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Keywords:	Adult anaesthesia < ANAESTHETICS, PAIN MANAGEMENT, Adult surgery < SURGERY

The optimal concentration of ropivacaine for peripheral nerve blocks in adult patients: A protocol for systematic review and meta-analysis

Jing Li [1, #], Jiamei Pan [1, #], Ying Xu [2], Yi Wang [1], Yiyong Wei [3, *], Donghang Zhang [4, *]

[1] Department of Anesthesiology, Affiliated Hospital of Zuni Medical University, Zunyi, 563000, China;

[2] Department of Oncology, The Second Affiliated Hospital of Zunyi Medical University, Zunyi, 563000, China;

[3] Department of Anesthesiology, Longgang District Maternity & Child Healthcare Hospital of Shenzhen City (Longgang Maternity and Child Institute of Shantou University Medical College), Shenzhen, 518100, China;

[4] Department of Anesthesiology, West China Hospital, Sichuan University, Chengdu, 610041, China.

[#] These authors contributed equally to this work.

[*]**Address corresponding to:**

Dr. Donghang Zhang,

E-mail: zhangdhscu@163.com

Dr. Yiyong Wei,

E-mail: 295502476@qq.com

Abstract

Introduction: Ropivacaine is the most widely used local anaesthetic for peripheral nerve blocks (PNB). The effects of various concentrations of ropivacaine in PNB have been investigated and compared by many randomized controlled trials (RCTs). This protocol aims to identify the optimal concentration of ropivacaine for PNB in adult patients.

Methods and analysis: PubMed, EMBASE, the Cochrane library, and Web of science will be searched from their inception to July 10, 2023. RCTs that compared the analgesic effects of different concentrations of ropivacaine for PNB will be included. Retrospective studies, meta-analysis, reviews, case reports, letters, conference abstracts, and pediatric studies will be excluded. The duration of analgesia will be named as the primary outcome. Secondary outcomes will include the onset time of motor and sensory blockade, postoperative pain scores, analgesics requirement over 24 hours, and the incidence of adverse effects. The study selection, data extraction, and quality assessment will be performed by two independent reviewers. Data processing and analysis will be performed by RevMan 5.4. The evidence quality will be assessed by the Grading of Recommendations Assessment, Development, and Evaluation approach (GRADE) approach.

Ethics and dissemination: Ethical approval is not applicable. The results of this study will be submitted to peer-reviewed journals.

PROSPERO registration number: CRD42023406362

Keywords: Ropivacaine; Concentration; Peripheral nerve blocks; RCTs; Meta-analysis; Protocol

Strengths and limitations of this study

- The results from subgroup analysis will provide evidence to guide ropivacaine use in certain surgical type or specific approach of PNB.
- We will use the GRADE approach to assess the quality of evidence for primary outcomes.
- Significant heterogeneity may exist among the included RCTs due to several factors, such us the type of surgery or nerve block, the usage of general anesthetics, opioids, or adjuvants, and the volumes of ropivacaine.

Introduction

Peripheral nerve blocks (PNB) are widely used to provide perioperative analgesia for various types of surgeries [1-3]. In addition to pain relief, PNB can also reduce the consumption of general anesthetics and/or opioids, decrease the incidence of postoperative complications, as well as improve the recovery quality [4-6]. Currently, ropivacaine is the most commonly used local anesthetic for PNB due to its lower toxicity in the central nervous system and hearts [7 8]. The concentration of ropivacaine used for PNB are various, and the efficacy and safety of different concentration of ropivacaine has been compared in several RCTs [9-14], but the results were inconsistent. Therefore, it is meaningful to perform a systematic review and meta-analysis to determine the optimal concentration of ropivacaine for PNB, which may provide longer analgesia without increasing the incidence of adverse effects. Furthermore, we will perform subgroup analysis to find the recommended ropivacaine concentration for specific type of nerve block.

Methods and analysis

Study registration

This protocol has been registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration number: CRD42023406362). This study is conducted according to the Preferred Reporting Items for Systematic Evaluation and Meta-Analysis (PRISMA-P) Protocols. Ethical approval is not required.

Search strategy

We will search PubMed, the Cochrane library, EMBASE, and Web of science from their inception to July 10, 2023 to identify RCTs that compared the analgesic effects of different concentration of ropivacaine for PNB. The keywords for search will include “ropivacaine”, “nerve block”, and “randomized controlled trials”. The search strategy for PubMed is presented in Table 1.

