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# BMJ Open

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

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Manuscripts

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4 **1 Title: Effect of oral preemptive analgesia on pain management after total knee**  
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6 **2 arthroplasty : A protocol for systematic review and meta-analysis**

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9 **3**

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37 Key words: Total knee arthroplasty; Preemptive analgesia; Pain management;  
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39 Systematic review; Meta-analysis; Protocol  
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## 20 ABSTRACT

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

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

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

43 **PROSPERO registration number** CRD42022380782

## 44 Article Summary

45 Strengths and limitations of this study

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

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

## 54

### 55 INTRODUCTION

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

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

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

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4 80 survey conducted by the health services.<sup>11</sup> According to research conducted in the  
5  
6 81 United States, patients undergoing joint replacement surgery are more likely to  
7  
8 82 consume opioids than those undergoing other surgical procedures.<sup>12 13</sup> All of the  
9  
10 83 aforementioned may delay the recovery process, diminish the patient's postoperative  
11  
12 84 quality of life, and even increase the TKA revision rate, thereby increasing the  
13  
14 85 patient's financial burden. Adoption of a high-quality pain management model is thus  
15  
16 86 an urgent requirement for initial functional recovery after TKA.

17  
18 87 Preemptive analgesia is an efficient method for achieving rapid postoperative  
19  
20 88 recuperation and optimising pain management. Preemptive refers to analgesic  
21  
22 89 interventions administered prior to the onset of noxious stimuli to prevent the  
23  
24 90 development of central sensitization, incision, and inflammatory damage, and has  
25  
26 91 been shown to be more effective than the same interventions administered after  
27  
28 92 surgery.<sup>14 15</sup> By preventing the sensitization of the central nervous system caused by  
29  
30 93 painful stimuli, appropriate interventions can attenuate the response to future injurious  
31  
32 94 sensory input and reduce the sensitization of the central nervous system, so that  
33  
34 95 normally painful stimuli become less painful or even painless. The mechanism of  
35  
36 96 action may involve the inhibition of cytokine and prostaglandin release-induced  
37  
38 97 modifications in central sensory processes, as well as the suppression of inflammatory  
39  
40 98 reactions.<sup>16-18</sup> Current research indicates that preemptive analgesia can minimise the  
41  
42 99 chance of developing chronic pain, improve pain management, and boost the efficacy  
43  
44 100 of other treatment modalities.<sup>19</sup> The network meta-analysis (NMA) revealed that  
45  
46 101 various preventive analgesic medicines or strategies reduced postoperative pain,  
47  
48 102 opioid intake, and postoperative side effects to diverse degrees.<sup>20</sup> As the notion of  
49  
50 103 preemptive analgesia has acquired widespread recognition in the field of surgery, the  
51  
52 104 investigation of preemptive analgesia to improve the overall benefit to the  
53  
54 105 postoperative patient has become one of the clinical and scientific hotspots of the  
55  
56 106 moment. Diverse techniques, such as preemptive epidural, local wound infiltration,  
57  
58 107 opioids, NMDA receptor antagonists, and nonsteroidal anti-inflammatory drugs  
59  
60 108 (NSAIDs), are used for preemptive analgesia.<sup>21 22</sup> This study focuses on the role of  
109 109 oral medicine as a preventative multimodal analgesic.

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4 110 Nevertheless, there is debate in the existing literature regarding the efficacy and  
5  
6 111 safety of preventive analgesics. Wang C et al. examined the efficacy and safety of  
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8 112 preoperative selective COX-2 inhibitor administration in TKA patients. A  
9  
10 113 meta-analysis discovered that selective COX-2 inhibitors decreased postoperative  
11  
12 114 pain and opioid intake in TKA patients, but there were no significant differences in  
13  
14 115 time to operation or adverse effects.<sup>23</sup> However, in another randomised controlled  
15  
16 116 trial, Qiuru Wang et al. reported that the opioid oxycodone did not produce a  
17  
18 117 substantial preemptive analgesic effect in TKA patients.<sup>24</sup> Similar contradictory  
19  
20 118 results were observed in investigations of medications such as gabapentins and  
21  
22 119 acetaminophen.<sup>25</sup> Evidently, a rigorous clinical review and evidence validating the  
23  
24 120 efficacy and advantages of preemptive analgesia in TKA are still lacking.

25 121 The objective of this systematic review (SR) and meta-analysis was to evaluate the  
26  
27 122 efficacy of several oral preemptive analgesics for the management of pain in TKA  
28  
29 123 patients.

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## 32 33 125 **METHODS**

### 34 35 126 **Eligibility criteria**

36  
37 127 Protocol for meta-analysis registered with International Prospective Register of  
38  
39 128 Systematic Review (Prospero CRD 42022380782). This review protocol will adhere  
40  
41 129 to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols  
42  
43 130 (PRISMA-P) guideline.<sup>26</sup>

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45 131

### 46 47 132 **Study design**

48  
49 133 We will include randomised controlled trials (RCTs) that reported the efficacy of  
50  
51 134 preemptive analgesia in TKA. The use of quasi-RCTs and non-RCTs, including  
52  
53 135 sequentially assigned RCTs within the clinic, retrospective studies, letters, review  
54  
55 136 articles, case reports, editorials, and animal experimental research, would be  
56  
57 137 eliminated.

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59 138

60 139 Type of participants/populations

1  
2  
3  
4 140 All participants/populations with an indication for TKA surgery as determined by  
5  
6 141 physicians and undergoing the procedure will be included. The participants in this  
7  
8 142 study will not be limited by age, gender, race, surgery history, or underlying  
9  
10 143 condition.

11  
12 144  
13 145 Type of interventions

14  
15 146 In RCTs aimed at preemptive analgesia, any oral preemptive analgesic chosen prior to  
16  
17 147 TKA will be permitted. The sample size, perioperative care, and underlying treatment  
18  
19 148 of the study will not be restricted. However, nonpharmacological preemptive  
20  
21 149 analgesia methods will be excluded.

