, Florida; Lafayette

Instrument, Lafayette, Indiana; and MicroFET, Hoggan Health Industries, West Jordan, Utah).[110 111]

2. Perioperative rescue analgesia information

- Perioperative cumulative analgesic consumption: cumulative analgesic consumption for intraoperative anesthesia and cumulative rescue analgesics for preoperative/postoperative analgesia will be included if possible. Any kind of analgesics, such as opioid analgesics and non-steroidal analgesics administered by different delivery methods, such as PCA (patient-controlled analgesia) devices, intravenous, oral, or intramuscular will be included if possible.
- Time to first analgesic request: time from the end of the preoperative pain management procedure to the first analgesic request or time from the end of surgery to the first analgesic request will be included if possible.

3. Perioperative complications: if possible

- Block-related adverse events included vascular puncture, paresthesia, local anesthetic toxicity, anaphylaxis, permanent nerve injury, bleeding, or infection.
- Intraoperative adverse effects included hyoxemia(oxygen saturation less than 90% or oxygen partial arterial pressure≤60 mmHg); hypotension (defined as a decrease of >20% from preanesthetic patient baseline values or a systolic blood pressure less than 90 mmHg);

arrhythmia [including bradycardia (defined as HR <55 beats/min); tachycardia (defined as HR>100 beats/min); any other types of arrhythmias]; and blood loss.

- Other adverse effects: including postoperative nausea/vomiting, pruritus, urinary retention, respiratory depression, sweating, dizziness, pruritus, urticaria, postoperative arrhythmia, and postoperative pulmonary complications, were defined as the composite of any respiratory infection, respiratory failure, pleural effusion, atelectasis, or pneumothorax.

4. **Patient recovery:** Length of stay, recovery time (defined as the time until recovery room discharge criteria were met after surgery), the quality of postoperative recovery score (such as the Quality of Recovery-40 questionnaire) [112] and patients' ambulation (such as time-to-first ambulation and initial ambulation distance) will be included if possible.

5. **Patient satisfaction:**

If possible, patient satisfaction with performing the perioperative pain management techniques or postoperative analgesia will be included. Satisfaction could be measured by a 5-point Likert scale (1=very dissatisfied; 2=dissatisfied; 3=neutral; 4=satisfied; 5= very satisfied), 10-point Likert scale (1= completely unsatisfied; 10=completely satisfied) or

a postoperative questionnaire whether the patient would choose the same anesthetic or analgesia handling by the answer of "yes" or "no". [113]

Exploratory outcomes

1. **Perioperative sensory block:** Sensory block was evaluated using a 3-point scale [0=no block, 1=analgesia (patient can feel touch, not cold), 2=anesthesia (patient cannot feel touch)], which was assessed in the anterior, lateral and medial aspects of the mid-thigh. [107]
2. **Block end time:** defined as the return of motor (if initially impaired) and/or sensory function, which was acquired from patients' recall.
3. **Perioperative mortality** was defined as all-cause death during the operation procedure, within 30 days after surgery, or death during hospitalization.

Search strategy

Two reviewers (Z-JQ and DL) will independently conduct the search, and any disagreements will be resolved by consulting a third reviewer (Z-WY) as much as possible. English and Chinese electronic databases will be searched for published literature from inception to August 2022. PubMed, Ovid Medline, Cochrane Library, Embase, and Web of Science will be included in the English databases. The Chinese BioMedical Literature (Sino-Med), China National Knowledge Infrastructure (CNKI), Wanfang database and VIP Database will be included in the Chinese databases. The trial registry database (Clinical Trials.gov and WHO

International Clinical Trials Registry Platform) will also be scrutinized to avoid missing ongoing or unpublished clinical trials. In addition, reference lists of each study will also be scanned for missing studies.

The search strategy will use the following search terms: pericapsular nerve group block, PENG block, elderly, hip, and randomized controlled trial. Related search terms will also be translated into Chinese for literature research and study identification in Chinese databases. The search strategies are listed in Supplementary Appendix file 1. Comprehensive updating of the literature search results will be performed prior to the final publication of systematic reviews to avoid missing published studies during the systematic review preparation.

Data collection and analysis

Selection of studies

At least two review authors (Z-JQ and DL) will be responsible for screening the potentially eligible studies by reading titles and abstracts. All identified and relevant full-text publications will be retrieved by screening the full text thoroughly, and the reasons for excluding the ineligible studies will be recorded. Any disagreement will be resolved through discussion or by consulting a third review author (Z-JQ and CG) as much as possible. A fourth reviewer (Z-WY) will carefully check out all procedures before the final confirmation of the data extraction. Data extraction will be performed by at least two authors, and a third author will be consulted if there is any

disagreement. Duplicate publications and companion papers of the same trial will be assessed by all review authors. The study selection process is displayed in the PRISMA flow diagram (figure 1).

