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Title: Effect of oral preemptive analgesia on pain management after total knee arthroplasty：A protocol for systematic review and meta-analysis

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Key words: Total knee arthroplasty; Preemptive analgesia; Pain management; Systematic review; Meta-analysis; Protocol

ABSTRACT

Introduction Total knee arthroplasty (TKA) is currently regarded as an effective treatment for knee osteoarthritis, relieving patients' pain and significantly enhancing their quality of life and activity levels, allowing them to return to work and daily life after surgery. However, some TKA patients suffer from varying degrees of postoperative residual pain and opioid abuse, which negatively impacts their recovery and quality of life. It has been reported that pre-operative treatment with multimodal analgesics improves postoperative pain and reduces opioid consumption. However, there is no conclusive evidence that preemptive analgesia provides the same benefits in TKA. In order to inform future research, this protocol focuses on the efficacy and safety of oral analgesics used in TKA preemptive analgesia.

Methods and analysis We will search the literature on the involvement of preemptive analgesia in the management of pain in TKA from the PubMed, EMBASE, MEDLINE, the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews, from their inception to 1 February, 2023. Additionally, clinical registry platforms will be investigated to collect data for ongoing studies. Using the Cochrane Risk of Bias Tool, the quality assessment will be conducted. RevMan 5.4 will be used for the meta-analysis. I^2 will evaluate and quantify the heterogeneity of the literature. In addition, subgroup and sensitivity analyses, assessment of evidence quality, and publication bias will be conducted.

Ethics and dissemination No ethical approval and consent is required for this systematic review. Moreover, the results of this systematic review will be disseminated through peer-reviewed publications and conference presentations.

PROSPERO registration number CRD42022380782

Article Summary

Strengths and limitations of this study

- This study will provide a thorough analysis of the role of oral multimodal analgesics in TKA preemptive analgesia.
- Through subgroup analysis, we wanted to evaluate the various confounding factors and discuss the effect of different drug doses on the conclusions.

- The study design strictly adheres to the PRISMA-P recommendations to ensure the reproducibility of the findings.
- The inclusion of studies in databases containing only English-language entries may result in potential bias.

INTRODUCTION

As the world's population grows and inevitably ages, the number of people diagnosed with osteoarthritis is expected to rise by 40% by 2035.[1] Knee osteoarthritis is one of the primary patient groups and a significant source of pain and disability. Murphy et al. estimate that the lifetime risk of symptomatic knee osteoarthritis is around 45%.[2] This means that these groups will produce a large number of potential total knee arthroplasty (TKA) patients. TKA is currently regarded as an effective treatment for knee osteoarthritis, relieving patients' pain and significantly enhancing their quality of life and activity levels, allowing them to return to work and daily activities after surgery.[3] Given the substantial medium- or long-term benefits of TKA, both clinicians and patients have embraced the procedure.

However, not every patient will recover well. Despite the fact that the success rate of TKA is between 80 and 90%, up to 30% of patients are reported to be dissatisfied. The level of dissatisfaction with pain relief among these individuals ranged from 14% to 28%.[4 5] This was primarily due to the persistent post-operative knee pain. Due to the significance of the knee in daily activities, even when mobility is commensurate with activity levels, some TKA patients report significant residual pain, which frequently develops into chronic pain.[6 7] Managing pain following knee surgery is another inevitable challenge for clinicians. Because pain is considered a subjective sensation, the degree and threshold of perception vary from person to person; this, combined with the complexity of factors affecting postoperative pain, makes it challenging to analyse and manage pain through specific pain mechanisms.[8-10]

The various adverse effects of opioid abuse include nausea, vomiting, sedation, intestinal obstruction, respiratory depression, and itchiness. Three weeks after hospital discharge, over 70% of post-TKA patients are still taking opioids, according to a

survey conducted by the health services.[11] According to research conducted in the United States, patients undergoing joint replacement surgery are more likely to consume opioids than those undergoing other surgical procedures.[12 13] All of the aforementioned may delay the recovery process, diminish the patient's postoperative quality of life, and even increase the TKA revision rate, thereby increasing the patient's financial burden. Adoption of a high-quality pain management model is thus an urgent requirement for initial functional recovery after TKA.

Preemptive analgesia is an efficient method for achieving rapid postoperative recuperation and optimising pain management. Preemptive refers to analgesic interventions administered prior to the onset of noxious stimuli to prevent the development of central sensitization, incision, and inflammatory damage, and has been shown to be more effective than the same interventions administered after surgery.[14 15] By preventing the sensitization of the central nervous system caused by painful stimuli, appropriate interventions can attenuate the response to future injurious sensory input and reduce the sensitization of the central nervous system, so that normally painful stimuli become less painful or even painless. The mechanism of action may involve the inhibition of cytokine and prostaglandin release-induced modifications in central sensory processes, as well as the suppression of inflammatory reactions.[16-18] Current research indicates that preemptive analgesia can minimise the chance of developing chronic pain, improve pain management, and boost the efficacy of other treatment modalities.[19] The network meta-analysis (NMA) revealed that various preventive analgesic medicines or strategies reduced postoperative pain, opioid intake, and postoperative side effects to diverse degrees.[20] As the notion of preemptive analgesia has acquired widespread recognition in the field of surgery, the investigation of preemptive analgesia to improve the overall benefit to the postoperative patient has become one of the clinical and scientific hotspots of the moment. Diverse techniques, such as preemptive epidural, local wound infiltration, opioids, NMDA receptor antagonists, and nonsteroidal anti-inflammatory drugs (NSAIDs), are used for preemptive analgesia.[21 22] This study focuses on the role of oral medicine as a preventative multimodal analgesic.

Nevertheless, there is debate in the existing literature regarding the efficacy and safety of preventive analgesics. Wang C et al. examined the efficacy and safety of preoperative selective COX-2 inhibitor administration in TKA patients. A meta-analysis discovered that selective COX-2 inhibitors decreased postoperative pain and opioid intake in TKA patients, but there were no significant differences in time to operation or adverse effects.[23] However, in another randomised controlled trial, Qiuru Wang et al. reported that the opioid oxycodone did not produce a substantial preemptive analgesic effect in TKA patients.[24] Similar contradictory results were observed in investigations of medications such as gabapentins and acetaminophen.[25] Evidently, a rigorous clinical review and evidence validating the efficacy and advantages of preemptive analgesia in TKA are still lacking.