22  
23 150

24  
25 151 Type of comparator groups

26  
27 152 Comparator groups may employ a different type or method of preoperative analgesic  
28  
29 153 medication, a placebo, or no preoperative analgesic medication. Studies with other  
30  
31 154 types of interventions in the comparator groups will be excluded.

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35 156 Types of outcome measures

36  
37 157 *Primary outcomes*

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39 158 Primary outcomes included the degree of improvement in knee pain and activity, and  
40  
41 159 the use of perioperative analgesics.

42  
43 160 ● The visual analogue scale (VAS) dynamic pain score from 24 to 72h after  
44  
45 161 surgery.

46  
47 162 ● The numerical pain rating scale (NRS) score from 24 to 72h after surgery.

48  
49 163 ● The keen Society Score (KSS) will be used to assess post-operative knee  
50  
51 164 function.

52  
53 165 ● Consumption of analgesics from 24 to 72h after surgery.

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57 167 *Secondary outcomes*

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59 168 The following data will be collected for analysis as secondary outcomes: blood loss,  
60  
169 length of hospitalization, adverse events, duration of surgery, postoperative nausea



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4 170 and vomiting, time to first mobilization, quality of life (QoL), readmission rates or  
5 171 perioperative care.

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### 8 9 173 **Search strategy**

10  
11 174 A systematic search of the PubMed, EMBASE, MEDLINE, the Cochrane Central  
12  
13 175 Register of Controlled Trials and the Cochrane Database of Systematic Reviews, from  
14  
15 176 their inception to 1 February, 2023. There will be no restrictions on language,  
16  
17 177 country, publication status or year of publication. Included in the list of predefined  
18  
19 178 search terms are TKA, Preemptive Analgesia, RCTs, and similar topics. The search  
20  
21 179 strategy will be modified for each individual database. Take PubMed as an example,  
22  
23 180 the detailed search strategy was shown in **table 1**.

24  
25 181 As a supplement, the following clinical registry platforms will be searched to  
26  
27 182 collect data from ongoing studies: WHO International Clinical Trial Registration  
28  
29 183 Platform (<http://www.who.int/trialsearch/>), Australian New Zealand Clinical Trials  
30  
31 184 (<http://www.anzctr.org.au/>) and National Institutes of Health clinical registry  
32  
33 185 (<http://www.clinicaltrials.gov/>). If there is missing data, we will contact the  
34  
35 186 correspondent or first author to complete it.

36  
37 187

### 38 39 188 **Study selection process**

40  
41 189 EndNote X9 (Thomson Reuters, New York, USA) software will be used to manage  
42  
43 190 the literature and perform filtering, and categorize the document and remove  
44  
45 191 duplicates. After classifying the literature and removing duplicates, two independent  
46  
47 192 reviewers (F-JX and WZ) review the titles and abstracts of the identified studies to  
48  
49 193 exclude irrelevant parts. The full text will then be downloaded and submitted to two  
50  
51 194 reviewers (S-JJ and X-RH) for the whole-length articles screening to identify studies  
52  
53 195 that are ultimately suitable for meta-analysis. Throughout the procedure, any  
54  
55 196 disagreement will be resolved by a third researcher (KS). **Figure 1** is a schematic  
56  
57 197 diagram of literature selection in this study.

58  
59 198

### 60 199 **Data extraction and management**

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

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

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

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

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

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

214

### 215 **Risk of bias assessment**

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

222

### 223 **Data synthesis and meta-analysis**

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

226

227 Selection of effect measure

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

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4 230 surgery, time to first mobilization and QoL will use the standardized mean difference  
5 231 (SMD) as the effect measure. Dichotomous variables including adverse events,  
6 232 postoperative nausea and vomiting, readmission rates and perioperative care will use  
7  
8 233 relative ratio (RR) to evaluate the effect measure. All effect measure will be expressed  
9  
10 234 with 95% confidence intervals (CIs).

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13 235

#### 14 236 Statistical heterogeneity

15 237 Examine and quantify the heterogeneity by inspecting the Forest plot, and assess the  
16  
17 238 size of the heterogeneity by  $I^2$ . Heterogeneity will not be considered when  $I^2$  value is  
18  
19 239 less than 50%. At this point the meta-analysis will be performed by using the fixed-  
20  
21 240 effect model. On the contrary, when the  $I^2$  value is greater than 50%, we consider that  
22  
23 241 there to be substantial heterogeneity and will use the random-effect model for data  
24  
25 242 analysis. If the meta-analysis is inappropriate, we will undertake a descriptive  
26  
27 243 synthesis using a best-evidence synthesis approach.

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#### 32 245 Subgroup and sensitivity analyses

33 246 When the heterogeneity is excessive, we will investigate the potential origins of major  
34  
35 247 inconsistencies or heterogeneity by meta-regression analysis and grouping. Age, types  
36  
37 248 of analgesics, duration of treatment, anaesthetic dosage, duration of operation, blood  
38  
39 249 loss, and follow-up time are among the complicating factors that need to be analyzed.  
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41 250 To uncover sources of bias and check the consistency of the meta-analysis  
42  
43 251 conclusions, we will conduct a sensitivity analysis by excluding each study  
44  
45 252 individually.

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#### 49 254 Meta-analysis

50 255 When the heterogeneity is moderate, we will further conduct a meta-analysis of the  
51  
52 256 outcomes of each RCT individually. When multiple outcomes were available from a  
53  
54 257 single study, the value was used which was thought to be best correlated to that time  
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56 258 interval. A random effect model will be used for all analyses based upon the  
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58 259 DerSimonian and Laird approach.<sup>28</sup> RevMan 5.4 (The Nordic Cochrane Center, The

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4 260 Cochrane Collaboration, Denmark) will be used to perform the meta-analysis.