Data extraction

Two review authors (Z-JQ and ZL) will use a standardized data collection form (Excel version 2013, Microsoft Inc, Washington DC, USA) for data extraction from each included study. The data extraction form included participants' demographic data, type of hip disease or hip surgery, type of anesthesia: local, spinal or general anesthesia, period of perioperative pain management (preoperative analgesia, intraoperative anesthesia and postoperative analgesia), inclusion and exclusion criteria, detailed information of analgesia techniques (type of perioperative analgesia techniques: PENG block or other analgesia techniques; type, concentration, dose, volume and adjuvant of local anesthetics), and any outcomes including primary, secondary, and exploratory outcomes. Study design characteristics including randomization method, allocation concealment, blinding (patients, treatment providers, outcome investigators), incomplete outcome data collection and statistical analysis, and outcome reporting) will be recorded simultaneously. Continuous and dichotomous data will be recorded as the mean± SD and the percentages or the proportion. If necessary, a third review author (D-XQ) will cross-check the data to ensure precision. When the necessary information or data

for analysis is missing or incomplete, we will contact the corresponding author of the research via email for the original data as much as possible. Necessary numerical data in the graphs will be extracted by Adobe Photoshop if necessary. [114] Extracted information and data are presented in table 1.

Table 1 Information and data extraction schedule

Subject	Content
Publication information	Title; author; Publish year; Country of origin; Corporate sponsorship; Contact email.
Participant	Sample size; Age; Sex; Height and weight or BMI; ASA physical status classification levels; Type of hip disease or hip surgery; Inclusion and exclusion criteria if necessary.
Intervention	Detail information of PENG block techniques (guidance techniques; target area of block; block needle; needle tracking techniques: in-plane and out-of-plane) Detail information of local anesthetics (type, concentration, dose, volume and adjuvant of local anesthetics).
Control	Detail information of block analgesia techniques (including guidance techniques; target area of block; block needle; needle tracking techniques: in-plane and out-of-plane; detail information of local anesthetics including type, concentration, dose, volume and adjuvant of local anesthetics) and non-block analgesia techniques (including type, dose, and administration method of analgesics).
Outcome	Primary outcome (pain intensity after perioperative pain management); Secondary outcome measurements (perioperative quadriceps strength; perioperative rescue analgesia information: perioperative cumulative analgesic consumption; time to first analgesic request; patients' recovery; perioperative complications; patients' satisfaction); Exploratory outcomes (perioperative sensory block; block ended time; perioperative mortality).
Study design	Randomization method; Blinding; Allocation concealment; Statistical analysis; Sample size calculation; Outcome reporting.
Other information	Type of anesthesia: local, spinal or general anesthesia; Period of perioperative pain management (preoperative analgesia, intraoperative anesthesia and postoperative analgesia); Anesthesia time; Operation time; Assessment method or equipment of outcomes.

Quality assessment

The risk of bias in each included study will be assessed independently by two review authors (DL and ZL) under the guidance of the Cochrane

risk of bias tool.[115] Methodology (including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, other risks of bias, and overall risk of bias) will be evaluated. Each included study will be assessed by the risk of bias assessment tool from the Cochrane Handbook for Systematic Reviews of Interventions and then categorized into three levels (low risk of bias, unclear of bias, and high risk of bias). [105,116, 117] Any discrepancies will be settled through discussions by all review authors or arbitration of a third reviewer (Z-WY). Assessment of risk of bias is listed in Supplementary Appendix fie 2.

Measures of treatment effect

Mean differences (MDs) with 95% confidence intervals (CIs) will be used for continuous outcome data reported by the same scale, and standardized mean differences (SMDs) with 95% confidence intervals (CIs) will be used for continuous outcome data reported by different scales. The relative risks (RRs) with 95% CIs will be used for dichotomous outcome data.

Assessment of heterogeneity

The application of a fixed-effects model or random-effects model based on statistical heterogeneity is not recommended by the Cochrane guidelines.[105] Assessment of heterogeneity will be primarily inspected by forest plots. If there is no indication of funnel plot asymmetry, a random-

effects meta-analysis will be performed. [105] If there is an indication of funnel plot asymmetry, then both a fixed-effect and a random-effect meta-analysis are problematic. In this situation, a sensitivity analysis will be performed by excluding small studies or meta-regression will be addressed directly. A P value <0.05 was assumed to be statistically significant.

Trial Sequential Analysis

The required information size (RIS) will be calculated to correct the risks of random errors by trial sequential analysis (TSA) using the TSA program version 0.9.5.10 Beta (Copenhagen Trial Unit, Copenhagen, Denmark). [118-120] TSA program version is available at http://www.ctu.dk/tsa.[121] Each outcome will be detected by RIS, the cumulative Z-curve, and the TSA monitoring boundaries.[122 123]

For continuous outcomes, the observed SD, a mean difference of the observed SD/2 (clinically meaningful value), an alpha (type I error) of 2.5%, and a beta (type II error) of 10% will be used in the TSA.[124] For dichotomous outcomes, the proportion or percentage from the control group, a relative risk variation of 20% (clinically meaningful value), an alpha (type I error) of 2.5%, and a beta (type II error) of 10% will be used in the TSA. [125]

Subgroup analysis

The results will be comprehensively interpreted through an analysis of subgroups or subsets as much as possible. If sufficient trials are available,

data from different participants' ages, different types of hip disease or different kinds of surgical techniques of hip surgery, pain management during different perioperative periods, different pain management techniques in the control group, different types of anesthesia, and different types, concentrations, doses, volumes, and adjuvants of local anesthetics for PENG block will be analyzed independently.

