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Comparative efficacy and safety of intra-articular analgesics after knee arthroscopy: a Bayesian network meta-analysis protocol

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ABSTRACT

Introduction Most of the patients who received arthroscopic knee surgery will suffer moderate to severe pain, which can delay the rehabilitation process and increase the risk of postoperative complications. Therefore, seeking a safe and effective postoperative analgesia is necessary for promoting the application of arthroscopic surgery. This protocol aims to detail a planned systematic review and meta-analysis on the comparative efficacy and safety of single-dose intra-articular injection of analgesics for pain relief after knee arthroscopy.

Method and analysis PubMed, Embase, Web of Science and Cochrane Library will be searched from inception to 1 June 2020 to retrieve randomised controlled trials (RCTs) that compared the commonly used single-dose intra-articular analgesics (ie, morphine; bupivacaine (including levobupivacaine); ropivacaine and magnesium alone or in combination) with placebo or between each other for postoperative pain relief among patients who had received knee arthroscopy. The primary outcome is pain intensity at 2-hour and 24-hour postoperatively; the secondary outcomes include side effects (eg, knee effusion, nausea, vomiting and flushing), the number of patients requiring supplementary analgesia and the time to first analgesic request. The methodological quality of the included RCTs will be assessed based on the Cochrane risk of bias table. The Bayesian network meta-analysis will be conducted using WinBUGS V.1.4.3.

Ethics and dissemination Since no private or confidential patient data will be contained in the reporting, approval from an ethics committee is not required. Our study raises no ethical issue, and the results will be published in a peer-reviewed journal.

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Strengths and limitations of this study

- This will be the first Bayesian network meta-analysis aiming at comparing the analgesic effects of commonly used single-dose intra-articular analgesics after arthroscopic knee surgery and to identify the safest and most effective option.
- Our systematic search has a wide-reaching scope. The quality of all included articles will be assessed using validated tools.
- Due to the long-time span of the literature included, a variety of factors may contribute to the heterogeneity of targeted indexes and affect the results.

INTRODUCTION

Knee arthroscopy is a surgical procedure widely adopted by orthopaedic surgeons to visualise, diagnose and treat medical problems inside the knee joint.[1] Compared with the open knee surgery, knee arthroscopy is able to minimise soft tissue damage and hospitalisation time, which prompts it to be one of the most common orthopaedic operations performed worldwide.[2] However, a varying degree of pain is often accompanied with this procedure and limits its application.[3] Solheim *et al* reported that approximately 60% of the patients experienced moderate to severe pain after receiving arthroscopic knee surgery, which could be a factor delaying the patients' rehabilitation process and increasing the risk of developing postoperative complications.[4] Therefore, seeking a safe and effective postoperative analgesia is necessary for further promoting the application of arthroscopic surgery.

Single-dose intra-articular (IA) analgesics have been widely used for pain relief after arthroscopic knee surgery as a simple and economical technique. Several meta-analyses have assessed the efficacy and safety of commonly used single-dose IA analgesics, including morphine,[5] bupivacaine,[6] ropivacaine,[7] magnesium[8] or the combination of morphine and bupivacaine,[9–11] and the conclusions have provided important guidance to clinical practice. However, determination of the safest and the most effective option is still a challenge because the comparative efficacy and safety of these analgesics remain unknown.

To fill the knowledge gap, we plan to conduct a network meta-analysis (NMA) to

evaluate the comparative efficacy and safety of commonly used IA analgesics so as to identify the optimal option for pain relief after arthroscopic knee surgery.

METHODS

Literature search

This protocol was developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Protocols 2015 checklist,[12] and the actual study will be implemented in accordance with the PRISMA statement.[13] The MEDLINE/PubMed database, Cochrane Central Register of Controlled Trials, Web of Science and EMBASE database will be searched from inception to 1 June 2020 to retrieve the relevant studies that compared commonly used single-dose IA analgesics alone or in combination (ie, morphine, bupivacaine (including levobupivacaine), ropivacaine or magnesium) with placebo or between each other after knee arthroscopic surgery. Types of arthroscopic knee surgery include diagnostic arthroscopy, meniscectomy, debridement and cruciate ligament reconstruction. The detailed search strategies are illustrated in 'online supplemental appendix'.