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8 262 Publication bias

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10 263 If more than 10 studies are ultimately included, we will draw the Begg funnel plot to  
11  
12 264 assess publication bias. The Egger test was then used to assess the asymmetry of the  
13  
14 265 funnel plot.<sup>29 30</sup>

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18 267 Quality of evidence

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20 268 On the basis of the five components (limitations of design, inconsistency of results,  
21  
22 269 indirectness, imprecision, and other factors), we will assess the quality of the evidence  
23  
24 270 for all outcomes. The quality of evidence is divided into four levels: very low, low,  
25  
26 271 model and high. GRADE profiler software will be used for the above evidence quality  
27  
28 272 grading.<sup>31</sup>

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32 274 **Patient and public involvement**

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34 275 There will be no patients involved in this study.

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38 277 **Ethics and dissemination**

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40 278 No ethical approval and consent is required for this systematic review. Moreover, the  
41  
42 279 results of this systematic review will be disseminated through peer-reviewed  
43  
44 280 publications and conference presentations.

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48 282 **DISCUSSION**

49  
50 283 The majority of studies believe that preemptive analgesia is essential for promoting  
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52 284 rapid recovery in TKA patients. Existing research on the role of oral analgesics in  
53  
54 285 TKA pain treatment have generally concentrated on the efficacy of the medications,  
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56 286 lacking a comprehensive evaluation of the overall benefits and safety of these drugs  
57  
58 287 and neglecting the influence of confounding factors on clinical study outcomes.<sup>32</sup> A  
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60 288 recent big NMA assessed the efficacy of oral preemptive analgesics on perioperative  
289 pain, showing the superiority of preemptive analgesia over traditional pain

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4 290 management methods. However, the study did not account for variability between  
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6 291 procedures and did not conduct additional subgroup analyses of drug doses, which  
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8 292 may have been a major source of heterogeneity.<sup>33</sup> In our study, it is of considerable  
9  
10 293 interest to undertake a novel and systematic investigation of TKA. It can enrich the  
11  
12 294 evidence-based evidence for preemptive analgesia in TKA and provide a more  
13  
14 295 convincing reference for pain management to surgeons. As only English-language  
15  
16 296 database reports were considered for inclusion in this protocol, the exclusion of other  
17  
18 297 databases may pose a risk of bias.

19 298

21 299 **Contributors** F-JX and WZ conceptualised the study and contributed equally to this  
22  
23 300 work. F-JX, WZ, Y-ML and S-JJ designed the study and drafted the initial  
24  
25 301 manuscript. X-RH, X-FL, H-JP, KS were involved in the review and revision of the  
26  
27 302 protocol. The grammar of this protocol has been improved by H-JP. Y-ML supervised  
28  
29 303 the study. All authors read and approved the final version of the manuscript.

31 304

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34  
35 306 of Traditional Chinese Medicine (2020LC0050).

37 307

39 308 **Competing interests** None declared.

41 309

43 310 **Patient and public involvement** Patients and/or the public were not involved in the  
44  
45 311 design, or conduct, or reporting, or dissemination plans of this research.

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**393 Figure legend**

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

**395**

**396 Table legend**

**397** Table 1. Search strategy used in the PubMed database.

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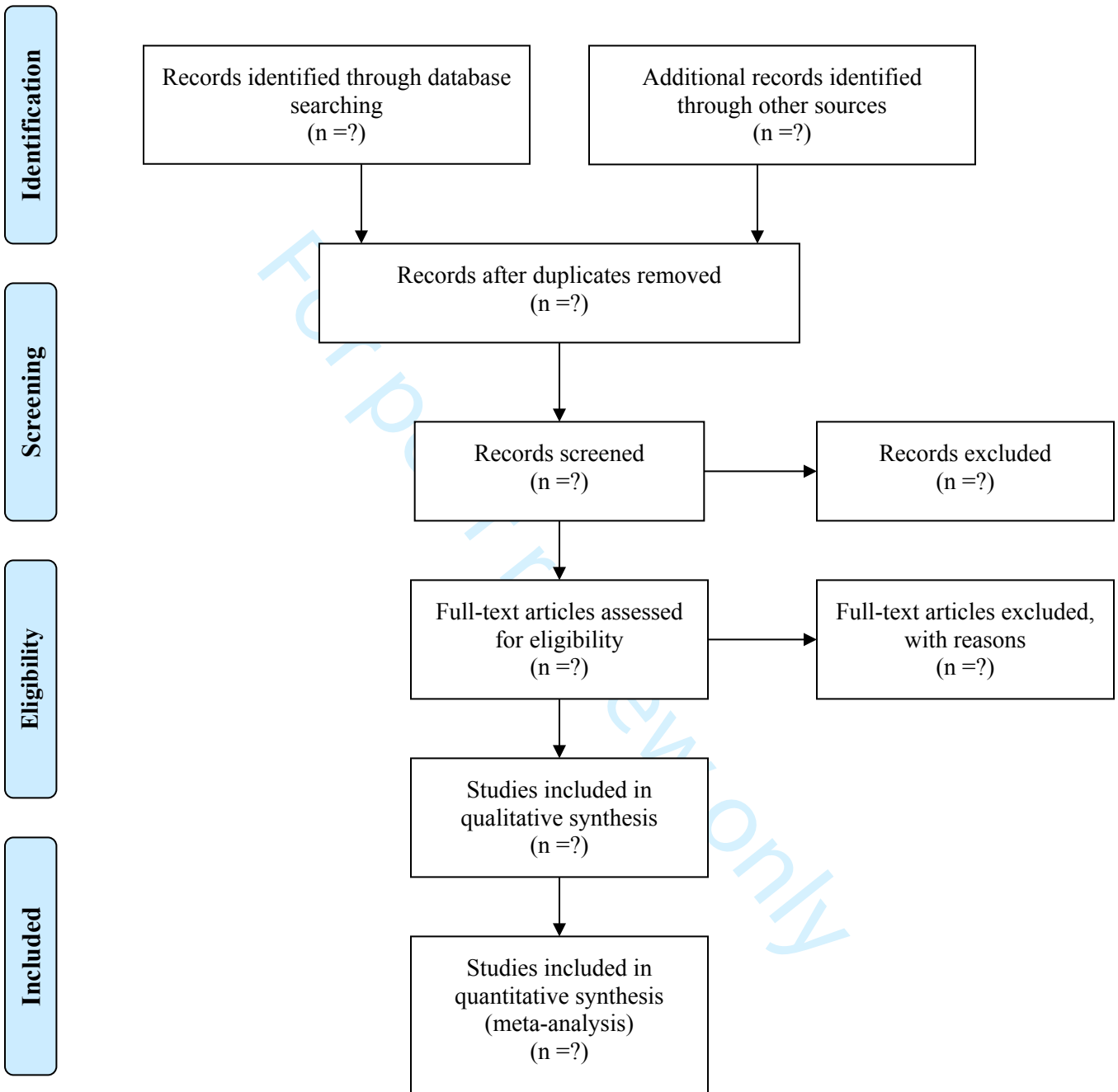
Table 1 Search strategy used in the PubMed database