► Different participants' ages (PENG block for perioperative analgesia in elderly patients with different ages as follows: 65 years≤ Patients<75 years; 75 years≤ Patients<80 years; Patients≥80 years).

► Different types of hip disease or different kinds of surgical techniques of hip surgery (hip disease, such as hip fracture and hip osteoarthritis; hip surgery, such as different kinds of surgical techniques of hip arthroplasty, hip fracture fixation, and hip arthroscopy procedures).

► Pain management of different perioperative periods (PENG block for preoperative analgesia, intraoperative anesthesia, and postoperative analgesia).

► Different pain management techniques in the control group (such as block analgesia techniques, including lumbar plexus block, femoral nerve block, fascia-iliac compartment block, 3-in-1 femoral nerve block, sacral plexus block, obturator and sciatic nerve block, and quadratus lumborum block. Non-block analgesia techniques such as opioid and no-opioid analgesics).

► Different types of anesthesia (such as local anesthesia, spinal anesthesia or general anesthesia).

► Different volumes, concentrations, doses, and adjuvants of local anesthetics for PENG block.

The interaction p value will be considered to test the statistically significant subgroup difference; if testing for interaction $p<0.05$ (a significant difference between subgroups exists), the results for individual subgroups will be reported separately. [105]

Sensitivity analysis

Sensitivity analysis will be applied after the analysis of subgroups or subsets to evaluate the stability of the combined results, which could be affected by uncertain assumptions of data and usage. Significant changes in the pooled results may indicate significant heterogeneity in the included studies. Low-quality studies, defined as high-risk bias studies according to the Cochrane risk of bias tool assessment, will be excluded. Then, the included studies will be re-analyzed to detect obvious differences between the combined effects. The stability of the pooled estimations will be detected by removing each included study if necessary.

Assessment of publication biases

Egger's regression test and funnel plot analysis will be performed to estimate the potential publication bias, while more than ten original studies involved an outcome.[126] [127] The symmetric pattern of the funnel plot by

trim-and-fill analysis will also be used to confirm the potential publication bias. The effect sizes of each included study will normally be symmetrically distributed around the center of a funnel plot in the absence of publication bias.[128] Publication biases will be detected by Stata/MP 16.0 (Stata Corp, College Station, TX, USA).

Grading the quality of evidence

The quality of evidence for each outcome will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria.[129] The quality of effect estimates will be classified as high, moderate, low or very low depending on the risk of bias, consistency, directness, precision and publication bias.[129] Data from randomized controlled trials are classified as high-quality evidence according to GRADE. However, it can be degraded according to the risk of bias, imprecision, inconsistency, indirectness, or publication bias.

Patient and public involvement statement

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

DISCUSSION

More and more elderly patients suffer from hip diseases in the global accelerating aging process. As the main therapy for hip diseases, hip surgery is often associated with moderate to severe perioperative pain. Optimal perioperative analgesia can decrease the risk of perioperative

complications and facilitate elderly patient perioperative recovery. Opioid analgesics are often selected hesitantly as opioid-related complications, which can delay patient recovery and discharge. Regional anesthesia and analgesic techniques for perioperative pain management have gradually become the clinical focus in elderly patients with hip diseases to facilitate patient recovery. A simple, easy-to-perform, adequate analgesia and motor-sparing regional analgesia technique is ideal for perioperative pain management of hip diseases.

The PENG block is a relatively new, easy-to-perform, analgesia adequate, and motor-sparing peripheral nerve block technique. The benefit of PENG block for perioperative analgesia in hip surgery was based on many publications of case reports, case series, reviews, and retrospective studies. However, prospective and randomized controlled trials are rare. Due to the limited clinical evidence, the efficacy and safety of the PENG block remain unclear.

This systematic review will provide an overview of the current state of evidence on the clinical efficacy and safety of the PENG block for perioperative analgesia in elderly patients with hip disease. We will examine the perioperative analgesia efficacy, the advantage of motor function preservation and the incidence of block-related adverse events of PENG block. The results of this systematic review will facilitate clinical decision-making on better perioperative pain management of elderly

patients with hip disease.

This systematic review protocol was rigorously performed according to the Preferred Reporting Items for Systematic Review and Meta-Analyses Protocols (PRISMA-P) guidelines. The strengths of our systematic review are as follows: First, a comprehensive literature search of English and Chinese databases will be performed. Second, we will perform multivariable analysis (including subgroup analysis, trial sequential analysis for random errors, sensitivity analysis, study quality assessment, funnel plots, and Egger's regression test for publication bias) to improve the quality of the evidence. Third, literature retrieval, data extraction, and study quality assessment will be performed independently according to the guidelines by at least two review authors. Any disagreement will be resolved through discussion or by consulting another review author as much as possible.

Limitations are as follows: First, studies with different perioperative periods, hip diseases, or hip surgeries will be included, leading to potential heterogeneity. Second, PENG block is a relatively new peripheral nerve block technique, so the sample size of each included study may be limited, and the number of studies with available data for subgroup analyses may be small. Third, studies with high-level evidence such as well-designed randomized controlled trials with double-blind designs may be limited, as it is difficult to perform blinding for different block techniques in different

puncture positions. Fourth, PENG block is a relatively new peripheral nerve block technique. It is difficult to define a significant clinical plausible value of mean difference and relative risk increase/decrease during literature research or clinical experience. Therefore, a significant clinical plausible value will be defined according to TSA guidelines.

