PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Comparative efficacy and safety of intra-articular analgesics after knee arthroscopy: a Bayesian network meta-analysis protocol
AUTHORS	He, Yuchen; He, Hongyi; Xie, Dong-xing; Li, Xiaoxiao; Wang, Yilun

VERSION 1 – REVIEW

REVIEWER	Kariem El-Boghdadly 1. Guy's & St Thomas' NHS Foundation Trust London, UK 2. King's College London, UK
REVIEW RETURNED	11-Nov-2019

GENERAL COMMENTS	- The following review is fully impartial and is not meant to be in any way personal towards the authors, who have done a great job designing an interesting study. My review merely aims at highlighting some of the strengths and weaknesses, with the hope of improving the quality of the published literature in this field. I will refrain from commenting on grammatical errors or Journal style and focus on the scientific value of the manuscript itself. - Overall, the authors ask an interesting study question, and the methodology they report appears sufficiently rigorous. The question asked is novel and interesting. This reviewer is unaware of a similar study published elsewhere. - I have some areas that the authors may consider developing or implementing further in this study: - They should ensure levobupivacaine is included - The authors should collect information on the peri-operative analgesic regimen as well. - The authors do not plan to collect many secondary outcomes, which would add to our understanding. Authors may wish to consider also collecting the following outcomes: --- Pain scores at other time-points --- Opioid consumption --- Functional outcomes --- Patient satisfaction --- Quality of recovery --- Wound infection - How will the authors handle pain scores that are not collected using a VAS (e.g. NRS, Likert scale)? - How will the authors handle incomplete data reporting? Will authors attempt to contact authors of the original research manuscripts? How will authors handle data that is only reported visually and not in the text? - Do the authors plan on powering to a minimum number of studies/participants for an intervention arm to be included? - The statistical analysis plan is beyond the expertise of this particular reviewer, but one wonders what the clinical differences

	would be sought and reported. What minimum clinically important difference will the authors select? - Do the authors have any plans to undertake sensitivity or sub-group analyses (e.g. type of surgery)?

REVIEWER	Sten Rasmussen Department of orthopaedic surgery, sport and arthroscopy. Aalborg University Hospital Department of clinical medicine. Aalborg University Denmark
REVIEW RETURNED	09-Dec-2019

GENERAL COMMENTS	The authors have the knowledge from previous reviews to perform this statistical model of meta-analysis. I will look forward to see the results. I have a few comments: 1. Why have the authors not includes web og science into the search? 2. Remember to report search date and time or eventual repeated search 3. Is the search conducted in cooperation with a certified librarian? 4. Correct reference 12 would be Higgins BMJ 2011. It is a wrong reference number in line 12 page 7 - i should be 12 not 13! 5. Reference 13 should be referenced together with ref 14-16!

REVIEWER	Pt university of padova
REVIEW RETURNED	20-Feb-2020

GENERAL COMMENTS	The protocol seems interesting and well written. I have a big doubt: why are you performing a Bayesian meta-analysis as you don't have any a priori knowledge about the data? Which kind of prior will you use? I also want to give a few suggestions to the authors: - consider to find a considerable heterogeneity and in this case you will have to perform subgroup analysis and meta-regression, which variable are you extracting for be prepared to this worst scenario? Also a sensitivity analysis should be considered. - I would consider funnel plots and tests for asimmetry; - I would consider also the case in which there are missing data.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Kariem El-Boghdadly's Comments:
Comment 1: • They should ensure levobupivacaine is included
Response: We appreciate the reviewer's suggestion, and we have included levobupivacaine in our revised manuscript.
Action: "The MEDLINE/PubMed database, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science and EMBASE database will be searched from inception until June 1st 2020 to retrieve the relevant studies that compared commonly used single-dose IA analgesics alone or in combination (i.e., morphine, bupivacaine [including levobupivacaine], ropivacaine, or magnesium) with placebo or between each other after knee arthroscopic surgery." (Line 81-87)

Comment 2: • The authors should collect information on the peri-operative analgesic regimen as well.