Study selection

Qualified randomised controlled trials (RCTs) shall be identified for inclusion by two researchers independently based on the predetermined inclusion criteria. Consensus shall be reached by discussion in case of disagreement.

Articles meeting all the following criteria will be included for analysis: (1) RCTs; (2) studies concerning arthroscopic surgery at knee joint; (3) studies concerning single-dose IA interventions after surgery; (4) studies comparing any of the interventions (bupivacaine; morphine; ropivacaine and magnesium sulfate alone or in combination) with placebo or between each other; (5) studies reporting pain or other adverse side effects in patients and (6) studies published in English.

The exclusion criteria include: (1) case reports, reviews, animal trials, letters to the editor, retrospective studies and other non-RCTs; (2) experimental or controlled injections mixed with other drugs; (3) inability to extract data; (4) partial texts or abstract only and (5) arthroscopic surgeries not performed in the knee joint.

Data extraction

Available information and outcomes of each included study will be extracted by two researchers independently. 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. 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 perioperative analgesic regimen. If there are more than two groups in one study, only data from the relevant groups will be extracted. Besides, two independent strata in one study will be included and treated as two trials.

The methodological quality of the included RCTs will be assessed based on the Cochrane risk of bias table. Seven items of risk of bias will be evaluated, including: random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete outcome data, selective reporting and other biases (mainly including conflict of interests). 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.[14]

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 (eg, Western Ontario McMaster Osteoarthritis Index, Functional Independence Measure and Short Musculoskeletal Function Assessment), the time to first analgesic request and the incidence of adverse reactions.

Statistical analyses

Comparisons among concerned analgesics in terms of efficacy and safety will be conducted using Bayesian NMA, which is a method that can narrow the width of the credible interval (CrI) of the estimate by incorporating more studies into each group.[15–17] The same technique has been used in some of our previous publications.[18–20] The posterior density of unknown variables will be estimated by the Markov Chain Monte Carlo method,[17 21 22] and the difference between RCTs, if any, will be accounted for by a random effects model. Two Markov chains will be designed to run simultaneously, each with a different set of initial values that are selected arbitrarily for convergence. For each set of initial values, a total of 50 000 simulations will be conducted with the first 10 000 simulations being abandoned as the burn-in period. The WinBUGS code can be found from the following link: http://www.bristol.ac.uk/social-community-medicine/projects/mpes/. The pooled effect sizes, that is, 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). 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 VAS.[23 24] 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: $\tau 2>0.4$).[25] 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. The posterior mean residual deviance will be calculated to measure how the established model fits the data.[26] Specifically, a model is considered fitting the data adequately if the mean residual deviance is closer to the number of data points in the model.[26] Asymmetry will be assessed by funnel plots and tests. The treatments will be ranked according to the posterior probability of the effect sizes, and the ranking results are reflected by the surface under the cumulative ranking curve (SUCRA). SUCRA equal to 100% indicates the most effective treatment, while SUCRA equal to 0% indicates the least effective treatment.[27 28]

The NMA will be conducted using WinBUGS (V.1.4.3, MRC Biostatistics Unit, Cambridge, UK), and SUCRA figures will be drawn in Stata software (V.15.1, StataCorp).

Patient and public involvement

As the proposed systematic review will be conducted based on published studies, no patients and members of the public will be directly involved. All the data to be used in this study already existents in the published literature and/or aforementioned sources.

DISCUSSION

Previous meta-analyses showed that single-dose IA morphine,[5] bupivacaine,[6] bupivacaine plus morphine,[9] ropivacaine[7] and magnesium[29] were effective for postoperative pain management in patients undergoing arthroscopic knee surgery without increasing any adverse reactions. However, no systematic and comprehensive comparison has been reported yet regarding the safety and efficacy of these drugs. The proposed study is likely to be the first NMA to compare the analgesic effects of commonly used single-dose IA analgesics after arthroscopic knee surgery in order to determine the safest and the most effective option. The analysis results will provide a theoretical basis for clinical application.

Ethics and dissemination

Since no private or confidential patient data will be contained in the reporting, approval from an ethics committee is not required. Our study raises no ethical issue, and the results will be published in a peer-reviewed journal.

Contributors YH and YW will conceive the study methods, perform database search, article selection, data extraction and statistical analysis, and draft the manuscript. XL, HH and DX will support with the data extraction process. All authors will read and approve the final manuscript.

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Competing interests None declared.

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