ETHICS AND DISSEMINATION

Ethical approval was not required for this systematic review protocol. The findings will be disseminated through peer-reviewed publications.

Timelines

Formal screening of search results will begin in August 2022. Data extraction will begin in November 2022. The project will be complete in January 2023.

Author Contributions

Z-JQ and DL conceived the idea for this systematic review. All authors (Z-JQ, DL, CG, ZL, D-XQ, Z-WY) developed the methodology for the systematic review. The manuscript was drafted by Z-JQ and DL, and revised by all authors. CG and Z-WY will screen potential studies, and perform duplicate independent data abstraction. Z-JQ and ZL will undertake a risk of bias assessment and assess the evidence quality. Z-JQ and DL will conduct the data synthesis. All authors contributed to the research and agreed to be responsible for all aspects of the work.

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Competing interests

None declared.

Data availability statement

Not applicable for this protocol.

Patient consent for publication

No patient was involved.

Provenance and peer review

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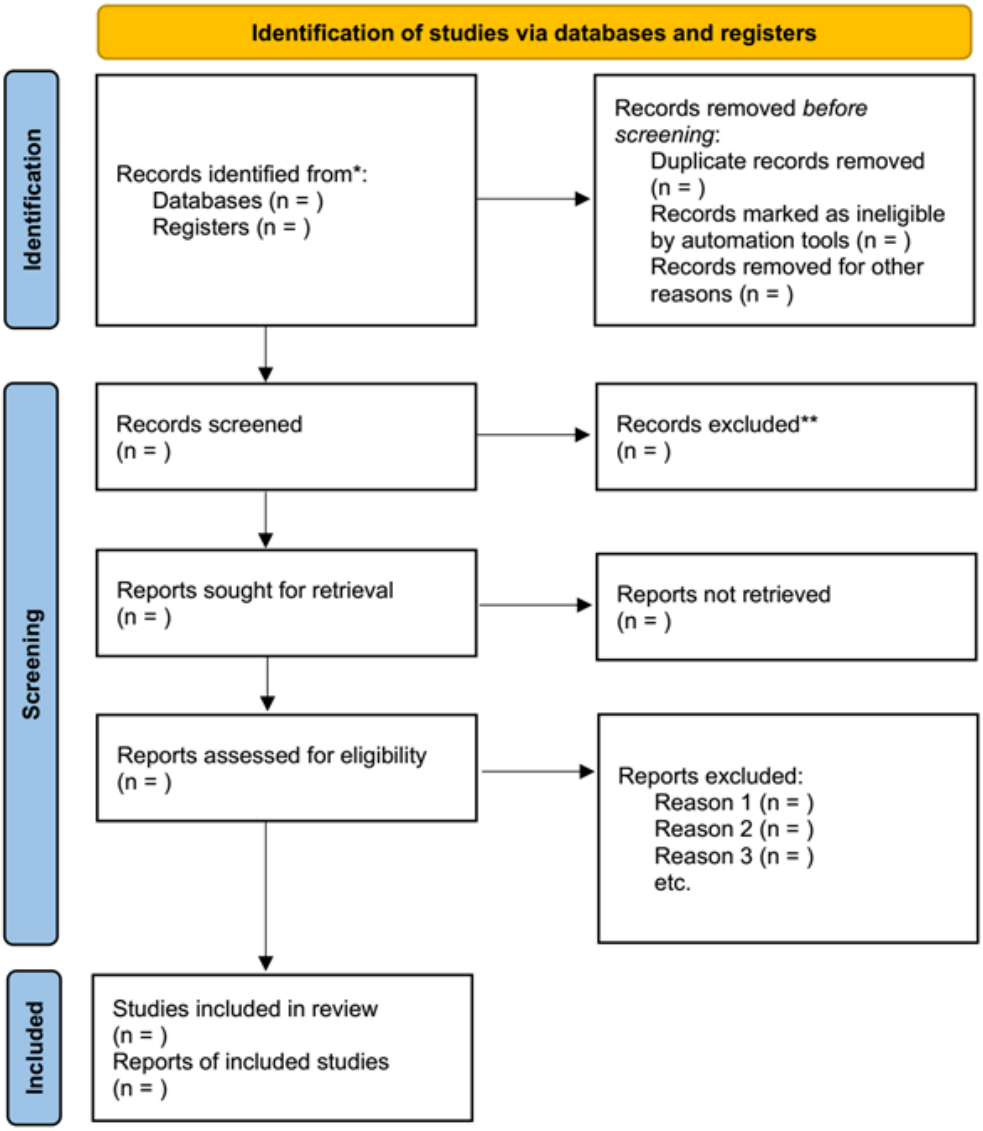
Figure Legends

Figure 1. The PRISMA flow diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analysis.



