PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

Title (Provisional)

Pain control post total knee replacement in patients given local infiltrative analgesia combined with adductor canal block compared to either modality alone: A systematic review and meta-analysis

Authors

Mott, Andrew; Brady, Samantha; Briggs, Isabelle; Barrett, Maggie; Fulbright, Helen; Hamilton, Thomas William; Hewitt, Catherine; Palan, Jeya; Pandit, Hemant

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VERSION 1 - REVIEW

Reviewer **1**

Name **Sá Ferreira, Arthur**

Affiliation **Augusto Motta University Centre, Postgraduate Program in Rehabilitation Sciences**

Date **25-Oct-2023**

COI **I have no conflicts of interest to declare.**

Comments

This manuscript reports a systematic review with meta-analysis study to investigate the efficacy of local infiltration analgesia (LIA) combined with adductor canal block (ACB) compared to either LIA or ACB alone on post-operative pain following total knee replacement. The review was prospectively registered with PROSPERO (CRD42023436895). The manuscript is of interest and seems generally well-written in a concise scientific style. I have only minor comments for the authors to consider.

Minor comments

1. Study aims and conclusions. Consider reporting the primary and secondary endpoints (rest, 48h, and 72h with activity) in these sections.

2. The original PRISMA from 2008 (ref. 11) was updated in 2020 (https://pubmed.ncbi.nlm.nih.gov/33780438/). Any particular reason to not use the most updated source?

3. Citation for the Cochrane Handbook (ref. 18) needs adjustment (please see: https://training.cochrane.org/handbook): “Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). Cochrane, 2023. Available from www.training.cochrane.org/handbook.” Or “Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions. 2nd Edition. Chichester (UK): John Wiley & Sons, 2019.”

4. Statistics. 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).

Reviewer	**2**
Name	**Domagalska, Małgorzata**
Affiliation	**Poznan University of Medical Sciences, Department of Palliative Medicine**
Date	**31-Oct-2023**
COI	**Not applicable**

I have reviewed the abstract, introduction, methods and materials, results, statistics, and discussion. I have also checked the references, and all appear relatively current and appropriate. Finally, I have also reviewed the figures, tables, and legends.

I find the review well-written, well-done, and informative.

Reviewer	**3**
Name	**Andreano, Anita**
Affiliation	**University of Milano-Bicocca, Monza, Italy, Center of Biostatistics for Clinical Epidemiology, School of Medicine and Surgery**
Date	**06-Feb-2024**
COI	**None**

The statistical methods are appropriate. However, methods and results could be explained more clearly in some circumstances. Also, sources of heterogeneity should be considered and, if possible, analysed.

• I think that more information on how different scales for each outcome were combined (eg. Smd for NRS and VAS for pain at rest) would be helpful in the methods, as well as reporting which scales were found in the different RTCs for the different outcomes (maybe at the beginning of the results section of each outcome).

• I cannot find a description of how clinical heterogeneity was assessed (subgroup analysis? Meta-regression?). Also, either with sub-headings or by adding an extra column, the information on the measurement scale could be visualized on the forest plots, to aid in the visual exploration of heterogeneity. Concerning the assessment of statistical heterogeneity, for some outcomes (eg. Pain on movement 12 hours), the I

is very high (>90%). Instead of performing a meta-analysis on all studies, could you try to individuate the potential causes of heterogeneity and either perform meta-analysis on a more homogeneous subgroup or, if possible, perform a meta-regression?

• I will avoid showing the summary measures for outcomes with only one study, e.g., pain at rest 72 hours.

• Results, page 6 lines 30-33: “There were 12 studies which compared LIA alone vs Combination and 5 studies which compared ACB alone vs Combination. Four of the included studies compared LIA alone vs. ACB alone vs. combination.” If the 13 complete studies were meta-analysed, the reported number of studies for the various combinations should refer to those 13 studies (or you could report for both the 25 and 13) but 12+5+4=21, so it is not very clear which studies these numbers refer to.

VERSION 1 - AUTHOR RESPONSE

Thank you to the reviewers and editor for their time to review our article.

We have addressed your comments and think this has greatly improved our article.

We look forward to your response.

Comment	Response
Please revise the formatting of your abstract so that it includes the following sections: Objectives >> Design >> Data Sources >> Eligibility Criteria >> Data extraction and synthesis >> Results >> Conclusions. Please see the following published Abstract as an example: https://bmjopen.bmj.com/content/12/2/e054120	This has been revised to the suggested format.