Inclusion and exclusion

Inclusion criteria: (1) Study type: RCTs, (2) Participants: Adult patients (> 18 years) underwent surgeries with PNB, (3) Comparisons: Different concentration of ropivacaine for PNB, and (4) Primary outcomes: Duration of analgesia; Secondary outcomes: the onset time of motor and sensory blockade, postoperative pain scores, analgesics requirement over 24 hours, and the incidence of adverse effects. Retrospective studies, meta-analysis, reviews, case reports, letters, and conference abstracts will be excluded.

Study selection

Two authors will independently select eligible studies by screening their title, abstract, as well as the full-text. Disagreement will be resolved by discussion with a third author. The flowchart for study selection is shown in Figure 1.

Data extraction

The following information will be extracted: author, publication year, countries, sample, characteristics of participants, surgical type, type of anesthesia and nerve blocks, adjuvants, comparisons, outcomes, and perioperative analgesia.

Risk of bias assessment

We will assess the risk of bias for included studies using the Cochrane Collaboration's tool [15]. Six items will be focused: random sequence generation (selection bias); allocation concealment (selection bias); blinding of participants and personnel (performance bias); blinding of outcome assessment (detection bias); incomplete outcome data (attrition bias); and selective reporting (reporting bias). The estimated results for each item will be graded as 'unclear', 'low' or 'high'.

Statistical analysis

Data analysis will be performed by RevMan 5.4. Continuous data will be summarized using mean differences (MD) with 95% confidence intervals (CI). Dichotomous data will be summarized by risk ratios (RR) with 95% CI. Statistical heterogeneity will be assessed by the I^2 test. Data will be synthesized using fixed-effect model if $I^2 < 50\%$. Significant heterogeneity will be considered to be existed when $I^2 > 50\%$, then a random-effect model will be applied. Subgroup analysis and meta-regression will be further conducted to explore the heterogeneity source. We will also perform sensitivity analysis to test whether the results are robust and reliable. $P < 0.05$ means statistically significant. The GRADE approach will assess the quality of evidence for each outcome, and the evidence will be rated as 'very low' , 'low', 'moderate', or 'high'.

Patient and Public Involvement

None.

Ethics and dissemination

Ethical approval is not applicable. The results of this study will be submitted to peer-reviewed journals.

Discussion

This protocol for a systematic review and meta-analysis aims to identify the optimal concentration of ropivacaine for PNB in adult patients. Optimal concentration of ropivacaine will offer longer analgesia but not bring higher incidence of adverse effects. However, significant heterogeneity may exist among the included RCTs due to several factors, such us the type of surgery or nerve block, the usage of general anesthetics, opioids, or adjuvants, and the volumes of ropivacaine. Therefore, we will use subgroup analysis and meta-regression to explore the source of heterogeneity. We will also perform sensitivity analysis to test whether the pooled results are robust and reliable. Furthermore, subgroup analysis will recommend the optimal concentration of ropivacaine for specific nerve block or general anesthesia. Additionally, we will use the GRADE approach to assess the quality of evidence for primary outcomes. Therefore, this study may provide evidence to guide clinical use of ropivacaine for PNB in adult patients.

Author contributions

Conceptualization: Yiyong Wei and Donghang Zhang.

Data curation: Jing Li and Jiamei Pan.

Formal analysis: Jing Li, Jiamei Pan, Ying Xu, and Yi Wang.

Methodology: Jing Li and Yiyong Wei.

Validation: Jing Li, Jiamei Pan, and Yiyong Wei..

Writing – original draft: Jing Li, Jiamei Pan, Ying Xu, Yi Wang, and Yiyong Wei.

Writing – review & editing: Yiyong Wei and Donghang Zhang.

Competing interests

None.