The PRISMA flow diagram

Supplementary Appendix file 1: Search strategy

Search strategy of PubMed as follows:

#1 “Hip "[MeSH Terms] OR Hips [tiab] OR Coxa [tiab] OR Coxas [tiab]

#2 “arthroscopy” [Mesh] or Arthroscopies[af] or Arthroscopic Surgical Procedures [af] or Arthroscopic Surgical Procedure[af] or Procedure, Arthroscopic Surgical[af] or Procedures, Arthroscopic Surgical[af] or Surgical Procedure, Arthroscopic[af] or Surgery, Arthroscopic [af] or Surgical Procedures, Arthroscopic[af] or Arthroscopic Surgery [af] or Arthroscopic Surgeries[af] or Surgeries, Arthroscopic[af]

#3 #1 AND #2

#4 “Hip Fracture” [Mesh] OR “Femoral Neck Fractures” [Mesh] OR Femoral Neck Fracture [tiab] OR Femur Neck Fractures[tiab] OR Femur Neck Fracture [tiab] OR Fractures, Hip [af] OR Trochanteric Fractures [af] OR Fractures, Trochanteric [af] OR Intertrochanteric Fractures [af] OR Fractures, Intertrochanteric [af] OR Subtrochanteric Fractures [af] OR Fractures, Subtrochanteric [af] Femoral Fracture[af] OR Fracture, Femoral [af] OR Fractures, Femoral [af] (hip* or intertrochanteric or subtrochanteric or trochanteric or pertrochanteric or peritrochanteric or femur or femoral or acetabul*) AND fracture*

#5 “Osteoarthritis, Hip” [Mesh] OR Hip Osteoarthritis[af] OR Osteoarthritis Of Hip [af] OR Osteoarthritis Of Hips[af] OR Coxarthrosis [af] OR Coxarthroses [af] OR Osteoarthritis of the Hip[af]

#6 Hip Injuries [Mesh] OR Hip Dislocation [Mesh] OR Injuries, Hip [af] OR Dislocation, Hip [af] OR Dislocations, Hip[af] OR Hip Dislocations[af] OR Hip Displacement[af] OR Displacement, Hip[af] OR Displacements, Hip[af] OR Hip Displacements[af] OR Hip Dysplasia[af] OR Dysplasia, Hip[af] OR Dysplasias, Hip[af] OR Hip Dysplasias [af]

#7 “Hip Prosthesis” [Mesh] OR “Arthroplasty, Replacement, Hip” [Mesh] OR Hip Prostheses [af] OR Prostheses, Hip[af] OR Prosthesis, Hip[af] OR Femoral Head Prosthesis[af] OR Femoral Head Prostheses[af] OR Prostheses, Femoral Head [af] OR Prosthesis, Femoral Head [af] OR Arthroplasties, Replacement, Hip [af] OR Arthroplasty, Hip Replacement [af] OR Hip Prosthesis Implantation [af] OR Hip Prosthesis Implantations [af] OR Implantation, Hip Prosthesis [af] OR Prosthesis Implantation, Hip [af] OR Hip Replacement Arthroplasty [af] OR Replacement Arthroplasties, Hip [af] OR Replacement Arthroplasty, Hip [af] OR Arthroplasties, Hip

Replacement [af] OR Hip Replacement Arthroplasties [af] OR Hip Replacement, Total [af] OR Total Hip Replacement [af] OR Total Hip Arthroplasty [af] OR Arthroplasty, Total Hip [af] OR Hip Arthroplasty, Total [af] OR Total Hip Arthroplasties [af] OR Replacement, Total Hip [af] OR Total Hip Replacements [af]

#8 #3 OR #4 OR #5 OR #6 OR #7

#9 “Aged” [Mesh] or "Aged, 80 and over"[Mesh] or "Aged, 65 and over"[Mesh] or Centenarians [Mesh] or Nonagenarians [Mesh]or Octogenarians [Mesh] or Geriatrics [Mesh] or Elderly [af] or Centenarian [af] or Nonagenarian [af] or Oldest Old [af] or Octogenarian [af] or aging [af] or aged [af] or elderly[af] or senior [af] or old [af] or old-age[af].

#10 “pericapsular nerve group block” [af] OR PENG [af]

#11 #8 AND #9 AND #10

#12 “controlled clinical trial” [Publication Type] OR “randomized controlled trial” [Publication Type] OR “randomized” [Title/Abstract] OR “randomized” [Title/Abstract] OR “Placebo” [Title/Abstract] OR “randomly” [Title/Abstract] OR “Clinical trial” [Title]

#13 (animals [MeSH Terms]) NOT ((human [MeSH Terms]) AND (animals [MeSH Terms]))

#14 #11 and #12 not #13

Search strategy of Cochrane library as follows:

#1 MeSH descriptor: [Hip] explode all trees.

#2 (Hips OR Coxa OR Coxas): ti,ab,kw

#3 #1 or # 2

#4 MeSH descriptor: [arthroscopy] explode all trees

#5 (arthroscop*): ti,ab,kw

#6 #4 or # 5

#7 #3 and # 6

#8 MeSH descriptor: [Hip Fracture] explode all trees

#9 (hip surgery OR hip prosthes* OR hip replacement* OR hip arthroplast* OR femoral head prosthes* OR joint prosthes*): ti,ab,kw

#10 ((hip* or fem?r* or intertrochant* or trochant* or pertrochant* or intertrochant* or peritrochant* or subtrochant* or intracapsular* or extracapsular* or acetabul*) and fracture*)

#11 MeSH descriptor: [Osteoarthritis, Hip] explode all trees

#12 (Hip Osteoarthritis OR Osteoarthritis Of Hip OR Osteoarthritis Of Hips OR Coxarthrosis OR Coxarthroses OR Osteoarthritis of the Hip): ti,ab,kw

