PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effect of oral preemptive analgesia on pain management after total knee arthroplasty : A protocol for systematic review and meta-analysis
AUTHORS	Xiong, Fan-jie; Zhao, Wei; Jia, Shi-jian; Huang, Xiao-rong; Luo, Xiang-fei; Pu, Hong-jiang; Song, Kai; Li, Yan-ming

VERSION 1 – REVIEW

REVIEWER	Sá Ferreira, Arthur Augusto Motta University Centre, Postgraduate Program in Rehabilitation Sciences
REVIEW RETURNED	23-Jan-2023

GENERAL COMMENTS	This manuscript reports a study protocol for a systematic review and meta-analysis to evaluate the efficacy of several oral preemptive analgesics for the management of pain in patients with total knee arthroplasty. The study protocol is pre-registered (PROSPERO CRD 42022380782) and follows adequate reporting guidelines (PRISMA-P). Major comments 1. Abstract (lines 37-38) and Statistical Analysis (lines 237-239). Please revise the sentence about I-squared as it measures the percentage of total variability due to between-study heterogeneity (https://doi.org/10.1186/1471-2288-8-79). 2. Search strategy (lines 176-177) mentions there will be no restrictions on language. However, in the Discussion section (lines 295-297) it is mentioned that only English-language database reports will be considered for inclusion. Please clarify this information for consistency.

REVIEWER	Domagalska, Małgorzata Poznan University of Medical Sciences, Department of Palliative Medicine
REVIEW RETURNED	12-Feb-2023

GENERAL COMMENTS	The manuscript describes the protocol for a systematic review and meta-analysis of the literature concerning the effect of oral preemptive analgesia on pain management after total knee arthroplasty. The topic is exciting and clinically significant. I have some minor suggestions for revisions: 1. lines 58 and 60 refer to groups. Could you specify what kind of groups?

	2. line 83: "aforementioned" Did you mean "before mentioned."
	3. line 106: I would suggest mentioning also regional nerve blocks as an essential part of multimodal opioid-sparing analgesia protocol
	4. line 140: Could You specify primary or revision TKA? It would suggest separating these two groups.
	5. line 152: I would suggest adding "oral" before "preoperative analgesic medication."
	6. In the methods section, please use the future tense.
	7. I would consider including non-English studies. However, limited inclusion of non-English studies might lead to ignoring kay data and introduce bias to the otherwise high-quality review.
	8. In the discussion section, I would suggest explaining why you chose only preemptive oral analgesia. Why not intravenous preemptive analgesia like dexamethasone or regional preemptive analgesia like nerve blocks?

VERSION 1 – AUTHOR RESPONSE

Reviewer #1:
Dr. Arthur Sá Ferreira, Augusto Motta University Centre

Comments:
This manuscript reports a study protocol for a systematic review and meta-analysis to evaluate the efficacy of several oral preemptive analgesics for the management of pain in patients with total knee arthroplasty. The study protocol is pre-registered (PROSPERO CRD 42022380782) and follows adequate reporting guidelines (PRISMA-P).

Major comments:
1. Abstract (lines 37-38) and Statistical Analysis (lines 237-239). Please revise the sentence about I-squared as it measures the percentage of total variability due to between-study heterogeneity (https://doi.org/10.1186/1471-2288-8-79).
Response: Many thanks! Your comments have assisted us in enhancing the quality of the manuscript. We agree with your suggestion that "I2 is used to measure the percentage of total variability due to heterogeneity between studies" and we have made the appropriate changes and cited the references (p.2, lines 37-39) (p.9, lines 239-246) (p.9, line 258).

2. Search strategy (lines 176-177) mentions there will be no restrictions on language. However, in the Discussion section (lines 295-297) it is mentioned that only English-language database reports will be considered for inclusion. Please clarify this information for consistency.
Response: The literature expected to be included in this research protocol comes from English language databases, including PubMed, EMBASE, MEDLINE, the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews, WHO International Clinical Trial Registration Platform Australian New Zealand Clinical Trials and National Institutes of Health clinical registry. To prevent a recurrence of the confusion, we changed the original draft and added the definitive article (p.7, lines 177-178). We acknowledge the potential for bias in the rejection of non-English databases. However, for several reasons, including limitations in translation resources, potential language bias, and the focus of our review on a specific geographical region where English is the primary language, we have still decided to carefully exclude non-English databases to ensure that valuable, high-quality evidence is provided.

Reviewer #2:
Dr. Małgorzata Domagalska, Poznan University of Medical Sciences, Poznan University of Medical Sciences

Comments:
The manuscript describes the protocol for a systematic review and meta-analysis of the literature

concerning the effect of oral preemptive analgesia on pain management after total knee arthroplasty.