The objective of this systematic review (SR) and meta-analysis was to evaluate the efficacy of several oral preemptive analgesics for the management of pain in TKA patients.

METHODS

Eligibility criteria

Protocol for meta-analysis registered with International Prospective Register of Systematic Review (Prospero CRD 42022380782). This review protocol will adhere to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) guideline.[26]

Study design

We will include randomised controlled trials (RCTs) that reported the efficacy of preemptive analgesia in TKA. The use of quasi-RCTs and non-RCTs, including sequentially assigned RCTs within the clinic, retrospective studies, letters, review articles, case reports, editorials, and animal experimental research, would be eliminated.

Type of participants/populations

All participants/populations with an indication for TKA surgery as determined by physicians and undergoing the procedure will be included. The participants in this study will not be limited by age, gender, race, surgery history, or underlying condition.

Type of interventions

In RCTs aimed at preemptive analgesia, any oral preemptive analgesic chosen prior to TKA will be permitted. The sample size, perioperative care, and underlying treatment of the study will not be restricted. However, nonpharmacological preemptive analgesia methods will be excluded.

Type of comparator groups

Comparator groups may employ a different type or method of preoperative analgesic medication, a placebo, or no preoperative analgesic medication. Studies with other types of interventions in the comparator groups will be excluded.

Types of outcome measures

Primary outcomes

Primary outcomes included the degree of improvement in knee pain and activity, and the use of perioperative analgesics.

- The visual analogue scale (VAS) dynamic pain score from 24 to 72h after surgery.
- The numerical pain rating scale (NRS) score from 24 to 72h after surgery.
- The keen Society Score (KSS) will be used to assess post-operative knee function.
- Consumption of analgesics from 24 to 72h after surgery.

Secondary outcomes

The following data will be collected for analysis as secondary outcomes: blood loss, length of hospitalization, adverse events, duration of surgery, postoperative nausea

and vomiting, time to first mobilization, quality of life (QoL), readmission rates or perioperative care.

Search strategy

A systematic search of the PubMed, EMBASE, MEDLINE, the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews, from their inception to 1 February, 2023. There will be no restrictions on language, country, publication status or year of publication. Included in the list of predefined search terms are TKA, Preemptive Analgesia, RCTs, and similar topics. The search strategy will be modified for each individual database. Take PubMed as an example, the detailed search strategy was shown in **table 1**.

As a supplement, the following clinical registry platforms will be searched to collect data from ongoing studies: WHO International Clinical Trial Registration Platform (http://www.who.int/trialsearch/), Australian New Zealand Clinical Trials (http://www.anzctr.org.au/) and National Institutes of Health clinical registry (http://www.clinicaltrials.gov/). If there is missing data, we will contact the correspondent or first author to complete it.

Study selection process

EndNote X9 (Thomson Reuters, New York, USA) software will be used to manage the literature and perform filtering, and categorize the document and remove duplicates. After classifying the literature and removing duplicates, two independent reviewers (F-JX and WZ) review the titles and abstracts of the identified studies to exclude irrelevant parts. The full text will then be downloaded and submitted to two reviewers (S-JJ and X-RH) for the whole-length articles screening to identify studies that are ultimately suitable for meta-analysis. Throughout the procedure, any disagreement will be resolved by a third researcher (KS). **Figure 1** is a schematic diagram of literature selection in this study.

Data extraction and management

Two independent reviewers (X-FL and H-JP) used Microsoft Excel to independently extract and manage the data. The extracted data items include:

1) Study characteristics: title, first author name, publication year, country of publication and funding source.

2) Participants: sample size, gender, average age, race, disease course and preoperative pain score/knee function score.

3) Interventions/comparator groups: types of the treatment, types of analgesics, timing of intervention, clinical dosage and course of treatment.

4) Outcomes: Data relating to the primary and secondary outcomes at each measurement time will be recorded.

Before the formal data extraction, 10 studies were randomly selected to test and modify the pre-designed table. All data will be cross-checked. In addition, during the data extraction process, if there is any objection can be negotiated, or by a third reviewer (Y-ML) accuracy and consistency checking of data.

Risk of bias assessment

According to the current version of the Cochrane Risk of Bias Tool, two reviewers (F-JX and WZ) independently assessed the risk of bias, which included the seven specific domains： (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome data, (5) incomplete outcome data, (6) selective reporting, and (7) other bias.[27] If required, the third reviewer (Y-ML) will resolve divergent opinions.

Data synthesis and meta-analysis

Due to the study's exclusive reliance on RCTs, it may be susceptible to bias. Therefore, the outcomes of this study's data analysis should be carefully assessed.

Selection of effect measure

In this study, continuous outcome variables including VAS score, NRS score, KSS score, consumption of analgesics, blood loss, length of hospitalization, duration of

surgery, time to first mobilization and QoL will use the standardized mean difference (SMD) as the effect measure. Dichotomous variables including adverse events, postoperative nausea and vomiting, readmission rates and perioperative care will use relative ratio (RR) to evaluate the effect measure. All effect measure will be expressed with 95% confidence intervals (CIs).

Statistical heterogeneity

Examine and quantify the heterogeneity by inspecting the Forest plot, and assess the size of the heterogeneity by I^2. Heterogeneity will not be considered when I^2 value is less than 50%. At this point the meta-analysis will be performed by using the fixed-effect model. On the contrary, when the I^2 value is greater than 50%, we consider that there to be substantial heterogeneity and will use the random-effect model for data analysis. If the meta-analysis is inappropriate, we will undertake a descriptive synthesis using a best-evidence synthesis approach.

Subgroup and sensitivity analyses

When the heterogeneity is excessive, we will investigate the potential origins of major inconsistencies or heterogeneity by meta-regression analysis and grouping. Age, types of analgesics, duration of treatment, anaesthetic dosage, duration of operation, blood loss, and follow-up time are among the complicating factors that need to be analyzed. To uncover sources of bias and check the consistency of the meta-analysis conclusions, we will conduct a sensitivity analysis by excluding each study individually.

Meta-analysis

When the heterogeneity is moderate, we will further conduct a meta-analysis of the outcomes of each RCT individually. When multiple outcomes were available from a single study, the value was used which was thought to be best correlated to that time interval. A random effect model will be used for all analyses based upon the DerSimonian and Laird approach.[28] RevMan 5.4 (The Nordic Cochrane Center, The

Cochrane Collaboration, Denmark) will be used to perform the meta-analysis.