Funding

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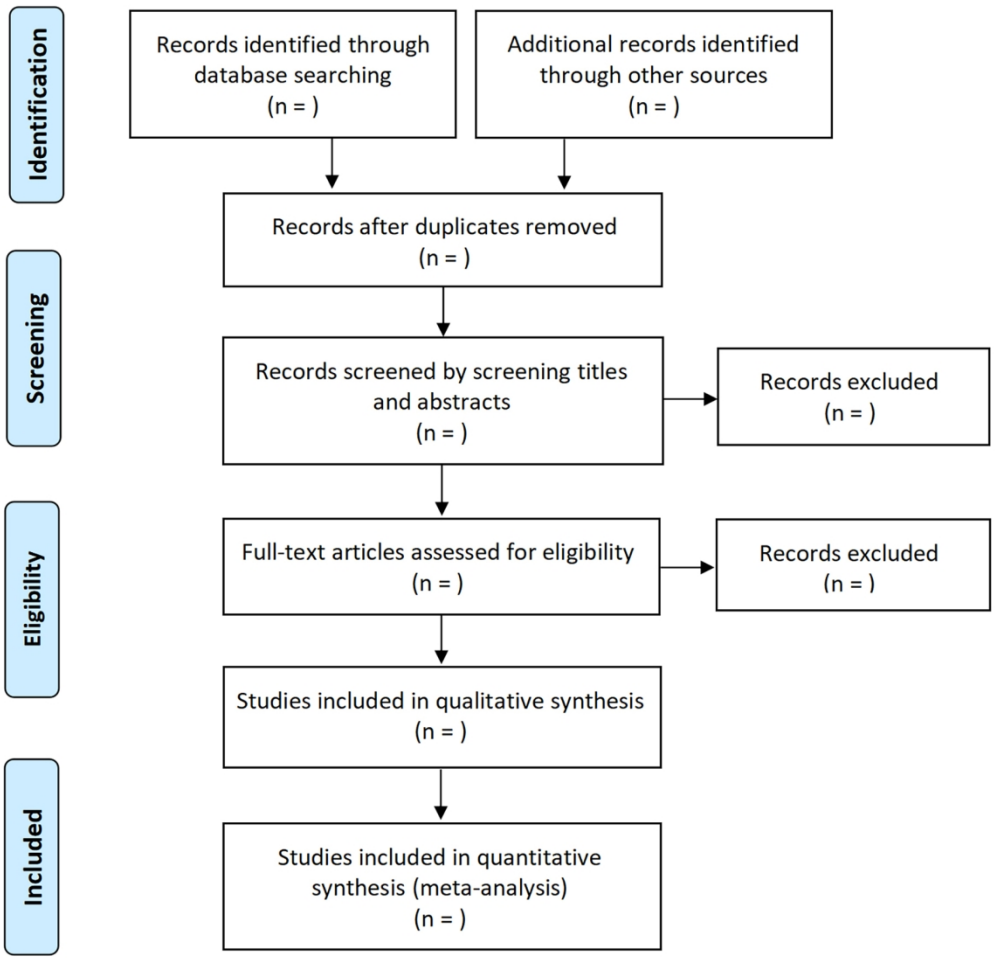
Table 1. The search strategy in PubMed.

Number	Search terms
#1	Ropivacaine [Mesh]
#2	Ropivacaine [Title/Abstract]
#3	#1 OR #2
#4	Nerve block [Title/Abstract]
#5	Nerve blockade [Title/Abstract]
#6	Peripheral nerve block [Title/Abstract]
#7	Peripheral nerve blockade [Title/Abstract]
#8	#4 OR #5 OR #6 OR #7
#9	Randomized controlled trial [Title/Abstract]
#10	Randomized [Title/Abstract]
#11	Clinical study [Title/Abstract]
#12	Clinical trial [Title/Abstract]
#13	Controlled clinical trial [Title/Abstract]
#14	#9 OR #10 OR #11 OR #12 OR #13
#15	#3 AND #8 AND #14



Flowchart of study selection

153x148mm (300 x 300 DPI)

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Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Surgery
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Methods and analysis: PubMed, EMBASE, the Cochrane library, and Web of science will be searched from their inception to July 10, 2023. RCTs that compared the analgesic effects of different concentrations of ropivacaine for PNB will be included. Retrospective studies, meta-analysis, reviews, case reports, letters, conference abstracts, and pediatric studies will be excluded. The duration of analgesia will be named as the primary outcome. Secondary outcomes will include the onset time of motor and sensory blockade, postoperative pain scores, analgesics requirement over 24 hours, and the incidence of adverse effects. The study selection, data extraction, and quality assessment will be performed by two independent reviewers. Data processing and analysis will be performed by RevMan 5.4. The evidence quality will be assessed by the Grading of Recommendations Assessment, Development, and Evaluation approach (GRADE) approach.

Ethics and dissemination: Ethical approval is not applicable. The results of this study will be submitted to peer-reviewed journals.