#13 MeSH descriptor: [Hip Injuries] explode all trees

#14 ((disloca* or displace* or dysplas*) and hip*)

#15 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14

#16 MeSH descriptor: [Aged] explode all trees

#17 MeSH descriptor: [Aged, 80 and over] explode all trees

#18 MeSH descriptor: [Aged, 65 and over] explode all trees

#19 MeSH descriptor: [Geriatrics] explode all trees

#20 MeSH descriptor: [Nonagenarians] explode all trees

#21 MeSH descriptor: [Octogenarians] explode all trees

#22((Geriatric* or Elder* or old-age or pensioner*or aging or aged or elderly or senior or old or Oldest Old or old-age or Nonagenarian* or Octogenarian*)

#23 #16 or #17 or #18 or #19 or #20 or #21 or #22

#24 (pericapsular nerve group block or PENG): ti,ab,kw

#25 (controlled clinical trial):pt or (randomized controlled trial):pt or (random*): ti,ab,kw or (Clinical trial):ti,ab,kw

#26 #15 and #23 and #24 and #25

Search strategy of Web of Science as follows:

#1 TS= (Hip or Hips or Coxa or Coxas)

#2 TS= (arthroscop*)

#3 #1 and #2

#4 TS= (Hip* or femu* or femo* or intertrochant* or trochant* or pertrochant* or intertrochant* or peritrochant* or subtrochant* or intracapsular* or extracapsular* or acetabul*)

#5 TS= (fracture*)

#6 #4 and #5

#7 TS= (Hip Osteoarthritis or Osteoarthritis of Hip or Osteoarthritis of Hips or Coxarthrosis or Coxarthroses or Osteoarthritis of the Hip)

#8 TS= (Hip Injuries or Hip disloca* or Hip displace* or Hip dysplas*)

#9 #3 OR #6 OR #7 OR #8

#10 TS= (Geriatric* or Elder* or old-age or pensioner*or aging or aged or elderly or senior or old or Oldest Old or old-age or Nonagenarian* or Octogenarian*)

#11 TS= (pericapsular nerve group block or PENG)

#12 TS= (random* or Clinical trial)

#13 #9 and #10 and #11 and #12

Search strategy for Ovid Medline as follows:

#1 exp Hip/

#2 (Hips OR Coxa OR Coxas) .mp.

#3 #1 or # 2

#4 exp arthroscopy/

#5 (arthroscop*).mp.

#6 #4 or # 5

#7 #3 and # 6

#8 exp Hip Fracture/

#9 (hip surgery OR hip prosthes* OR hip replacement* OR hip arthroplast* OR femoral head prosthes* OR joint prosthes*).mp.

#10 ((hip* or fem?r* or intertrochant* or trochant* or pertrochant* or intertrochant* or peritrochant* or subtrochant* or intracapsular* or extracapsular* or acetabul*) and fracture*).mp.

#11 exp Osteoarthritis, Hip/

#12 (Hip Osteoarthritis or Osteoarthritis of Hip or Osteoarthritis of Hips or Coxarthrosis or Coxarthroses or Osteoarthritis of the Hip) .mp.

#13 exp Hip Injuries/

#14 ((disloca* or displace* or dysplas*) and hip*).mp.

#15 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14

#16 exp Aged/

#17 exp Aged, 80 and over/

#18 exp Aged, 65 and over/

#19 exp Geriatrics/

#20 exp Nonagenarians/

#21 exp Octogenarians/

#22((Geriatric* or Elder* or old-age or pensioner*or aging or aged or elderly or senior or old or Oldest Old or old-age or Nonagenarian* or Octogenarian*).mp.

#23 #16 or #17 or #18 or #19 or #20 or #21 or #22

#24 (pericapsular nerve group block or PENG) .mp.

#25 #15 and #23 and #24

#26 randomized controlled trial.pt.

#27controlled clinical trial.pt.

#28 randomized.ab.

#29 placebo.ab.

#30 clinical trials as topic.sh.

#31 randomly.ab.

#32 trial.ti.

#33 #26 or #27 or #28 or #29 or #30 or #31 or #32

#34 (animals not (humans and animals)).sh.

#35 #25 and #33 not #34

Search strategy for Embase as follows:

#1 exp Hip/

#2 (Hips OR Coxa OR Coxas) .mp.

#3 #1 or # 2

#4 exp arthroscopy/

#5 (arthroscop*).mp.

#6 #4 or # 5

#7 #3 and # 6

#8 exp Hip Fracture/

#9 (hip surgery OR hip prosthes* OR hip replacement* OR hip arthroplast* OR femoral head prosthes* OR joint prosthes*).mp.

#10 ((hip* or fem?r* or intertrochant* or trochant* or pertrochant* or intertrochant* or peritrochant* or subtrochant* or intracapsular* or extracapsular* or acetabul*) and fracture*).mp.

#11 exp Osteoarthritis, Hip/

#12 (Hip Osteoarthritis or Osteoarthritis of Hip or Osteoarthritis of Hips or Coxarthrosis or

Coxarthroses or Osteoarthritis of the Hip) .mp.