Publication bias

If more than 10 studies are ultimately included, we will draw the Begg funnel plot to assess publication bias. The Egger test was then used to assess the asymmetry of the funnel plot.[29 30]

Quality of evidence

On the basis of the five components (limitations of design, inconsistency of results, indirectness, imprecision, and other factors), we will assess the quality of the evidence for all outcomes. The quality of evidence is divided into four levels: very low, low, model and high. GRADE profiler software will be used for the above evidence quality grading.[31]

Patient and public involvement

There will be no patients involved in this study.

Ethics and dissemination

No ethical approval and consent is required for this systematic review. Moreover, the results of this systematic review will be disseminated through peer-reviewed publications and conference presentations.

DISCUSSION

The majority of studies believe that preemptive analgesia is essential for promoting rapid recovery in TKA patients. Existing research on the role of oral analgesics in TKA pain treatment have generally concentrated on the efficacy of the medications, lacking a comprehensive evaluation of the overall benefits and safety of these drugs and neglecting the influence of confounding factors on clinical study outcomes.[32] A recent big NMA assessed the efficacy of oral preemptive analgesics on perioperative pain, showing the superiority of preemptive analgesia over traditional pain

management methods. However, the study did not account for variability between procedures and did not conduct additional subgroup analyses of drug doses, which may have been a major source of heterogeneity.[33] In our study, it is of considerable interest to undertake a novel and systematic investigation of TKA. It can enrich the evidence-based evidence for preemptive analgesia in TKA and provide a more convincing reference for pain management to surgeons. As only English-language database reports were considered for inclusion in this protocol, the exclusion of other databases may pose a risk of bias.

Contributors F-JX and WZ conceptualised the study and contributed equally to this work. F-JX, WZ, Y-ML and S-JJ designed the study and drafted the initial manuscript. X-RH, X-FL, H-JP, KS were involved in the review and revision of the protocol. The grammar of this protocol has been improved by H-JP. Y-ML supervised the study. All authors read and approved the final version of the manuscript.

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Competing interests None declared.

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

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Figure legend

Figure 1. PRISMA flow diagram of study identification and selection.

Table legend

Table 1. Search strategy used in the PubMed database.

Table 1 Search strategy used in the PubMed database	
Number	Search terms
#1	Total knee arthroplasty [Mesh]
#2	Total knee arthroplasty [Title/Abstract] OR Knee Replacement Arthroplasty [Title/Abstract] OR Total Knee Replacement [Title/Abstract] OR Arthroplasties, Replacement, Knee [Title/Abstract] OR Arthroplasty, Knee Replacement [Title/Abstract] OR Arthroplasty, Total Knee [Title/Abstract] OR Knee Arthroplasty, Total [Title/Abstract] OR Replacement, Total Knee [Title/Abstract] OR Knee Replacement, Total [Title/Abstract]
#3	#1 OR #2
#4	Analgesia [Mesh]
#5	Analgesia [Title/Abstract] OR Analgesics [Title/Abstract] OR Anodynes [Title/Abstract] OR Analgesic Drugs [Title/Abstract] OR Analgesic [Title/Abstract] OR Analgesic Agents [Title/Abstract] OR Antinociceptive Agents [Title/Abstract] OR Analgesics, Non-Narcotic [Title/Abstract] OR Analgesics, Short-Acting [Title/Abstract] OR Analgesics, Opioid [Title/Abstract] OR Anti-Inflammatory Agents, Non-Steroidal [Title/Abstract]
#6	#4 OR #5
#7	Preoperative Period [Title/Abstract] OR Preoperative [Title/Abstract] OR Preemptive [Title/Abstract]
#8	Randomized controlled trial [Publication Type]
#9	Controlled clinical trial [Publication Type]
#10	Randomized [Title/Abstract]
#11	Randomly [Title/Abstract]
#12	Trial [Title/Abstract]
#13	#8 OR #9 OR #10 OR #11 OR #12
#14	#3 AND #6 AND #7 AND #13

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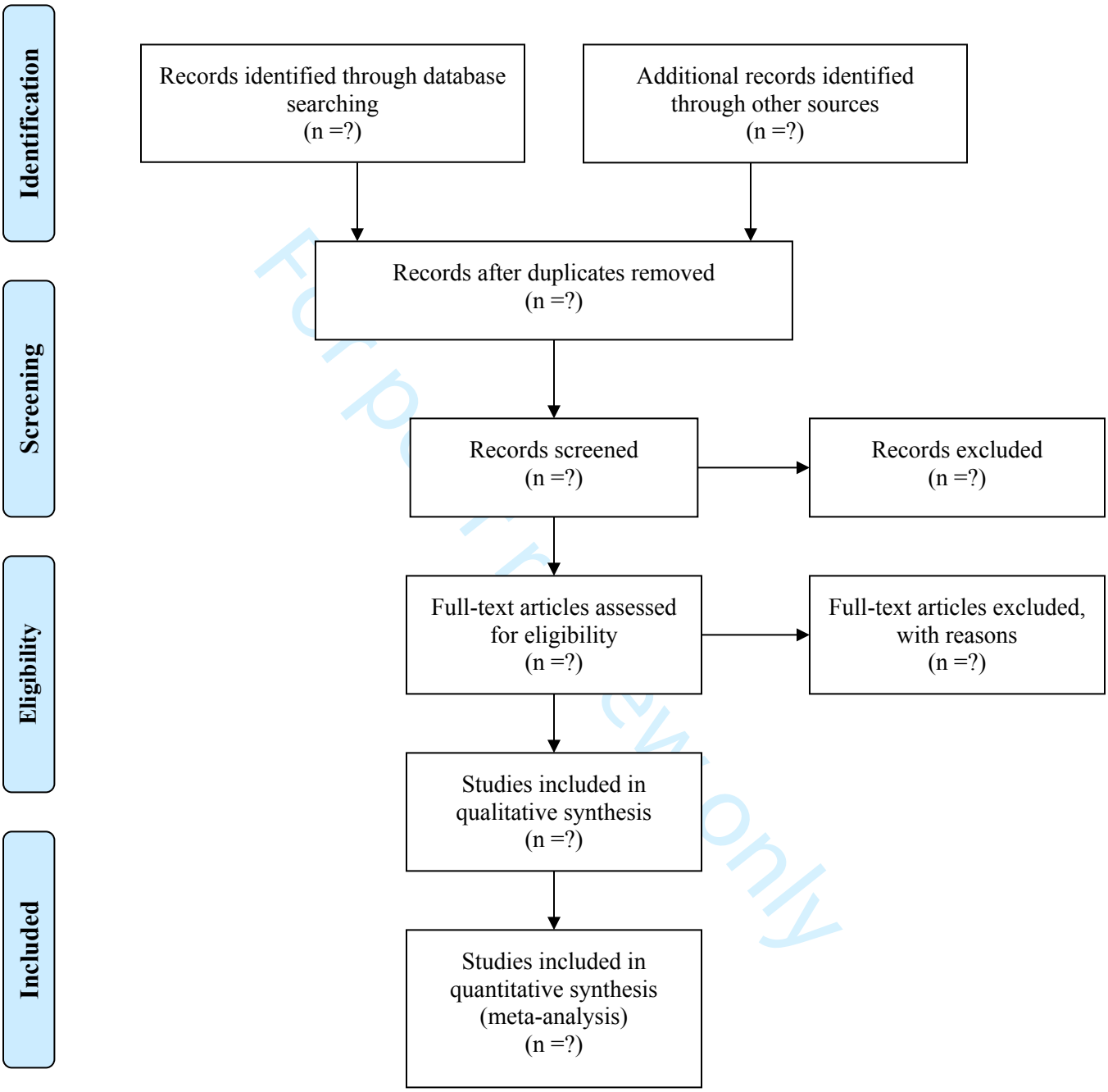