PROSPERO registration number: CRD42023406362

Keywords: Ropivacaine; Concentration; Peripheral nerve blocks; RCTs; Meta-analysis; Protocol

Strengths and limitations of this study

- Subgroup analysis will be used to explore the heterogeneity resource and provide evidence to guide ropivacaine use in certain surgical type or specific approach of PNB.
- We will use the GRADE approach to assess the quality of evidence for primary outcomes.
- Significant heterogeneity may exist among the included RCTs due to several factors, such as the type of surgery or nerve block, the usage of general anesthetics, opioids, or adjuvants, and the volumes of ropivacaine

Introduction

Peripheral nerve blocks (PNB) are widely used to provide perioperative analgesia for various types of surgeries (1-3). In addition to pain relief, PNB can also reduce the consumption of general anesthetics and/or opioids, decrease the incidence of postoperative complications, as well as improve the recovery quality (4-6). Currently, ropivacaine is the most commonly used local anesthetic for PNB due to its lower toxicity in the central nervous system and hearts (7-8). The concentration of ropivacaine used for PNB are various, and the efficacy and safety of different concentration of ropivacaine has been compared in several RCTs (9-14), but the results were inconsistent. Therefore, it is meaningful to perform a systematic review and meta-analysis to determine the optimal concentration of ropivacaine for PNB, which may provide longer analgesia without increasing the incidence of adverse effects. Furthermore, we will perform subgroup analysis to find the recommended ropivacaine concentration for specific type of nerve block.

Methods and analysis

Study registration

This protocol has been registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration number: CRD42023406362). This study is conducted according to the Preferred Reporting Items for Systematic Evaluation and Meta-Analysis (PRISMA-P) Protocols. Ethical approval is not required.

Search strategy

We will search PubMed, the Cochrane library, EMBASE, and Web of science from their inception to July 10, 2023 to identify RCTs that compared the analgesic effects of different concentration of ropivacaine for PNB. The keywords for search will include "ropivacaine", "nerve block", and "randomized controlled trials". The language will be restricted to English. The search strategy for PubMed and other databases is presented in Table 1 and supplementary file 1, respectively.

Inclusion and exclusion

Inclusion criteria: (1) Study type: RCTs, (2) Participants: Adult patients (> 18 years) underwent surgeries with PNB, (3) Comparisons: Different concentration of ropivacaine for PNB, and (4) Primary outcomes: Duration of analgesia (time to first analgesic request); Secondary outcomes: the onset time of motor and sensory blockade, postoperative pain scores, analgesics requirement over 24 hours, and the incidence of adverse effects (e.g., nausea, vomiting, drowsiness, dizziness, itching and constipation). Retrospective studies, meta-analysis, reviews, case reports, letters, and conference abstracts will be excluded.

Study selection

Two authors will independently select eligible studies by screening their title, abstract, as well as the full-text. Disagreement will be resolved by discussion with a third author. The flowchart for study selection is shown in Figure 1.

Data extraction

The following information will be extracted: author, publication year, countries, sample, characteristics of participants, surgical type, type of anesthesia and nerve blocks, adjuvants, comparisons, outcomes, and perioperative analgesia.

Risk of bias assessment

We will assess the risk of bias for included studies using the Cochrane Collaboration's tool (15). Six items will be focused: random sequence generation (selection bias); allocation concealment (selection bias); blinding of participants and personnel (performance bias); blinding of outcome assessment (detection bias); incomplete outcome data (attrition bias); and selective reporting (reporting bias). The estimated results for each item will be graded as 'unclear', 'low' or 'high'.

Statistical analysis

Data analysis will be performed by RevMan 5.4. Continuous data will be summarized using mean differences (MD) with 95% confidence intervals (CI). Dichotomous data will be summarized by risk ratios (RR) with 95% CI. Statistical heterogeneity will be assessed by the I^2 test. Data will be synthesized using fixed-effect model if $I^2 < 50\%$. Significant heterogeneity will be considered to be existed when $I^2 > 50\%$, then a random-effect model will be applied. Subgroup analysis and meta-regression will be further conducted to explore the heterogeneity source. We will also perform sensitivity analysis to test whether the results are robust and reliable. $P < 0.05$ means statistically significant. The GRADE approach will assess the quality of evidence for each outcome, and the evidence will be rated as 'very low' , 'low', 'moderate', or 'high'.

Patient and Public Involvement

None.