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 #
<b>ADMINISTRATIVE INFORMATION</b>			
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	-
<b>INTRODUCTION</b>			
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
<b>METHODS</b>			
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 $\tau$ )	#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.**

*From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.*

# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-070998.R1
Article Type:	Protocol
Date Submitted by the Author:	06-Mar-2023
Complete List of Authors:	Xiong, Fan-jie; The First Affiliated Hospital of Traditional Chinese Medicine of Chengdu Medical College Zhao, Wei; The First Affiliated Hospital of Traditional Chinese Medicine of Chengdu Medical College Jia, Shi-jian; The First Affiliated Hospital of Traditional Chinese Medicine of Chengdu Medical College Huang, Xiao-rong; The First Affiliated Hospital of Traditional Chinese Medicine of Chengdu Medical College Luo, Xiang-fei; The First Affiliated Hospital of Traditional Chinese Medicine of Chengdu Medical College Pu, Hong-jiang; University of York Song, Kai; Sichuan Vocational College of Health and Rehabilitation Li, Yan-ming; The First Affiliated Hospital of Traditional Chinese Medicine of Chengdu Medical College, Department of Acupuncture
<b>Primary Subject Heading</b>:	Surgery
Secondary Subject Heading:	Anaesthesia, Rehabilitation medicine
Keywords:	Knee < ORTHOPAEDIC & TRAUMA SURGERY, Anaesthesia in orthopaedics < ANAESTHETICS, Pain management < ANAESTHETICS

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Manuscripts

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4 **1 Title: Effect of oral preemptive analgesia on pain management after total knee**  
5 **2 arthroplasty : A protocol for systematic review and meta-analysis**  
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18 Key words: Total knee arthroplasty; Preemptive analgesia; Pain management;  
19 Systematic review; Meta-analysis; Protocol  
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## 20 **ABSTRACT**

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

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

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

44 **PROSPERO registration number** CRD42022380782

### 45 **Article Summary**

46 Strengths and limitations of this study

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

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4 50 duration of treatment, anesthetic dose, duration of operation, amount of blood  
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6 51 loss, and duration of follow-up will be performed.

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8 52 ● This review protocol is reported referring to the recommendations of the  
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10 53 Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols.

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12 54 ● The inclusion of studies in databases containing only English-language entries  
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14 55 may result in potential bias.

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## 17 57 **INTRODUCTION**

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19 58 As the world's population grows and inevitably ages, the number of people diagnosed  
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21 59 with osteoarthritis is expected to rise by 40% by 2035.<sup>1</sup> Knee osteoarthritis is a  
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23 60 common condition that causes significant pain and disability among patients.  
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25 61 According to Murphy et al., the lifetime risk of symptomatic knee osteoarthritis is  
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27 62 estimated to be approximately 45%.<sup>2</sup> As a result, this patient group constitutes a  
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29 63 significant proportion of potential total knee arthroplasty (TKA) candidates. TKA is  
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31 64 currently regarded as an effective treatment for knee osteoarthritis, relieving patients'  
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33 65 pain and significantly enhancing their quality of life and activity levels, allowing them  
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35 66 to return to work and daily activities after surgery.<sup>3</sup> Given the substantial medium- or  
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37 67 long-term benefits of TKA, both clinicians and patients have embraced the procedure.

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39 68 However, not every patient will recover well. Despite the fact that the success rate  
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41 69 of TKA is between 80 and 90%, up to 30% of patients are reported to be dissatisfied.  
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43 70 The level of dissatisfaction with pain relief among these individuals ranged from 14%  
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45 71 to 28%.<sup>4 5</sup> This was primarily due to the persistent post-operative knee pain. Due to  
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47 72 the significance of the knee in daily activities, even when mobility is commensurate  
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49 73 with activity levels, some TKA patients report significant residual pain, which  
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51 74 frequently develops into chronic pain.<sup>6 7</sup> Managing pain following knee surgery is  
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53 75 another inevitable challenge for clinicians. Because pain is considered a subjective  
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55 76 sensation, the degree and threshold of perception vary from person to person; this,  
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57 77 combined with the complexity of factors affecting postoperative pain, makes it  
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59 78 challenging to analyse and manage pain through specific pain mechanisms.<sup>8-10</sup>

60 79 The various adverse effects of opioid abuse include nausea, vomiting, sedation,

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4 80 intestinal obstruction, respiratory depression, and itchiness. Three weeks after hospital  
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6 81 discharge, over 70% of post-TKA patients are still taking opioids, according to a  
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8 82 survey conducted by the health services.<sup>11</sup> According to research conducted in the  
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10 83 United States, patients undergoing joint replacement surgery are more likely to  
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12 84 consume opioids than those undergoing other surgical procedures.<sup>12 13</sup> Both  
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14 85 post-operative knee pain and opioid abuse may delay the recovery process, diminish  
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16 86 the patient's postoperative quality of life, and even increase the TKA revision rate,  
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18 87 thereby increasing the patient's financial burden. Adoption of a high-quality pain  
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20 88 management model is thus an urgent requirement for initial functional recovery after  
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22 89 TKA.