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

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	-
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	#2
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	#1,11
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	
Support:			
Sources	5a	Indicate sources of financial or other support for the review	#11
Sponsor	5b	Provide name for the review funder and/or sponsor	#11
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	-
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	#3-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	#5-7
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	#5-7
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	#7
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	#7

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	#7
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)	#7-9
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	#7,8
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	#7,8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	#6,7
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	#8-10
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	#8,9
	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)	#9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	#8,9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	#9
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	#8,9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	#9

*** 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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Primary Subject Heading:	Surgery
Secondary Subject Heading:	Anaesthesia, Rehabilitation medicine
Keywords:	Knee < ORTHOPAEDIC & TRAUMA SURGERY, Anaesthesia in orthopaedics < ANAESTHETICS, Pain management < ANAESTHETICS

Title: Effect of oral preemptive analgesia on pain management after total knee arthroplasty : A protocol for systematic review and meta-analysis

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Key words: Total knee arthroplasty; Preemptive analgesia; Pain management; Systematic review; Meta-analysis; Protocol

ABSTRACT

Introduction Total knee arthroplasty (TKA) is currently regarded as an effective treatment for knee osteoarthritis, relieving patients' pain and significantly enhancing their quality of life and activity levels, allowing them to return to work and daily life after surgery. However, some TKA patients suffer from varying degrees of postoperative residual pain and opioid abuse, which negatively impacts their recovery and quality of life. It has been reported that pre-operative treatment with multimodal analgesics improves postoperative pain and reduces opioid consumption. However, there is no conclusive evidence that preemptive analgesia provides the same benefits in TKA. In order to inform future research, this protocol focuses on the efficacy and safety of oral analgesics used in TKA preemptive analgesia.

Methods and analysis We will search the literature on the involvement of preemptive analgesia in the management of pain in TKA from the PubMed, EMBASE, MEDLINE, the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews, from their inception to 1 February, 2023. Additionally, clinical registry platforms will be investigated to collect data for ongoing studies. Using the Cochrane Risk of Bias Tool, the quality assessment will be conducted. RevMan 5.4 will be used for the meta-analysis. The statistic I^2 will be used to measure the percentage of total variability due to heterogeneity between studies. Where appropriate, subgroup and sensitivity analyses, assessment of evidence quality, and publication bias will be conducted.

Ethics and dissemination No ethical approval and consent is required for this systematic review. Moreover, the results of this systematic review will be disseminated through peer-reviewed publications and conference presentations.

PROSPERO registration number CRD42022380782

Article Summary

Strengths and limitations of this study

- This is a protocol for a systematic review and meta-analysis of oral multimodal analgesics and postoperative pain after total knee arthroplasty.
- A subgroup analyses of confounding factors including age, type of analgesic,

duration of treatment, anesthetic dose, duration of operation, amount of blood loss, and duration of follow-up will be performed.

- This review protocol is reported referring to the recommendations of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols.
- The inclusion of studies in databases containing only English-language entries may result in potential bias.

INTRODUCTION

As the world's population grows and inevitably ages, the number of people diagnosed with osteoarthritis is expected to rise by 40% by 2035.[1] Knee osteoarthritis is a common condition that causes significant pain and disability among patients. According to Murphy et al., the lifetime risk of symptomatic knee osteoarthritis is estimated to be approximately 45%.[2] As a result, this patient group constitutes a significant proportion of potential total knee arthroplasty (TKA) candidates. TKA is currently regarded as an effective treatment for knee osteoarthritis, relieving patients' pain and significantly enhancing their quality of life and activity levels, allowing them to return to work and daily activities after surgery.[3] Given the substantial medium- or long-term benefits of TKA, both clinicians and patients have embraced the procedure.

However, not every patient will recover well. Despite the fact that the success rate of TKA is between 80 and 90%, up to 30% of patients are reported to be dissatisfied. The level of dissatisfaction with pain relief among these individuals ranged from 14% to 28%.[4 5] This was primarily due to the persistent post-operative knee pain. Due to the significance of the knee in daily activities, even when mobility is commensurate with activity levels, some TKA patients report significant residual pain, which frequently develops into chronic pain.[6 7] Managing pain following knee surgery is another inevitable challenge for clinicians. Because pain is considered a subjective sensation, the degree and threshold of perception vary from person to person; this, combined with the complexity of factors affecting postoperative pain, makes it challenging to analyse and manage pain through specific pain mechanisms.[8-10]

The various adverse effects of opioid abuse include nausea, vomiting, sedation,

intestinal obstruction, respiratory depression, and itchiness. Three weeks after hospital discharge, over 70% of post-TKA patients are still taking opioids, according to a survey conducted by the health services.[11] According to research conducted in the United States, patients undergoing joint replacement surgery are more likely to consume opioids than those undergoing other surgical procedures.[12] [13] Both post-operative knee pain and opioid abuse may delay the recovery process, diminish the patient's postoperative quality of life, and even increase the TKA revision rate, thereby increasing the patient's financial burden. Adoption of a high-quality pain management model is thus an urgent requirement for initial functional recovery after TKA.