Ethics and dissemination

Ethical approval is not applicable. The results of this study will be submitted to peer-reviewed journals.

Discussion

Ropivacaine is the most commonly used local anesthetic for PNB due to its lower central nervous system and cardiac toxicity. Currently, the concentration of ropivacaine used for PNB mainly varies from 0.25% to 1%. Emerging RCTs have compared the effects of different concentration of ropivacaine for PNB, but the optimal concentration remains unclear. This protocol for a systematic review and meta-analysis aims to identify the optimal concentration of ropivacaine for PNB in adult patients. Optimal concentration of ropivacaine will offer longer analgesia but not bring higher incidence of adverse effects. However, several limitations should be noticed. Firstly, significant heterogeneity may exist among the included RCTs due to several factors, such as the type of surgery or nerve block, the usage of general anesthetics, opioids, or adjuvants, and the volumes of ropivacaine. Secondly, it should be considered that the definition of the duration of analgesia among studies may be different, which will influence the results. It is better to minimize the heterogeneity by categorizing the analgesia duration differently according to their definition in individual study. Therefore, we will use subgroup analysis and meta-regression to explore the source of heterogeneity. We will also perform sensitivity analysis to test whether the pooled results are robust and reliable. Another limitation is that the number of studies that comparing the effects of different concentration of ropivacaine for PNB may be relatively small, especially for subgroup analysis. Therefore, well-designed, large sample RCTs may be needed to determine the optimal concentration of ropivacaine for PNB.

According to our protocol, subgroup analysis will recommend the optimal concentration of ropivacaine for specific nerve block or general anesthesia. Additionally, we will use the GRADE approach to assess the quality of evidence for primary outcomes. Therefore, this study may provide evidence to guide clinical use of ropivacaine for PNB in adult patients.

Author contributions

Conceptualization: Yiyong Wei and Donghang Zhang.

Methodology: Jing Li and Yiyong Wei.

Validation: Jing Li, Jiamei Pan, and Yiyong Wei..

Writing – original draft: Jing Li, Jiamei Pan, Ying Xu, Yi Wang, and Yiyong Wei.

Writing – review & editing: Yiyong Wei and Donghang Zhang.

Competing interests

None.

Funding

This study was supported by Grant No. 2022NSFSC1399 (To Donghang Zhang) from the Natural Science Foundation of Sichuan Province.

Acknowledgments

None.

Figure 1. The flowchart for study selection.

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Table 1. The search strategy in PubMed.