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24 90 Preemptive analgesia is an efficient method for achieving rapid postoperative  
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26 91 recuperation and optimising pain management. Preemptive refers to analgesic  
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28 92 interventions administered prior to the onset of noxious stimuli to prevent the  
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30 93 development of central sensitization, incision, and inflammatory damage, and has  
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32 94 been shown to be more effective than the same interventions administered after  
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34 95 surgery.<sup>14 15</sup> By preventing the sensitization of the central nervous system caused by  
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36 96 painful stimuli, appropriate interventions can attenuate the response to future injurious  
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38 97 sensory input and reduce the sensitization of the central nervous system, so that  
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40 98 normally painful stimuli become less painful or even painless. The mechanism of  
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42 99 action may involve the inhibition of cytokine and prostaglandin release-induced  
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44 100 modifications in central sensory processes, as well as the suppression of inflammatory  
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46 101 reactions.<sup>16-18</sup> Current research indicates that preemptive analgesia can minimise the  
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48 102 chance of developing chronic pain, improve pain management, and boost the efficacy  
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50 103 of other treatment modalities.<sup>19</sup> The network meta-analysis (NMA) revealed that  
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52 104 various preventive analgesic medicines or strategies reduced postoperative pain,  
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54 105 opioid intake, and postoperative side effects to diverse degrees.<sup>20</sup> As the notion of  
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56 106 preemptive analgesia has acquired widespread recognition in the field of surgery, the  
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58 107 investigation of preemptive analgesia to improve the overall benefit to the  
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60 108 postoperative patient has become one of the clinical and scientific hotspots of the  
109 109 moment. Diverse techniques, such as epidural analgesia, peripheral nerve blocks,

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4 110 local infiltration analgesia, opioids, NMDA receptor antagonists, and nonsteroidal  
5 111 anti-inflammatory drugs (NSAIDs), are used for preemptive analgesia.<sup>21 22</sup> This study  
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7 112 focuses on the role of oral medicine as a preventative multimodal analgesic.  
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10 113 Nevertheless, there is debate in the existing literature regarding the efficacy and  
11 114 safety of preventive analgesics. Wang C et al. examined the efficacy and safety of  
12 115 preoperative selective COX-2 inhibitor administration in TKA patients. A  
13 116 meta-analysis discovered that selective COX-2 inhibitors decreased postoperative  
14 117 pain and opioid intake in TKA patients, but there were no significant differences in  
15 118 time to operation or adverse effects.<sup>23</sup> However, in another randomised controlled  
16 119 trial, Qiuru Wang et al. reported that the opioid oxycodone did not produce a  
17 120 substantial preemptive analgesic effect in TKA patients.<sup>24</sup> Similar contradictory  
18 121 results were observed in investigations of medications such as gabapentins and  
19 122 acetaminophen.<sup>25</sup> Evidently, a rigorous clinical review and evidence validating the  
20 123 efficacy and advantages of preemptive analgesia in TKA are still lacking.  
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23 124 The objective of this systematic review (SR) and meta-analysis was to evaluate the  
24 125 efficacy of several oral preemptive analgesics for the management of pain in TKA  
25 126 patients.  
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## 29 128 **METHODS**

### 30 129 **Eligibility criteria**

31 130 Protocol for meta-analysis registered with International Prospective Register of  
32 131 Systematic Review (Prospero CRD 42022380782). In addition, the Preferred  
33 132 Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P)  
34 133 guidelines will be used to report this protocol.<sup>26</sup>  
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### 38 135 **Study design**

39 136 We will include randomised controlled trials (RCTs) that reported the efficacy of  
40 137 preemptive analgesia in TKA. The use of quasi-RCTs and non-RCTs, including  
41 138 sequentially assigned RCTs within the clinic, retrospective studies, letters, review  
42 139 articles, case reports, editorials, and animal experimental research, will be eliminated.  
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5 141 Type of participants/populations

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7 142 All participants/populations with an indication for TKA surgery as determined by  
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9 143 physicians and undergoing the procedure will be included. The participants in this  
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11 144 study will not be limited by age, gender, race, surgery history, primary or revision  
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13 145 TKA or underlying condition.  
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17 147 Type of interventions

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19 148 In RCTs aimed at preemptive analgesia, any oral preemptive analgesic chosen prior to  
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21 149 TKA will be permitted. The sample size, perioperative care, and underlying treatment  
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23 150 of the study will not be restricted. However, nonpharmacological preemptive  
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25 151 analgesia methods will be excluded.  
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29 153 Type of comparator groups

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31 154 Comparator groups may employ a different type or method of oral preoperative  
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33 155 analgesic medication, a placebo, or no preoperative analgesic medication. Studies  
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35 156 with other types of interventions in the comparator groups will be excluded.  
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39 158 Types of outcome measures

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41 159 *Primary outcomes*

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43 160 Primary outcomes included the degree of improvement in knee pain and activity, and  
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45 161 the use of perioperative analgesics.

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47 162 ● The visual analogue scale (VAS) dynamic pain score from 24 to 72h after  
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49 163 surgery.

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51 164 ● The numerical pain rating scale (NRS) score from 24 to 72h after surgery.

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53 165 ● The keen Society Score (KSS) will be used to assess post-operative knee  
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55 166 function.