Preemptive analgesia is an efficient method for achieving rapid postoperative recuperation and optimising pain management. Preemptive refers to analgesic interventions administered prior to the onset of noxious stimuli to prevent the development of central sensitization, incision, and inflammatory damage, and has been shown to be more effective than the same interventions administered after surgery.[14] [15] By preventing the sensitization of the central nervous system caused by painful stimuli, appropriate interventions can attenuate the response to future injurious sensory input and reduce the sensitization of the central nervous system, so that normally painful stimuli become less painful or even painless. The mechanism of action may involve the inhibition of cytokine and prostaglandin release-induced modifications in central sensory processes, as well as the suppression of inflammatory reactions.[16-18] Current research indicates that preemptive analgesia can minimise the chance of developing chronic pain, improve pain management, and boost the efficacy of other treatment modalities.[19] The network meta-analysis (NMA) revealed that various preventive analgesic medicines or strategies reduced postoperative pain, opioid intake, and postoperative side effects to diverse degrees.[20] As the notion of preemptive analgesia has acquired widespread recognition in the field of surgery, the investigation of preemptive analgesia to improve the overall benefit to the postoperative patient has become one of the clinical and scientific hotspots of the moment. Diverse techniques, such as epidural analgesia, peripheral nerve blocks,

local infiltration analgesia, opioids, NMDA receptor antagonists, and nonsteroidal anti-inflammatory drugs (NSAIDs), are used for preemptive analgesia.[21 22] This study focuses on the role of oral medicine as a preventative multimodal analgesic.

Nevertheless, there is debate in the existing literature regarding the efficacy and safety of preventive analgesics. Wang C et al. examined the efficacy and safety of preoperative selective COX-2 inhibitor administration in TKA patients. A meta-analysis discovered that selective COX-2 inhibitors decreased postoperative pain and opioid intake in TKA patients, but there were no significant differences in time to operation or adverse effects.[23] However, in another randomised controlled trial, Qiuru Wang et al. reported that the opioid oxycodone did not produce a substantial preemptive analgesic effect in TKA patients.[24] Similar contradictory results were observed in investigations of medications such as gabapentins and acetaminophen.[25] Evidently, a rigorous clinical review and evidence validating the efficacy and advantages of preemptive analgesia in TKA are still lacking.

The objective of this systematic review (SR) and meta-analysis was to evaluate the efficacy of several oral preemptive analgesics for the management of pain in TKA patients.

METHODS

Eligibility criteria

Protocol for meta-analysis registered with International Prospective Register of Systematic Review (Prospero CRD 42022380782). In addition, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines will be used to report this protocol.[26]

Study design

We will include randomised controlled trials (RCTs) that reported the efficacy of preemptive analgesia in TKA. The use of quasi-RCTs and non-RCTs, including sequentially assigned RCTs within the clinic, retrospective studies, letters, review articles, case reports, editorials, and animal experimental research, will be eliminated.

Type of participants/populations

All participants/populations with an indication for TKA surgery as determined by physicians and undergoing the procedure will be included. The participants in this study will not be limited by age, gender, race, surgery history, primary or revision TKA or underlying condition.

Type of interventions

In RCTs aimed at preemptive analgesia, any oral preemptive analgesic chosen prior to TKA will be permitted. The sample size, perioperative care, and underlying treatment of the study will not be restricted. However, nonpharmacological preemptive analgesia methods will be excluded.

Type of comparator groups

Comparator groups may employ a different type or method of oral preoperative analgesic medication, a placebo, or no preoperative analgesic medication. Studies with other types of interventions in the comparator groups will be excluded.

Types of outcome measures

Primary outcomes

Primary outcomes included the degree of improvement in knee pain and activity, and the use of perioperative analgesics.

- The visual analogue scale (VAS) dynamic pain score from 24 to 72h after surgery.
- The numerical pain rating scale (NRS) score from 24 to 72h after surgery.
- The keen Society Score (KSS) will be used to assess post-operative knee function.
- Consumption of analgesics from 24 to 72h after surgery.

Secondary outcomes

The following data will be collected for analysis as secondary outcomes: blood loss, length of hospitalization, adverse events, duration of surgery, postoperative nausea and vomiting, time to first mobilization, quality of life (QoL), readmission rates or perioperative care.

Search strategy

A systematic search of the PubMed, EMBASE, MEDLINE, the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews, from their inception to 1 February, 2023. There will be no restrictions on country, publication status or year of publication in the search of the above databases. Included in the list of predefined search terms are TKA, Preemptive Analgesia, RCTs, and similar topics. The search strategy will be modified for each individual database. Take PubMed as an example, the detailed search strategy was shown in **table 1**.

As a supplement, the following clinical registry platforms will be searched to collect data from ongoing studies: WHO International Clinical Trial Registration Platform (http://www.who.int/trialsearch/), Australian New Zealand Clinical Trials (http://www.anzctr.org.au/) and National Institutes of Health clinical registry (http://www.clinicaltrials.gov/). The detailed retrieval search strategies we have developed for each database are in **supplementary file**. If there is missing data, we will contact the correspondent or first author to complete it.

Study selection process

EndNote X9 (Thomson Reuters, New York, USA) software will be used to manage the literature and perform filtering, and categorize the document and remove duplicates. After classifying the literature and removing duplicates, two independent reviewers (F-JX and WZ) will review the titles and abstracts of the identified studies to exclude irrelevant parts. The full text will then be downloaded and submitted to two reviewers (S-JJ and X-RH) for the whole-length articles screening to identify studies that are ultimately suitable for meta-analysis. Throughout the procedure, any disagreement will be resolved by a third researcher (KS). **Figure 1** is a schematic

diagram of literature selection in this study.

Data extraction and management

Two independent reviewers (X-FL and H-JP) will use Microsoft Excel to independently extract and manage the data. The extracted data items include:

1) Study characteristics: title, first author name, publication year, country of publication and funding source.

2) Participants: sample size, gender, average age, race, disease course and preoperative pain score/knee function score.

3) Interventions/comparator groups: types of the treatment, types of analgesics, timing of intervention, clinical dosage and course of treatment.

4) Outcomes: Data relating to the primary and secondary outcomes at each measurement time will be recorded.

Before the formal data extraction, 10 studies were randomly selected to test and modify the pre-designed table. All data will be cross-checked. In addition, during the data extraction process, if there is any objection can be negotiated, or by a third reviewer (Y-ML) accuracy and consistency checking of data.