Number	Search terms
#1	Ropivacaine [Mesh]
#2	Ropivacaine [Title/Abstract]
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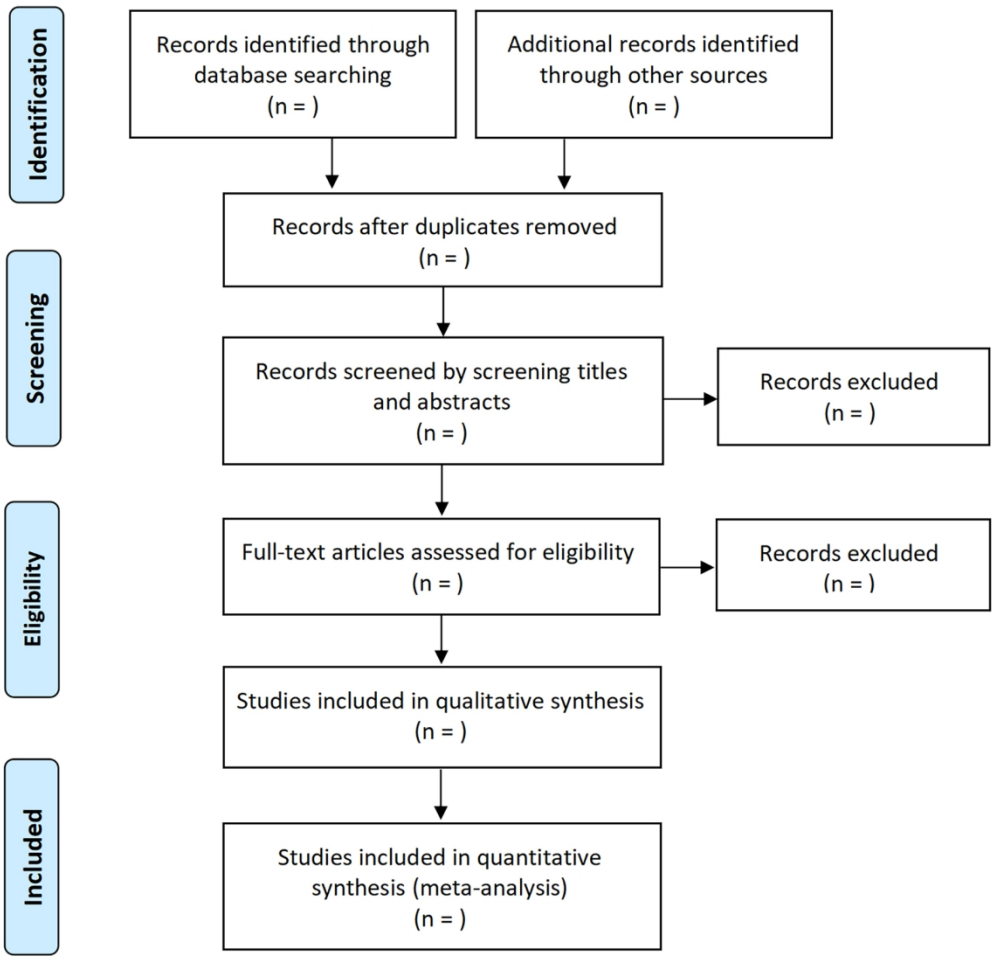
#5	Nerve blockade [Title/Abstract]
#6	Peripheral nerve block [Title/Abstract]
#7	Peripheral nerve blockade [Title/Abstract]
#8	#4 OR #5 OR #6 OR #7
#9	Randomized controlled trial [Title/Abstract]
#10	Randomized [Title/Abstract]
#11	Clinical study [Title/Abstract]
#12	Clinical trial [Title/Abstract]
#13	Controlled clinical trial [Title/Abstract]
#14	#9 OR #10 OR #11 OR #12 OR #13
#15	#3 AND #8 AND #14



The flowchart for study selection

153x148mm (300 x 300 DPI)

Search strategies

EMBASE

#1 'Ropivacaine'/exp OR 'Ropivacaine':ti,ab,kw

#2 'Nerve block'/exp OR 'Nerve block':ti,ab,kw OR 'Nerve blockade':ti,ab,kw OR 'Peripheral nerve block':ti,ab,kw OR 'Peripheral nerve blockade':ti,ab,kw

#3 'Randomized controlled trial'/exp OR 'Randomized controlled trial':ti,ab,kw OR 'Controlled clinical trial':ti,ab,kw OR 'Clinical trial':ti,ab,kw OR 'Clinical study':ti,ab,kw OR 'Randomized':ti,ab,kw

#4 #1 AND #2 AND #3

Cochrane library Trials

#1 MeSH descriptor: (Ropivacaine) explode all trees

#2 (Ropivacaine):ti,ab,kw

#3 #1 OR#2

#4 (Nerve block):ti,ab,kw

#5 (Nerve blockade):ti,ab,kw

#6 (Peripheral nerve block):ti,ab,kw

#7 (Peripheral nerve blockade):ti,ab,kw

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

#9 (Randomized controlled trial):ti,ab,kw

#10 (Controlled clinical trial):ti,ab,kw

#11 (Clinical trial):ti,ab,kw

#12 (Clinical study):ti,ab,kw

#13 (Randomized):ti,ab,kw

#14 #9 OR #10 OR #11 OR #12 OR #13

#15 #3 AND #8 AND #14

Web of science

#1 Ropivacaine (Topic)

#2 Nerve block (Topic) OR Nerve blockade (Topic) OR Peripheral nerve block (Topic)

OR Peripheral nerve blockade (Topic)

#3 Randomized controlled trial (Topic) OR Controlled clinical trial (Topic) OR Clinical trial (Topic) OR Clinical study (Topic) OR Randomized (Topic)

#4 #1 AND #2 AND #3

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 number
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Page 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Page 5
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Page 1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Page 9
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	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Page 9
Sponsor	5b	Provide name for the review funder and/or sponsor	Page 9
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Page 9
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Page 4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Page 4
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	Page 5
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	Page 5
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	Page 5

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Page 5
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)	Page 5
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	Page 6
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	Page 6
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Page 5
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	Page 6
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Page 6
	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)	Page 6
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Page 6
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Page 6
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Page 6
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Page 6

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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