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57 167 ● Consumption of analgesics from 24 to 72h after surgery.  
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60 169 *Secondary outcomes*

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4 170 The following data will be collected for analysis as secondary outcomes: blood loss,  
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6 171 length of hospitalization, adverse events, duration of surgery, postoperative nausea  
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8 172 and vomiting, time to first mobilization, quality of life (QoL), readmission rates or  
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10 173 perioperative care.

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### 13 175 **Search strategy**

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15 176 A systematic search of the PubMed, EMBASE, MEDLINE, the Cochrane Central  
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17 177 Register of Controlled Trials and the Cochrane Database of Systematic Reviews, from  
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19 178 their inception to 1 February, 2023. There will be no restrictions on country,  
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21 179 publication status or year of publication in the search of the above databases. Included  
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23 180 in the list of predefined search terms are TKA, Preemptive Analgesia, RCTs, and  
24  
25 181 similar topics. The search strategy will be modified for each individual database. Take  
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27 182 PubMed as an example, the detailed search strategy was shown in **table 1**.

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29 183 As a supplement, the following clinical registry platforms will be searched to  
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31 184 collect data from ongoing studies: WHO International Clinical Trial Registration  
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33 185 Platform (<http://www.who.int/trialsearch/>), Australian New Zealand Clinical Trials  
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35 186 (<http://www.anzctr.org.au/>) and National Institutes of Health clinical registry  
36  
37 187 (<http://www.clinicaltrials.gov/>). The detailed retrieval search strategies we have  
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39 188 developed for each database are in **supplementary file**. If there is missing data, we  
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41 189 will contact the correspondent or first author to complete it.

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### 44 191 **Study selection process**

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46 192 EndNote X9 (Thomson Reuters, New York, USA) software will be used to manage  
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48 193 the literature and perform filtering, and categorize the document and remove  
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50 194 duplicates. After classifying the literature and removing duplicates, two independent  
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52 195 reviewers (F-JX and WZ) will review the titles and abstracts of the identified studies  
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54 196 to exclude irrelevant parts. The full text will then be downloaded and submitted to  
55  
56 197 two reviewers (S-JJ and X-RH) for the whole-length articles screening to identify  
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58 198 studies that are ultimately suitable for meta-analysis. Throughout the procedure, any  
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60 199 disagreement will be resolved by a third researcher (KS). **Figure 1** is a schematic

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4 200 diagram of literature selection in this study.

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8 202 **Data extraction and management**

9  
10 203 Two independent reviewers (X-FL and H-JP) will use Microsoft Excel to  
11 204 independently extract and manage the data. The extracted data items include:

12  
13 205 1) Study characteristics: title, first author name, publication year, country of  
14 206 publication and funding source.

15  
16 207 2) Participants: sample size, gender, average age, race, disease course and  
17 208 preoperative pain score/knee function score.

18  
19 209 3) Interventions/comparator groups: types of the treatment, types of analgesics, timing  
20 210 of intervention, clinical dosage and course of treatment.

21  
22 211 4) Outcomes: Data relating to the primary and secondary outcomes at each  
23 212 measurement time will be recorded.

24  
25 213 Before the formal data extraction, 10 studies were randomly selected to test and  
26 214 modify the pre-designed table. All data will be cross-checked. In addition, during the  
27 215 data extraction process, if there is any objection can be negotiated, or by a third  
28 216 reviewer (Y-ML) accuracy and consistency checking of data.

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32 218 **Risk of bias assessment**

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34 219 According to the current version of the Cochrane Risk of Bias Tool, two reviewers  
35 220 (F-JX and WZ) will independently assess the risk of bias, which included the seven  
36 221 specific domains: (1) random sequence generation, (2) allocation concealment, (3)  
37 222 blinding of participants and personnel, (4) blinding of outcome data, (5) incomplete  
38 223 outcome data, (6) selective reporting, and (7) other bias.<sup>27</sup> If required, the third  
39 224 reviewer (Y-ML) will resolve divergent opinions.

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42  
43 226 **Data synthesis and meta-analysis**

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45 227 Due to the study's exclusive reliance on RCTs, it may be susceptible to bias.  
46 228 Therefore, the outcomes of this study's data analysis should be carefully assessed.

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48 229

### 230 Selection of effect measure

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

238

### 239 Statistical heterogeneity

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

248

### 249 Subgroup and sensitivity analyses

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

257

### 258 Meta-analysis

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



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4 260 conduct a meta-analysis of the outcomes of each RCT individually. When multiple  
5  
6 261 outcomes were available from a single study, the value was used which was thought  
7  
8 262 to be best correlated to that time interval. A random effect model will be used for all  
9  
10 263 analyses based upon the DerSimonian and Laird approach.<sup>30</sup> RevMan 5.4 (The Nordic  
11  
12 264 Cochrane Center, The Cochrane Collaboration, Denmark) will be used to perform the  
13  
14 265 meta-analysis.

#### 15 266 16 17 267 **Publication bias**

18  
19 268 If more than 10 studies are ultimately included, we will draw the Begg funnel plot to  
20  
21 269 assess publication bias. The Egger test was then used to assess the asymmetry of the  
22  
23 270 funnel plot.<sup>31 32</sup>

24  
25 271

#### 26 27 272 **Quality of evidence**

28  
29 273 On the basis of the five components (limitations of design, inconsistency of results,  
30  
31 274 indirectness, imprecision, and other factors), we will assess the quality of the evidence  
32  
33 275 for all outcomes. The quality of evidence is divided into four levels: very low, low,  
34  
35 276 model and high. GRADE profiler software will be used for the above evidence quality  
36  
37 277 grading.<sup>33</sup>

38  
39 278

#### 40 41 279 **Patient and public involvement**

42  
43 280 There will be no patients involved in this study.