Risk of bias assessment

According to the current version of the Cochrane Risk of Bias Tool, two reviewers (F-JX and WZ) will independently assess the risk of bias, which included the seven specific domains： (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome data, (5) incomplete outcome data, (6) selective reporting, and (7) other bias.[27] If required, the third reviewer (Y-ML) will resolve divergent opinions.

Data synthesis and meta-analysis

Due to the study's exclusive reliance on RCTs, it may be susceptible to bias. Therefore, the outcomes of this study's data analysis should be carefully assessed.

Selection of effect measure

In this study, continuous outcome variables including VAS score, NRS score, KSS score, consumption of analgesics, blood loss, length of hospitalization, duration of surgery, time to first mobilization and QoL will use the standardized mean difference (SMD) as the effect measure. Dichotomous variables including adverse events, postoperative nausea and vomiting, readmission rates and perioperative care will use relative ratio (RR) to evaluate the effect measure. All effect measure will be expressed with 95% confidence intervals (CIs).

Statistical heterogeneity

The statistic I^2 will be used to measure the percentage of total variability due to heterogeneity between studies.[28] When the I^2 range is 0% to 30%, it indicates that heterogeneity may not be important. When the I^2 range is 30% to 75%, it indicates that moderate or substantial heterogeneity may present.[29] If I^2 over 75%, a descriptive analysis using a best-evidence synthesis approach will be performed without meta-analysis. In addition, we will evaluate clinical heterogeneity by assessing potential differences in the included studies, as it may still exist even in the absence of statistical heterogeneity.

Subgroup and sensitivity analyses

When the heterogeneity is excessive, we will investigate the potential origins of major inconsistencies or heterogeneity by meta-regression analysis and grouping. Age, primary or revision TKA, types of analgesics, duration of treatment, anaesthetic dosage, duration of operation, blood loss, and follow-up time are among the complicating factors that need to be analyzed. To uncover sources of bias and check the consistency of the meta-analysis conclusions, we will conduct a sensitivity analysis by excluding each study individually.

Meta-analysis

When we considered the included studies to be sufficiently similar, we will further

conduct a meta-analysis of the outcomes of each RCT individually. When multiple outcomes were available from a single study, the value was used which was thought to be best correlated to that time interval. A random effect model will be used for all analyses based upon the DerSimonian and Laird approach.[30] RevMan 5.4 (The Nordic Cochrane Center, The Cochrane Collaboration, Denmark) will be used to perform the meta-analysis.

Publication bias

If more than 10 studies are ultimately included, we will draw the Begg funnel plot to assess publication bias. The Egger test was then used to assess the asymmetry of the funnel plot.[31 32]

Quality of evidence

On the basis of the five components (limitations of design, inconsistency of results, indirectness, imprecision, and other factors), we will assess the quality of the evidence for all outcomes. The quality of evidence is divided into four levels: very low, low, model and high. GRADE profiler software will be used for the above evidence quality grading.[33]

Patient and public involvement

There will be no patients involved in this study.

Ethics and dissemination

No ethical approval and consent is required for this systematic review. Moreover, the results of this systematic review will be disseminated through peer-reviewed publications and conference presentations.

DISCUSSION

The majority of studies believe that preemptive analgesia is essential for promoting rapid recovery in TKA patients. The preemptive analgesic regimen for TKA is a

combination of different types of drugs and routes of administration, including mainly epidural analgesia, peripheral nerve blocks, local infiltration analgesia, intravenous analgesia and oral analgesics (opioid/non-opioid). Although the main thrust of all the preemptive analgesia methods is to provide better postoperative pain relief and reduce opioid consumption, we found that the different methods differed in terms of strengths and limitations. According to the 2019 International Consensus on Anaesthesia-Related Outcomes after Surgery group (ICAROS) consensus recommendation on anaesthetic care for TKA that primary neuraxial anaesthetic techniques including epidural analgesia are the preferred choice for TKA.[34] Its main drawback, however, is the unintentional motor nerve block, which delays physiotherapy and rehabilitation.[35] Peripheral nerve blocks, represented by femoral nerve blocks, are a common analgesic technique for TKA, but there is a risk of damage to adjacent blood vessels and nerves, as well as damage to local muscle strength.[36] As an alternative analgesic option to femoral nerve blocks, local infiltration analgesia is less likely to produce the above-mentioned risks, but its disadvantage is that there is no consensus on its optimal composition and infiltration technique and it remains to be further investigated.[37] Intravenous glucocorticoids are currently an element of multimodal salvage analgesia and have shown equally positive results in reducing pain and opioid consumption, but given the long-term safety risks associated with glucocorticoids, more evidence is still required to support them in clinical practice.[38] Oral analgesics, on the other hand, are widely utilized and well-tolerated as an preemptive analgesic option that optimises cost-effectiveness to a higher extent and helps to improve patient compliance and reduce the risk of anaesthesia. This is the main reason why we are concerned about oral analgesia.

However, Existing research on the role of oral analgesics in TKA pain treatment have generally concentrated on the efficacy of the medications, lacking a comprehensive evaluation of the overall benefits and safety of these drugs and neglecting the influence of confounding factors on clinical study outcomes.[39] A recent big NMA assessed the efficacy of oral preemptive analgesics on perioperative pain, showing the superiority of preemptive analgesia over traditional pain management

methods. However, the study did not account for variability between procedures and did not conduct additional subgroup analyses of drug doses, which may have been a major source of heterogeneity.[40] In our study, it is of considerable interest to undertake a novel and systematic investigation of TKA. It can enrich the evidence-based evidence for preemptive analgesia in TKA and provide a more convincing reference for pain management to surgeons. As only English-language database reports were considered for inclusion in this protocol, the exclusion of other databases may pose a risk of bias.

Contributors F-JX and WZ conceptualised the study and contributed equally to this work. S-JJ obtained funding, and together with F-JX, WZ, and Y-ML designed the study and drafted the initial manuscript. X-RH, X-FL, H-JP, KS were involved in the review and revision of the protocol. The grammar of this protocol has been improved by H-JP. Y-ML supervised the study. All authors read and approved the final version of the manuscript.

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Competing interests None declared.