The topic is exciting and clinically significant. I have some minor suggestions for revisions:

1. lines 58 and 60 refer to groups. Could you specify what kind of groups?

Response: We've made modifications to the original manuscript statement. Knee osteoarthritis is an important disease type in which patients with total knee arthroplasty are our primary focus of this study (p.3, lines 59-63).

2. line 83:"aforementioned" Did you mean "before mentioned."

Response: Exactly, "aforementioned" refers to "post-operative knee pain" and "opioid abuse" in the previous text. In the meantime, this has been clarified this in the original article (p.4, lines 84-87).

3. line 106: I would suggest mentioning also regional nerve blocks as an essential part of multimodal opioid-sparing analgesia protocol

Response: Thank you for your suggestion, which is really pertinent to refining the arguments in our manuscript. We have noted the advantages of regional nerve blocks in multimodal analgesia and have modified the original text accordingly. In the discussion section we elaborate on why preemptive oral analgesia was chosen as the focus of the study rather than regional nerve blocks (p.4, line 109- p.5, line 110) (p.10, line 288- p.11, line 312).

4. line 140: Could You specify primary or revision TKA? It would suggest separating these two groups.

Response: In the study protocol, we will consider enrolling all patients with primary or revision TKA. This will be differentiated and further analysed in the subgroup analyses (p.6, lines 143-145) (p.9, lines 250-253).

5. line 152: I would suggest adding "oral" before "preoperative analgesic medication."

Response: We apologize for our lack of strictness. We have modified the original text (p.6, lines 154-155).

6. In the methods section, please use the future tense.

Response: We have altered the tense of the pertinent portion of the statement (p.5, line 139) (p.5, line 139) (p.7, line 194) (p.8, line 202) (p.8, line 219).

7. I would consider including non-English studies. However, limited inclusion of non-English studies might lead to ignoring kay data and introduce bias to the otherwise high-quality review.

Response: We appreciate your suggestion to include non-English studies in our review. Nonetheless, after careful consideration, we have decided not to include non-English studies in our review. This decision was based on several reasons, including limitations in translation resources, potential language bias, and the focus of our review on a specific geographical region where English is the primary language. We acknowledge that non-English language studies can provide valuable information and insights, but we believe that by focusing on English language studies, our review can still provide a comprehensive and high-quality summary of the available evidence. To ensure the transparency and quality of our review, we have clearly reported the search strategy (p.7, lines 186-187) and inclusion/exclusion criteria in our manuscript.

8. In the discussion section, I would suggest explaining why you chose only preemptive oral analgesia. Why not intravenous preemptive analgesia like dexamethasone or regional preemptive analgesia like nerve blocks?

Response: Preventive oral analgesia was chosen as our intervention because it is a regularly utilized and well-tolerated method of pain management in our target patient population. It is also a cost-effective and readily available method that helps to improve patient compliance. Of course, we also recognise that other preemptive analgesia methods, such as intravenous preemptive analgesia and peripheral preemptive analgesia, may have potential benefits for pain management. To our knowledge, the drawback of peripheral preemptive analgesia is the risk of nerve and blood vessel injury as well as muscular weakness. (Chan EY, Fransen M, Parker DA, et al. Femoral nerve blocks for acute postoperative pain after knee replacement surgery. Cochrane Database Syst Rev 2014;2014(5):CD009941.) Intravenous glucocorticoids (dexamethasone/methylprednisolone etc.) also have well-known long-term safety risks, such as infection or wound complications, and there is

limited strong evidence of benefit. （Hartman J, Khanna V, Habib A, et al. Perioperative systemic glucocorticoids in total hip and knee arthroplasty: A systematic review of outcomes. J Orthop 2017;14(2):294-301.）

We therefore still opted for preemptive oral analgesia. We have included a more detailed discussion in our manuscript outlining the potential advantages and disadvantages of these methods and why we did not choose to use them in our study (p.10, line 288- p.11, line 313).

VERSION 2 – REVIEW

REVIEWER	Sá Ferreira, Arthur Augusto Motta University Centre, Postgraduate Program in Rehabilitation Sciences
REVIEW RETURNED	06-Mar-2023

GENERAL COMMENTS	Thank you for the opportunity to discuss your manuscript. All comments were adequately addressed. I have no new comments.

REVIEWER	Domagalska, Małgorzata Poznan University of Medical Sciences, Department of Palliative Medicine
REVIEW RETURNED	06-Mar-2023

GENERAL COMMENTS	An exciting and very much-needed meta-analysis. This is an exceptionally well-conducted protocol for systematic review and meta-analyses. The objectives are clearly stated, and the methods are described clearly. However, I believe that the manuscript would benefit from proofreading. Many sentences should be rewritten for clarity reading. Also, the spelling and punctuation mistakes should be corrected.