44  
45 281

#### 46 47 282 **Ethics and dissemination**

48  
49 283 No ethical approval and consent is required for this systematic review. Moreover, the  
50  
51 284 results of this systematic review will be disseminated through peer-reviewed  
52  
53 285 publications and conference presentations.

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#### 56 57 287 **DISCUSSION**

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59 288 The majority of studies believe that preemptive analgesia is essential for promoting  
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289 rapid recovery in TKA patients. The preemptive analgesic regimen for TKA is a

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4 290 combination of different types of drugs and routes of administration, including mainly  
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6 291 epidural analgesia, peripheral nerve blocks, local infiltration analgesia, intravenous  
7  
8 292 analgesia and oral analgesics (opioid/non-opioid). Although the main thrust of all the  
9  
10 293 preemptive analgesia methods is to provide better postoperative pain relief and reduce  
11  
12 294 opioid consumption, we found that the different methods differed in terms of  
13  
14 295 strengths and limitations. According to the 2019 International Consensus on  
15  
16 296 Anaesthesia-Related Outcomes after Surgery group (ICAROS) consensus  
17  
18 297 recommendation on anaesthetic care for TKA that primary neuraxial anaesthetic  
19  
20 298 techniques including epidural analgesia are the preferred choice for TKA.<sup>34</sup> Its main  
21  
22 299 drawback, however, is the unintentional motor nerve block, which delays  
23  
24 300 physiotherapy and rehabilitation.<sup>35</sup> Peripheral nerve blocks, represented by femoral  
25  
26 301 nerve blocks, are a common analgesic technique for TKA, but there is a risk of  
27  
28 302 damage to adjacent blood vessels and nerves, as well as damage to local muscle  
29  
30 303 strength.<sup>36</sup> As an alternative analgesic option to femoral nerve blocks, local infiltration  
31  
32 304 analgesia is less likely to produce the above-mentioned risks, but its disadvantage is  
33  
34 305 that there is no consensus on its optimal composition and infiltration technique and it  
35  
36 306 remains to be further investigated.<sup>37</sup> Intravenous glucocorticoids are currently an  
37  
38 307 element of multimodal salvage analgesia and have shown equally positive results in  
39  
40 308 reducing pain and opioid consumption, but given the long-term safety risks associated  
41  
42 309 with glucocorticoids, more evidence is still required to support them in clinical  
43  
44 310 practice.<sup>38</sup> Oral analgesics, on the other hand, are widely utilized and well-tolerated as  
45  
46 311 an preemptive analgesic option that optimises cost-effectiveness to a higher extent  
47  
48 312 and helps to improve patient compliance and reduce the risk of anaesthesia. This is the  
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313 main reason why we are concerned about oral analgesia.

50  
51 314 However, Existing research on the role of oral analgesics in TKA pain treatment  
52  
53 315 have generally concentrated on the efficacy of the medications, lacking a  
54  
55 316 comprehensive evaluation of the overall benefits and safety of these drugs and  
56  
57 317 neglecting the influence of confounding factors on clinical study outcomes.<sup>39</sup> A recent  
58  
59 318 big NMA assessed the efficacy of oral preemptive analgesics on perioperative pain,  
60  
319 showing the superiority of preemptive analgesia over traditional pain management

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4 320 methods. However, the study did not account for variability between procedures and  
5  
6 321 did not conduct additional subgroup analyses of drug doses, which may have been a  
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8 322 major source of heterogeneity.<sup>40</sup> In our study, it is of considerable interest to  
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10 323 undertake a novel and systematic investigation of TKA. It can enrich the  
11  
12 324 evidence-based evidence for preemptive analgesia in TKA and provide a more  
13  
14 325 convincing reference for pain management to surgeons. As only English-language  
15  
16 326 database reports were considered for inclusion in this protocol, the exclusion of other  
17  
18 327 databases may pose a risk of bias.  
19

20 328

21 329 **Contributors** F-JX and WZ conceptualised the study and contributed equally to this  
22  
23 330 work. S-JJ obtained funding, and together with F-JX, WZ, and Y-ML designed the  
24  
25 331 study and drafted the initial manuscript. X-RH, X-FL, H-JP, KS were involved in the  
26  
27 332 review and revision of the protocol. The grammar of this protocol has been improved  
28  
29 333 by H-JP. Y-ML supervised the study. All authors read and approved the final version  
30  
31 334 of the manuscript.  
32

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36  
37 337 of Traditional Chinese Medicine (2020LC0050).  
38

39 338

40 339 **Competing interests** None declared.  
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43  
44 341 **Patient and public involvement** Patients and/or the public were not involved in the  
45  
46 342 design, or conduct, or reporting, or dissemination plans of this research.  
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445 **Figure legend**