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

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Figure legend

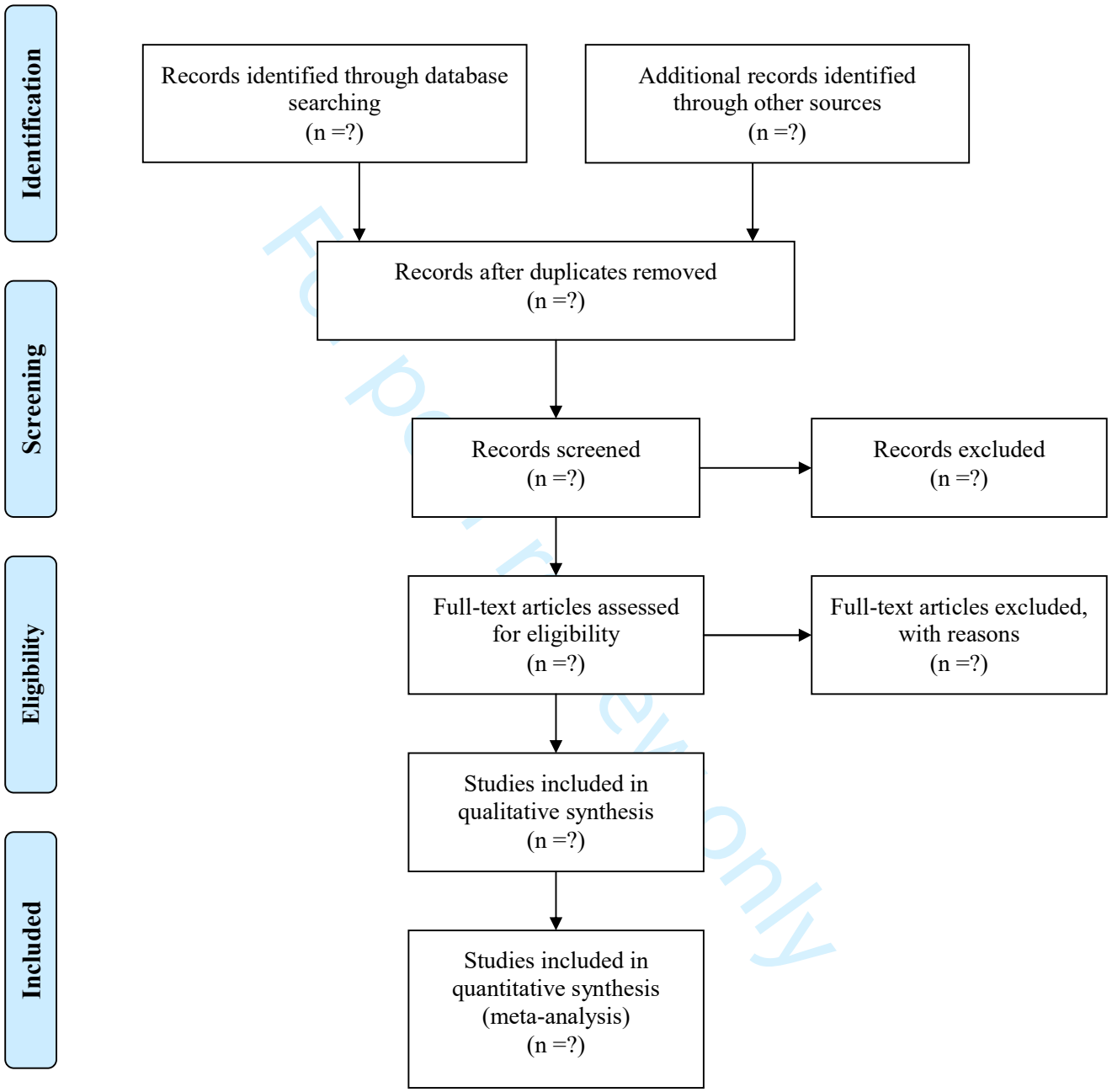
Figure 1. PRISMA flow diagram of study identification and selection.

Table legend

Table 1. Search strategy used in the PubMed database.

Table 1 Search strategy used in the PubMed database	
Number	Search terms
#1	Total knee arthroplasty [Mesh]
#2	Total knee arthroplasty [Title/Abstract] OR Knee Replacement Arthroplasty [Title/Abstract] OR Total Knee Replacement [Title/Abstract] OR Arthroplasties, Replacement, Knee [Title/Abstract] OR Arthroplasty, Knee Replacement [Title/Abstract] OR Arthroplasty, Total Knee [Title/Abstract] OR Knee Arthroplasty, Total [Title/Abstract] OR Replacement, Total Knee [Title/Abstract] OR Knee Replacement, Total [Title/Abstract]
#3	#1 OR #2
#4	Analgesia [Mesh]
#5	Analgesia [Title/Abstract] OR Analgesics [Title/Abstract] OR Anodynes [Title/Abstract] OR Analgesic Drugs [Title/Abstract] OR Analgesic [Title/Abstract] OR Analgesic Agents [Title/Abstract] OR Antinociceptive Agents [Title/Abstract] OR Analgesics, Non-Narcotic [Title/Abstract] OR Analgesics, Short-Acting [Title/Abstract] OR Analgesics, Opioid [Title/Abstract] OR Anti-Inflammatory Agents, Non-Steroidal [Title/Abstract]
#6	#4 OR #5
#7	Preoperative Period [Title/Abstract] OR Preoperative [Title/Abstract] OR Preemptive [Title/Abstract]
#8	Randomized controlled trial [Publication Type]
#9	Controlled clinical trial [Publication Type]
#10	Randomized [Title/Abstract]
#11	Randomly [Title/Abstract]
#12	Trial [Title/Abstract]
#13	#8 OR #9 OR #10 OR #11 OR #12
#14	#3 AND #6 AND #7 AND #13