Response: We are grateful to the reviewer's suggestion. The manuscript has been revised accordingly.
Action: "Specifically, the retained data for analysis includes the first author, year of publication, size of each group, doses of intervention, injection time, follow-up time points, type of operation and peri-operative analgesic regimen." (Line 110-113)

Comment 3: • The authors do not plan to collect many secondary outcomes, which would add to our understanding. Authors may wish to consider also collecting the following outcomes:
--- Pain scores at other time-points
--- Opioid consumption
--- Functional outcomes
--- Patient satisfaction
--- Quality of recovery
--- Wound infection
Response: We appreciate the reviewer's comment. As suggested, we have added another two common results as the secondary outcomes.
Action: "The pain intensity measured by a visual analogue scale (VAS) at 2-hour, 24-hour postoperatively and at the last follow-up will be chosen as the primary outcome. The VAS data, if ranged from 1 to 100, will be divided by 10 in order to derive a uniform scale of 1-10. The secondary outcome measures include the number of patients requiring supplementary analgesia, patient satisfaction rate, functional outcomes (e.g., Western Ontario McMaster Osteoarthritis Index [WOMAC], Functional Independence Measure [FIM], and Short Musculoskeletal Function Assessment [SMFA]), the time to first analgesic request, and the incidence of adverse reactions." (Line 124-132)

Comment 4: • How will the authors handle pain scores that are not collected using a VAS (e.g. NRS, Likert scale)?
Response: We appreciate the reviewer's comment. In this study, we will use standardized mean difference (SMD) for analysis. SMD is a summary statistic in meta-analysis, which is commonly used when all the included studies assessed the same outcome (e.g. post-operative pain) but in different ways (e.g., VAS, NRS, Likert scale). Specifically, SMD expresses the size of the intervention effect in each study relative to the between-participant variability in outcome measurements observed in that study. Thus, studies for which the difference in means is the same proportion of the standard deviation (SD) will have the same SMD, regardless of the actual scales used to make the measurements.1
Action: "The pooled effect sizes, i.e., SMDs or Risk Ratio (RRs), will be derived from the median of the posterior distribution, where the 97.5th and 2.5th percentiles of the posterior distribution are taken as the upper and lower limit of the 95% CrI respectively. The 95% CrI will be used to determine whether a difference is statistically-significant (0 for SMD or 1 for RR is not included)." (Line 146-151)
[1]. Higgins JP, Thomas J, Chandler J, et al. Cochrane handbook for systematic reviews of interventions: John Wiley & Sons 2019.

Comment 5: • How will the authors handle incomplete data reporting? Will authors attempt to contact authors of the original research manuscripts? How will authors handle data that is only reported visually and not in the text?
Response: We are grateful to the reviewer's questions. We sincerely acknowledge that incomplete data which is inevitable in all meta-analyses should be taken care of seriously. When facing incomplete data, we will first contact the primary investigator or the corresponding author(s) by email to request for the missing data. If this does not work, we will follow the suggestions listed in Cochrane handbook to deal with missing data via statistical methods. In addition, we will use GetData V.2.20 to extract data that is only reported visually in the figures.
Action: "The author(s) of a potentially relevant study will be contacted as far as possible if full-text is

not available. Data that is only reported visually in figures will be extracted using GetData V.2.20." (Line 108-110)

Comment 6: • Do the authors plan on powering to a minimum number of studies/participants for an intervention arm to be included?
Response: We appreciate the reviewer's question. We will not confine a minimum number of studies/participants for an intervention arm. The number of studies for each intervention may be limited, and we want to assess all the interventions that have been listed. However, we will consider excluding the studies with a small sample size in sensitivity analyses.

Comment 7: • The statistical analysis plan is beyond the expertise of this particular reviewer, but one wonders what the clinical differences would be sought and reported. What minimum clinically important difference will the authors select?
Response: We appreciate the reviewer's comment and apologize for the confusion. Based on our previously published paper and the NICE OA Guidelines 2014, we will select the minimal clinically important differences as greater than 0.5 SD change of the related 95% CI, corresponding to a 1.2 cm decrease on a 10 cm visual analogue scale.2 3
Action: "Clinically important difference (MCID) will be defined as 0.5 SD greater change of the related 95% CI, corresponding to a 1.2 cm decrease on a 10 cm visual analogue scale." (Line 151-153)
[2]. National Collaborating Centre for Chronic C. National Institute for Health and Clinical Excellence: Guidance. Osteoarthritis: National Clinical Guideline for Care and Management in Adults. London: Royal College of Physicians (UK)
[3]. Zeng C, Wei J, Persson MSM, et al. Relative efficacy and safety of topical non-steroidal anti-inflammatory drugs for osteoarthritis: a systematic review and network meta-analysis of randomised controlled trials and observational studies. Br J Sports Med 2018;52(10):642-50. doi: 10.1136/bjsports-2017-098043

Comment 8: • Do the authors have any plans to undertake sensitivity or sub-group analyses (e.g. type of surgery)?
Response: We appreciate the reviewer's comment. We will undertake sensitivity analyses by excluding any single study to see whether the results vary substantially. In addition, we may or may not conduct sub-group analyses according to the types of surgery (e.g., arthroscopic ACL reconstruction, arthroscopic meniscectomy, diagnostic arthroscopic surgery), depending on the number of studies in each sub-group. We will figure out the necessity of sub-group analyses after completing study selection.
Action: "Sensitivity analyses will be performed to explore possible explanations for heterogeneity and to examine the influence of various exclusion criteria on the overall effect sizes." (Line156-158)