#13 exp Hip Injuries/

#14 ((disloca* or displace* or dysplas*) and hip*).mp.

#15 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14

#16 exp Aged/

#17 exp Aged, 80 and over/

#18 exp Aged, 65 and over/

#19 exp Geriatrics/

#20 exp Nonagenarians/

#21 exp Octogenarians/

#22((Geriatric* or Elder* or old-age or pensioner*or aging or aged or elderly or senior or old or Oldest Old or old-age or Nonagenarian* or Octogenarian*).mp.

#23 #16 or #17 or #18 or #19 or #20 or #21 or #22

#24 (pericapsular nerve group block or PENG) .mp.

#25 #15 and #23 and #24

#26 exp randomized controlled trial/

#27(random*).mp.

#28 (placebo*).mp.

#29 Clinical trial.mp.

#30 clinical trials as topic.sh.

#31 #26 or #27 or #28 or #29 or #30

#32 (exp animal/ or nonhuman/ or exp animal experiment/) not human/

#33 #25 and #31 not #32

WHO ICTRP Trial registry

http://apps.who.int/trialsearch (WHO ICTRP register) will be searched via the advanced search page. Search terms were: (Hips OR Coxa OR Coxas or fem?r* or intertrochant* or trochant* or pertrochant* or intertrochant* or peritrochant* or subtrochant* or intracapsular* or extracapsular* or acetabul*) AND (Geriatric* or Elder* or old-age or pensioner*or aging or aged or elderly or senior or old or Oldest Old or old-age or Nonagenarian* or Octogenarian*) AND (pericapsular nerve group block or PENG).

Clinicaltrials.gov search strategy

http://clinicaltrials.gov (NIH register) will be searched via advanced search page. Search terms were: Condition or disease: (Hips OR Coxa OR Coxas or fem?r* or intertrochant* or trochant* or pertrochant* or intertrochant* or peritrochant* or subtrochant* or intracapsular* or extracapsular* or acetabul*) AND (Geriatric* or Elder* or old-age or pensioner*or aging or aged or elderly or senior or old or Oldest Old or old-age or Nonagenarian* or Octogenarian*).

Study type: Interventional Studies.

Intervention/treatment: (pericapsular nerve group block or PENG)

Chinese database

China National Knowledge Infrastructure (CNKI) search strategy

(髋[全部字段]or 关节[全部字段] or 股骨头[全部字段]or 关节唇[全部字段] or 股骨颈 [全部字段] or 转子 [全部字段] or 骨盆 [全部字段] or 关节炎[全部字段] or 骨折[全部字段]or 损伤[全部字段] or 脱位[全部字段] or 撞击[全部字段] or 关节镜[全部字段] or 微创[全部字段] or 保守[全部字段]or 置换[全部字段] or 成形[全部字段] or 假体[全部字段] or 固定[全部字段] or 外伤[全部字段]) and (关节囊周[全部字段] or PENG[全部字段] or 阻滞 [全部字段]) and (老年[全部字段] or 高龄[全部字段] or 老龄 or 80 岁以上[全部字段]) and (随机[全部字段] or 对照[全部字段])

Chinese BioMedical Literature (CBM)

(髋[全部字段] or 关节[全部字段] or 股骨头[全部字段]or 关节唇[全部字段] or 股骨颈 [全部字段] or 转子 [全部字段] or 骨盆 [全部字段] or 关节炎[全部字段] or 骨折[全部字段]or 损伤[全部字段] or 脱位[全部字段] or 撞击[全部字段] or 关节镜[全部字段] or 微创[全部字段] or 保守[全部字段]or 置换[全部字段] or 成形[全部字段] or 假体[全部字段] or 固定[全部字段] or 外伤[全部字段]) and (关节囊周[全部字段] or PENG[全部字段] or 阻滞 [全部字段]) and (老年[全部字段] or 高龄[全部字段] or 老龄 or 80 岁以上[全部字段]) and (随机[全部字段] or 对照[全部字段])

VIP database

关键词=(髋 or 关节 or 股骨头 or 关节唇 or 股骨颈 or 转子 or 骨盆 or 关节炎 or 骨折 or 损伤 or 脱位 or 撞击 or 关节镜 or 微创 or 保守 or 置换 or 成形 or 假体 or 固定 or 外伤) AND 关键词= (老年 or 高龄 or 老龄 or 80 岁以上) AND 关键词= (关节囊周 or PENG or 阻滞) AND

关键词= (随机 or 对照)

Wan fang database.

(髋[全部字段]or 关节[全部字段]股骨头[全部字段]or 关节唇[全部字段] or 股骨颈 [全部字段] or 转子 [全部字段] or 骨盆 [全部字段] or 关节炎[全部字段] or 骨折[全部字段]or 损伤[全部字段] or 脱位[全部字段] or 撞击[全部字段] or 关节镜[全部字段] or 微创[全部字段] or 保守[全部字段]or 置换[全部字段] or 成形[全部字段] or 假体[全部字段] or 固定[全部字段] or 外伤[全部字段]) and (关节囊周[全部字段] or PENG[全部字段] or 阻滞 [全部字段]) and (老年[全部字段] or 高龄[全部字段] or 老龄 or 80 岁以上[全部字段]) and (随机[全部字段] or 对照[全部字段])

Supplementary Appendix file 2 : Assessment of risk of bias

Random sequence generation

- ***Low risk:*** If sequence generation was achieved using computer random number generator or a random number table. Drawing lots, tossing a coin, shuffling cards, and throwing dice were also considered adequate if performed by an independent adjudicator.
- ***Unclear risk:*** If the method of randomisation was not specified, but the trial was still presented as being randomised.
- ***High risk:*** If the allocation sequence is not randomised or only quasi-randomised. These trials will be excluded.