450



PubMed (https://www.pubmed.ncbi.nlm.nih.gov)	
#1	Total knee arthroplasty [Mesh]
#2	Total knee arthroplasty [Title/Abstract] OR Knee Replacement Arthroplasty [Title/Abstract] OR Total Knee Replacement [Title/Abstract] OR Arthroplasties, Replacement, Knee [Title/Abstract] OR Arthroplasty, Knee Replacement [Title/Abstract] OR Arthroplasty, Total Knee [Title/Abstract] OR Knee Arthroplasty, Total [Title/Abstract] OR Replacement, Total Knee [Title/Abstract] OR Knee Replacement, Total [Title/Abstract]
#3	#1 OR #2
#4	Analgesia [Mesh]
#5	Analgesia [Title/Abstract] OR Analgesics [Title/Abstract] OR Anodynes [Title/Abstract] OR Analgesic Drugs [Title/Abstract] OR Analgesic [Title/Abstract] OR Analgesic Agents [Title/Abstract] OR Antinociceptive Agents [Title/Abstract] OR Analgesics, Non-Narcotic [Title/Abstract] OR Analgesics, Short-Acting [Title/Abstract] OR Analgesics, Opioid [Title/Abstract] OR Anti-Inflammatory Agents, Non-Steroidal [Title/Abstract]
#6	#4 OR #5
#7	Preoperative Period [Title/Abstract] OR Preoperative [Title/Abstract] OR Preemptive [Title/Abstract]
#8	Randomized controlled trial [Publication Type]
#9	Controlled clinical trial [Publication Type]
#10	Randomized [Title/Abstract]
#11	Randomly [Title/Abstract]
#12	Trial [Title/Abstract]
#13	#8 OR #9 OR #10 OR #11 OR #12
#14	#3 AND #6 AND #7 AND #13

MEDLINE (https://www.medline.eu/)	
#1	Total knee arthroplasty [Mesh]
#2	Total knee arthroplasty [Title/Abstract] OR Knee Replacement Arthroplasty [Title/Abstract] OR Total Knee Replacement [Title/Abstract] OR Arthroplasties, Replacement, Knee [Title/Abstract] OR Arthroplasty, Knee Replacement [Title/Abstract] OR Arthroplasty, Total Knee [Title/Abstract] OR Knee Arthroplasty, Total [Title/Abstract] OR Replacement, Total Knee [Title/Abstract] OR Knee Replacement, Total [Title/Abstract]
#3	#1 OR #2
#4	Analgesia [Mesh]
#5	Analgesia [Title/Abstract] OR Analgesics [Title/Abstract] OR Anodynes [Title/Abstract] OR Analgesic Drugs [Title/Abstract] OR Analgesic [Title/Abstract] OR Analgesic Agents [Title/Abstract] OR Antinociceptive Agents [Title/Abstract] OR Analgesics, Non-Narcotic [Title/Abstract] OR Analgesics, Short-Acting [Title/Abstract] OR Analgesics, Opioid [Title/Abstract] OR Anti-Inflammatory Agents, Non-Steroidal [Title/Abstract]
#6	#4 OR #5
#7	Preoperative Period [Title/Abstract] OR Preoperative [Title/Abstract] OR Preemptive [Title/Abstract]
#8	Randomized controlled trial [Publication Type]
#9	Controlled clinical trial [Publication Type]
#10	Randomized [Title/Abstract]
#11	Randomly [Title/Abstract]
#12	Trial [Title/Abstract]
#13	#8 OR #9 OR #10 OR #11 OR #12
#14	#3 AND #6 AND #7 AND #13

EMBASE (https://www.embase.com)	
#1	'total knee arthroplasty'/exp OR 'total knee arthroplasty':ab,ti OR 'knee replacement arthroplasty':ab,ti OR 'total knee replacement':ab,ti OR 'arthroplasties, replacement, knee':ab,ti OR 'arthroplasty, knee replacement':ab,ti OR 'arthroplasty, total knee':ab,ti OR 'knee arthroplasty, total':ab,ti OR 'replacement, total knee':ab,ti OR 'knee replacement, total':ab,ti OR 'TKA':ab,ti
#2	'analgesia'/exp OR 'analgesia':ab,ti OR 'analgesics':ab,ti OR 'anodynes':ab,ti OR 'analgesic Drugs':ab,ti OR 'analgesic':ab,ti OR 'analgesic agents':ab,ti OR 'antinociceptive agents':ab,ti OR 'analgesics, non-narcotic':ab,ti OR 'analgesics, short-acting':ab,ti OR 'analgesics, opioid':ab,ti OR 'anti-inflammatory agents, non-steroidal':ab,ti
#3	'preoperative period'/exp OR 'preoperative period':ab,ti OR 'preoperative':ab,ti OR 'preemptive ':ab,ti
#4	'randomized controlled trial'/exp
#5	#1 AND #2 AND #3 AND #4

Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews (https://www.cochranelibrary.com)	
#1	MeSH descriptor: [Arthroplasty, Replacement, Knee] explode all trees
#2	(Total knee arthroplasty OR Knee Replacement Arthroplasty OR Total Knee Replacement OR Arthroplasties, Replacement, Knee OR Arthroplasty, Knee Replacement OR Arthroplasty, Total Knee OR Knee Arthroplasty, Total OR Replacement, Total Knee OR Knee Replacement, Total):ti,ab,kw
#3	#1 OR #2
#4	MeSH descriptor: [Analgesia] explode all trees
#5	(Analgesia OR Analgesics OR Anodynes OR Analgesic Drugs OR

	Analgesic OR Analgesic Agents OR Antinociceptive Agents OR Analgesics, Non-Narcotic OR Analgesics, Short-Acting OR Analgesics, Opioid OR Anti-Inflammatory Agents, Non-Steroidal):ti,ab,kw
#6	#4 OR #5
#7	#3 AND #6

WHO International Clinical Trial Registration Platform (http://www.who.int/trialsearch/)
(Total knee arthroplasty OR Knee Replacement Arthroplasty OR Total Knee Replacement OR TKA) AND (Analgesia OR Analgesics OR Anodynes OR Analgesic Drugs OR Analgesic OR Analgesic Agents OR Antinociceptive Agents OR Analgesics, Non-Narcotic OR Analgesics, Short-Acting OR Analgesics, Opioid OR Anti-Inflammatory Agents, Non-Steroidal) AND (Preoperative Period OR Preoperative OR Preemptive)

Australian New Zealand Clinical Trials (http://www.anzctr.org.au/)	
Search fields	Search term
Condition or disease	Total knee arthroplasty
Study type	Interventional Studies (Clinical Trials)
Intervention/treatment	Analgesia

National Institutes of Health clinical registry (http://www.clinicaltrials.gov/)	
Search fields	Search term
Condition or disease	Total knee arthroplasty
Study type	Interventional Studies (Clinical Trials)
Intervention/treatment	Analgesia

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	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	#2
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	#1,12
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	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	#12
Sponsor	5b	Provide name for the review funder and/or sponsor	#12
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	#12
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	#3-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	#5-7
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	#5-7
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	#7
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	#7

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	#7
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)	#7-9
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	#7,8
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	#7,8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	#6,7
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	#8-10
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	#8-10
	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)	#9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	#8,9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	#9
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	#8,10
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	#10

*** 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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