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

447

448 **Table legend**

449 Table 1. Search strategy used in the PubMed database.

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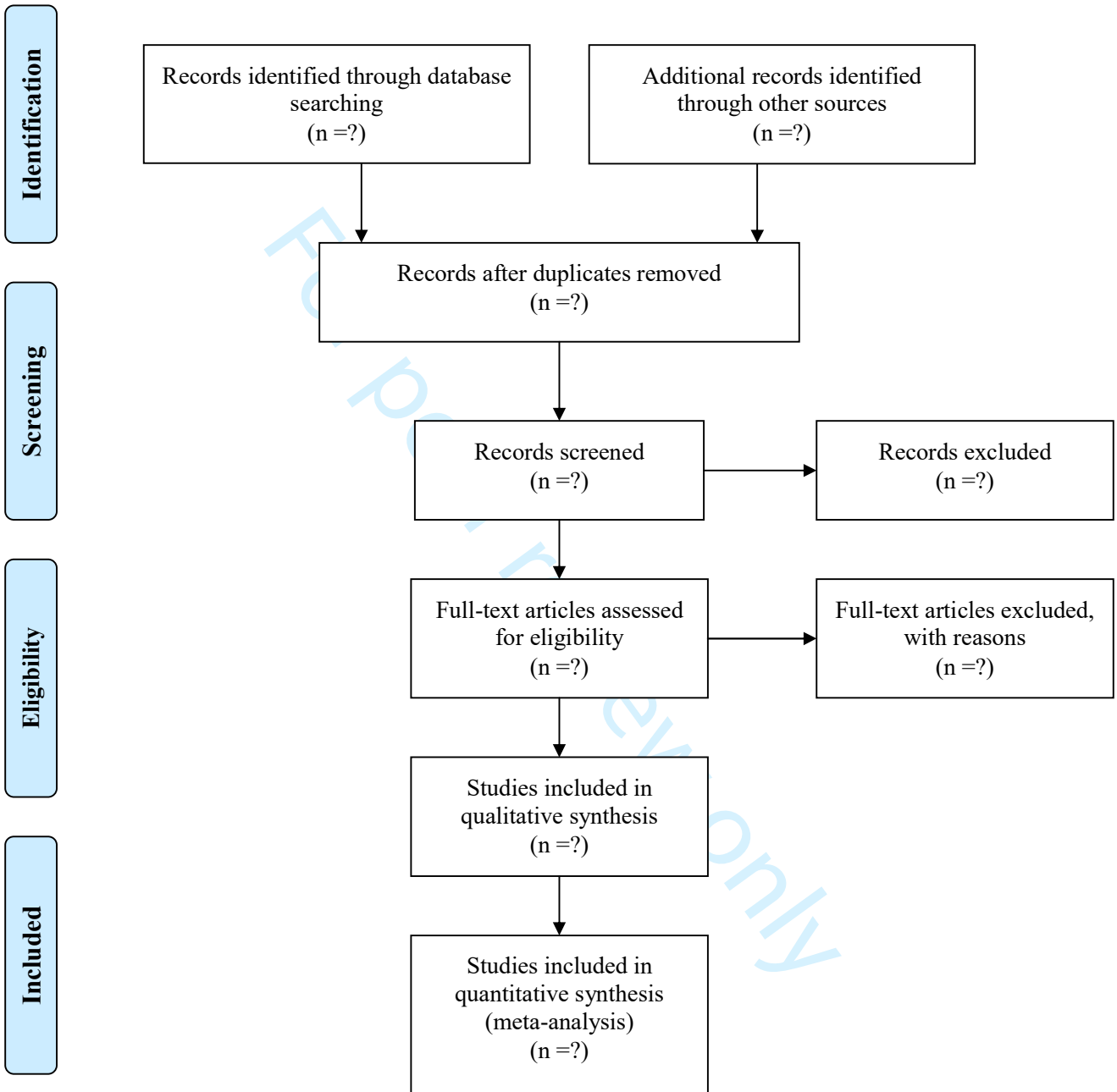


Table 1 Search strategy used in the PubMed database	
Number	Search terms
#1	Total knee arthroplasty [Mesh]
#2	Total knee arthroplasty [Title/Abstract] OR Knee Replacement Arthroplasty [Title/Abstract] OR Total Knee Replacement [Title/Abstract] OR Arthroplasties, Replacement, Knee [Title/Abstract] OR 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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6 #1 Total knee arthroplasty [Mesh]  
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11 Arthroplasties, Replacement, Knee [Title/Abstract] OR Arthroplasty, Knee  
12 Replacement [Title/Abstract] OR Arthroplasty, Total Knee [Title/Abstract]  
13 OR Knee Arthroplasty, Total [Title/Abstract] OR Replacement, Total Knee  
14 [Title/Abstract] OR Knee Replacement, Total [Title/Abstract]  
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21 #4 Analgesia [Mesh]  
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23 #5 Analgesia [Title/Abstract] OR Analgesics [Title/Abstract] OR Anodynes  
24 [Title/Abstract] OR Analgesic Drugs [Title/Abstract] OR Analgesic  
25 [Title/Abstract] OR Analgesic Agents [Title/Abstract] OR Antinociceptive  
26 Agents [Title/Abstract] OR Analgesics, Non-Narcotic [Title/Abstract] OR  
27 Analgesics, Short-Acting [Title/Abstract] OR Analgesics, Opioid  
28 [Title/Abstract] OR Anti-Inflammatory Agents, Non-Steroidal  
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**MEDLINE (<https://www.medline.eu/>)**

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6 #1 Total knee arthroplasty [Mesh]  
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11 Arthroplasties, Replacement, Knee [Title/Abstract] OR Arthroplasty, Knee  
12 Replacement [Title/Abstract] OR Arthroplasty, Total Knee [Title/Abstract]  
13 OR Knee Arthroplasty, Total [Title/Abstract] OR Replacement, Total Knee  
14 [Title/Abstract] OR Knee Replacement, Total [Title/Abstract]  
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21 #4 Analgesia [Mesh]  
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24 [Title/Abstract] OR Analgesic Drugs [Title/Abstract] OR Analgesic  
25 [Title/Abstract] OR Analgesic Agents [Title/Abstract] OR Antinociceptive  
26 Agents [Title/Abstract] OR Analgesics, Non-Narcotic [Title/Abstract] OR  
27 Analgesics, Short-Acting [Title/Abstract] OR Analgesics, Opioid  
28 [Title/Abstract] OR Anti-Inflammatory Agents, Non-Steroidal  
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39 #7 Preoperative Period [Title/Abstract] OR Preoperative [Title/Abstract] OR  
40 Preemptive [Title/Abstract]  
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45 #9 Controlled clinical trial [Publication Type]  
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47 #10 Randomized [Title/Abstract]  
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### 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 #
<b>ADMINISTRATIVE INFORMATION</b>			
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
<b>INTRODUCTION</b>			
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
<b>METHODS</b>			
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 $\tau$ )	#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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