Reviewer: 2
Sten Rasmussen's Comments:
Comment 1: • Why have the authors not includes web of science into the search?
Response: We are grateful to the reviewer's suggestion. We will include web of science into the search and make sure all the qualified articles are included in the analyses.
Action: "The MEDLINE/PubMed database, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science and EMBASE database will be searched from inception until June 1st 2020 to retrieve the relevant studies that compared commonly used single-dose IA analgesics alone or in combination." (Line 81-85)

Comment 2: • Remember to report search date and time or eventual repeated search.
Response: We are sincerely sorry for the confusion. We have added the missing date as suggested.
Action: "The MEDLINE/PubMed database, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science and EMBASE database will be searched from inception until June 1st

2020 to retrieve the relevant studies that compared commonly used single-dose IA analgesics alone or in combination." (Line 81-85)

Comment 3: • Is the search conducted in cooperation with a certified librarian?
Response: We appreciate the reviewer's question. We have not worked with any certified librarian for this research. However, we have already published several meta-analyses and accumulated good experience in literature searching. Certainly, if it is necessary or if we have problems with study search or selection, we would consider engaging a certified librarian for help.
Action: "Qualified randomized controlled trials (RCTs) shall be identified for inclusion by two researchers independently based on predetermined inclusion criteria. Consensus shall be reached by discussion in case of disagreement." (Line 92-94)

Comment 4: • Correct reference 12 would be Higgins BMJ 2011. It is a wrong reference number in line 12 page 7 - i should be 12 not 13! Reference 13 should be referenced together with ref 14-16!
Response: We are sorry for the mistakes.
Action: "This protocol was developed in accordance with the PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist,4 and the study will be implemented in accordance with the PRISMA statement.5" (Line 78-81)
"Each item of risk of bias will be evaluated using a three-level rating system: low risk, unclear risk and high risk; studies involving three or more high risks of bias will be considered as poor methodological quality.6" (Line 120-123)

Reviewer: 3
P Tellaroli's comments
Comment 1: • Why are you performing a Bayesian meta-analysis as you don't have any a priori knowledge about the data? Which kind of prior will you use?
Response: We are grateful to the reviewer's question. As a matter of fact, we will conduct this meta-analysis primarily based on the related meta-analysis results of our lab that were previously published. Post-operative pain is a great threat to the patients' rehabilitation and needs to be handled properly. Our team and other researchers have compared the efficacy and safety of several commonly-used single-dose IA analgesics with placebo and obtained significant results. However, identification of the most effective and the safest option is still a challenge because the comparative efficacy and safety among these analgesics remain unknown. The Bayesian approach towards network meta-analysis allows a unified, coherent analysis of data recorded at multiple time points in randomized trials that compare either of these preparations with placebo or between each other. It therefore allows us to estimate the relative safety and effectiveness of different analgesics and their combinations.

Comment 2: • Consider to find a considerable heterogeneity and in this case, you will have to perform subgroup analysis and meta-regression, which variable are you extracting for be prepared to this worst scenario? Also, a sensitivity analysis should be considered.
Response: We appreciate the reviewer's comment and question. We will undertake sensitivity analyses by excluding any single study to see whether the results vary substantially. In addition, we may or may not conduct sub-group analyses according to the types of surgery (e.g. arthroscopic ACL reconstruction, arthroscopic meniscectomy, diagnostic arthroscopic surgery), depending on the number of studies in each sub-group. We will figure out the necessity of sub-group analyses after completing study selection.
Action: "Heterogeneity, which is defined as the variability of results among the included trials, will be assessed by the value of $\tau 2$ (low level of heterogeneity: $\tau 2 < 0.04$; high level of heterogeneity: $\tau 2 > 0.4$). Sensitivity analyses will be performed to explore possible explanations for heterogeneity and to examine the influence of various exclusion criteria on the overall effect sizes." (Line153-158)

Comment 3: • I would consider funnel plots and tests for asymmetry;
Response: We appreciate the reviewer's suggestion.
Action: "Asymmetry will be assessed by funnel plots and tests." (Line 161-162)

Comment 4: • I would consider also the case in which there are missing data.
Response: We are grateful to the reviewer's comment. We sincerely acknowledge that incomplete data which is inevitable in all meta-analysis should be taken care of seriously. When facing incomplete data, we will first contact the primary investigator or the corresponding author(s) by email to request for the missing data. If this does not work, we will follow the suggestions listed in Cochrane handbook to deal with missing data via statistical methods
Action: "The author(s) of a potentially relevant study will be contacted as far as possible if full-text is not available." (Line 108-109)