Allocation concealment

- ***Low risk:*** If the allocation of patients was performed by a central independent unit, onsite locked computer or identical-looking numbered sealed envelopes.
- ***Uncertain risk:*** If the trial was classified as randomised but the allocation concealment process was not described.
- ***High risk:*** If the allocation sequence was familiar to the investigators who assigned participants.

Blinding of participants and treatment providers

- ***Low risk:*** If the participants and the treatment providers were blinded to intervention allocation and this was described.
- ***Uncertain risk:*** If the procedure of blinding was insufficiently described.
- ***High risk:*** If blinding of participants and the treatment providers was not performed.

Blinding of outcome assessment

- ***Low risk of bias:*** If it was mentioned that outcome assessors were blinded and this was described.
- ***Uncertain risk of bias:*** If it was not mentioned if the outcome assessors in the trial were blinded or the extent of blinding was insufficiently described.
- ***High risk of bias:*** If no blinding or incomplete blinding of outcome assessors was performed.

Incomplete outcome data

- ***Low risk of bias:*** If missing data were unlikely to make treatment effects depart from plausible

values. This could be either (1) there were no drop-outs or withdrawals for all outcomes, or (2) the numbers and reasons for the withdrawals and drop-outs for all outcomes were clearly stated and could be described as being similar to both groups. Generally, the trial is judged as at a low risk of bias due to incomplete outcome data if drop-outs are less than 5%. However, the 5% cut-off is not definitive.

- ***Uncertain risk of bias:*** If there was insufficient information to assess whether missing data were likely to induce bias on the results.
- ***High risk of bias:*** If the results were likely to be biased due to missing data either because the pattern of drop-outs could be described as being different in the two intervention groups or the trial used improper methods in dealing with the missing data (e.g. last observation carried forward).

Selective outcome reporting

- ***Low risk of bias:*** If a protocol was published before or at the time the trial was begun and the outcomes specified in the protocol were reported on. If there is no protocol or the protocol was published after the trial has begun, reporting of serious adverse events will grant the trial a grade of low risk of bias.
- ***Uncertain risk of bias:*** If no protocol was published and the outcome of serious adverse events were not reported on.
- ***High risk of bias:*** If the outcomes in the protocol were not reported on.

Other risks of bias

- ***Low risk of bias:*** If the trial appears to be free of other components that could put it at risk of bias.
- ***Unclear risk of bias:*** If the trial may or may not be free of other components that could put it at risk of bias.
- ***High risk of bias:*** If there are other factors in the trial that could put it at risk of bias (including, Design-specific risk of bias, stopped early due to some data-dependent process including a formal-stopping rule, baseline imbalance, claimed fraudulent, blocked randomization in unblinded trials, differential diagnostic activity, contamination, inappropriate measurement instrument for outcomes, deviation from the study protocol unrelated to the clinical practice, authors conducted trials on the same topic, academic bias, for-profit bias, inappropriate

financial conflict of interest).

Overall risk of bias

- ***Low risk of bias:*** The trial will be classified as overall 'low risk of bias' only if all of the bias domains described in the above paragraphs are classified as 'low risk of bias'.
- ***High risk of bias:*** The trial will be classified as 'high risk of bias' if any of the bias risk domains described in the above are classified as 'unclear' or 'high risk of bias'.
- We will assess the domains 'blinding of outcome assessment', 'incomplete outcome data', and 'selective out- come reporting' for each outcome result. Thus, we can assess the bias risk for each outcome assessed in addition to each trial. Our primary conclusions will be based on the results of our primary outcome results with overall low risk of bias. Both our primary and secondary conclusions will be presented in the summary of findings tables.

Criteria classification

- If all risk of bias domains were scored as having a low risk of bias, the trial was defined as having a low overall risk of bias.
- If one or more of the bias domains were scored as unclear or high risk of bias, the trial was defined as having a high overall risk of bias.
- Trials with a low risk of bias in all domains (including sequence generation, allocation concealment, blinding, incomplete data, selective outcome reporting, and other risks of bias) will be classified as having a low overall risk of bias.
- Trials with one or more of these domains scored as unclear or high risk of bias will be defined as having a high overall risk of bias.

PRISMA-P checklist

Table PRISMA-P (preferred reporting items for systematic review and meta-analysis protocols) 2015 checklist: recommended items to address in a systematic review protocol

Section and topic	Item No	Checklist item	Reported on page #
Administrative information			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	None
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3,8
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	24
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	None
Support:			
Sponsor	5b	Provide name for the review funder and/or sponsor	None
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	None
Introduction			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-7
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	7-13
Methods			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	8-13 ; 14-15

Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	13-16
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	13-14, S1
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	14-16
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	14-15
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	14-16
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	16
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	10-13
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	16-20
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	17
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	17
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	18-21
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	17
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	20
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	18-20