Please include the PROSPERO registration number at the end of the Abstract.	This has been added.
Please include any relevant statistical or quantitative results in the results section of the Abstract.	We have summarised the primary outcome and some secondary outcomes with quantitative results.
Please revise your Discussion section using our Instructions for authors for guidance on what to include in this section: https://bmjopen.bmj.com/pages/authors/#research	This has been amended in line with the guidance.
Please ensure that you have fully discussed the methodological limitations of the study in the Discussion section of the main text.	Further discussion of the methodological limitations has been added.
Please include, as a supplementary file, the precise, full search strategy (or strategies) for all databases, registers and websites, including any filters and limits used.	This file is included in the documentation supplied in the Figshare repository found here: https://figshare.com/account/projects/178566/articles/24146193. This has been clarified further in the text with the citation to the document as per BMJOpen guidance - https://bmjopen.bmj.com/pages/data-management
Please elaborate on the adverse events paragraph, we felt it nicely summarises the the most common adverse events, this is not done for each type of analgesia (combination vs single). We would be interested to know if there were different rates of adverse events depending on whether either modality is used alone or in combination.	Insufficient information was reported in the included trials to report meaningful modality specific events. We have added a sentence to confirm this.
Abstract, the first sentence of the aims is a little awkward to read, especially the phrase health care payers. The last sentence of the aims and the first sentence of the methods are repetitive. Introduction : Abbreviations such as NHS should be explained for an international audience.	This has been explained at first mention.
LIA and ACB are both commonly used in clinical practice, both independently and combination, and there is uncertainty as to the optimum analgesic strategy." I think the "in" is missing in this sentence.	Thank you for pointing this out. This sentence has been amended.
Results: In the first paragraph please point to the supplemental materials not just their reference, it is a little unclear otherwise.	Clarification has been added.
When stats are reported please report the type of statistic SMD /OR=, CI= P= etc.	The type of statistic has been added for each occurence in the text. The statistical methods section has been updated to reflect only SMD and MD are

Though I appreciate it is mentioned in the methods it is easier to read.	used. To make it clearer the estimate being reported has been added to Tables also.
Does the risk of bias paragraph fit more at the beginning of the results? It seems intuitive to first discuss the quality of the current studies and then go into what the literature says, in the discussion this sequence is followed as bias is mentioned first. However, I shall leave this up to your discretion.	We agree that this is more intuitive and have moved the risk of bias to after the initial results paragraph.
Figures The last two figures after the PRISMA 2020 checklist have no title or legend.	Due to these being supplemental figures the submission system does not allow the additions of titles or legends.
Study aims and conclusions. Consider reporting the primary and secondary endpoints (rest, 48h, and 72h with activity) in these sections.	This has now been included
The original PRISMA from 2008 (ref. 11) was updated in 2020 (https://pubmed.ncbi.nlm.nih.gov/33780438/). Any particular reason to not use the most updated source?	This has been updated to the most up to date guidance.
Citation for the Cochrane Handbook (ref. 18) needs adjustment (please see: https://training.cochrane.org/handbook): "Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). Cochrane, 2023. Available from www.training.cochrane.org/handbook." Or "Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions. 2nd Edition. Chichester (UK): John Wiley & Sons, 2019."	This reference has been updated.
Statistics. 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).	This has been amended.
I think that more information on how different scales for each outcome were combined (eg. Smd for NRS and VAS for pain at rest) would be helpful in the methods, as well as reporting which scales were found in the different RTCs for the different outcomes (maybe at the	The methods sections has been updated accordingly for the outcomes and at the start of the results the measures combined using SMD has been included.

beginning of the results section of each outcome).	
I cannot find a description of how clinical heterogeneity was assessed (subgroup analysis? Meta-regression?). Also, either with sub-headings or by adding an extra column, the information on the measurement scale could be visualized on the forest plots, to aid in the visual exploration of heterogeneity. Concerning the assessment of statistical heterogeneity, for some outcomes (eg. Pain on movement 12 hours), the I2 is very high (>90%). Instead of performing a meta-analysis on all studies, could you try to individuate the potential causes of heterogeneity and either perform meta-analysis on a more homogeneous subgroup or, if possible, perform a meta-regression?	There were insufficient numbers of studies to explore heterogeneity through conducting subgroup analyses or met-regression. Hence we performed a random effects meta-analysis to incorporate heterogeneity among studies.
I would avoid showing the summary measures for outcomes with only one study, e.g., pain at rest 72 hours.	This has been included as one of the pre-specified outcomes, context has been provided within the text that data is from a single study
Results, page 6 lines 30-33: “There were 12 studies which compared LIA alone vs Combination and 5 studies which compared ACB alone vs Combination. Four of the included studies compared LIA alone vs. ACB alone vs. combination.” If the 13 complete studies were meta-analysed, the reported number of studies for the various combinations should refer to those 13 studies (or you could report for both the 25 and 13) but 12+5+4=21, so it is not very clear which studies these numbers refer to.	This sentence has been amended. It refers only to the 13 completed studies. 8 LIA vs combination + 1 ACB vs Combination + 4 ACB vs LIA vs combination.

VERSION 2 - REVIEW

Reviewer **1**

Name **Sá Ferreira, Arthur**

Affiliation **Augusto Motta University Centre, Postgraduate Program in Rehabilitation Sciences**

Date **30-Apr-2024**

COI **None to declare.**

Thank you for the opportunity to review your manuscript. All my comments were adequately addressed. I have no new comments.