









RESEARCH ARTICLE

Perioperative prevention of persistent pain after total hip and knee arthroplasty—Protocol for two systematic reviews

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Abstract

Background: Between 9% and 20% of patients experience moderate to severe persistent postoperative pain after total hip or knee arthroplasty. Severe immediate postoperative pain limits rehabilitation and is associated with the development of persistent postoperative pain. Therefore, perioperative analgesic and physiotherapeutic interventions are of interest to reduce persistent pain. In two systematic reviews with identical methodology, we aim to investigate the effects of (a) perioperative analgesic interventions and (b) physiotherapeutic interventions in reducing persistent pain after total hip and knee arthroplasty.

Methods: We will include randomised and cluster-randomised controlled trials on perioperative analgesic and physiotherapeutic interventions for patients undergoing elective total hip or knee arthroplasty for osteoarthritis. After contact with the authors, trials without pain data 3–24 months postoperatively will be excluded. Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase and reference lists will be searched for eligible trials. Two authors will independently screen, extract data and assess the risk of bias. The primary outcome is pain scores 3–24 months postoperatively. Meta-analyses will be performed for interventions with two or more trials. We will conduct trial sequential analyses and assign Grading of Recommendations, Assessment, Development and Evaluation (GRADE) ratings.

Conclusion: No previous review on reduction of persistent postoperative pain has included non-pharmacological or invasive analgesic techniques. These two reviews with identical methodology will summarise the evidence of analgesic and physiotherapeutic perioperative interventions to prevent persistent pain.

PROSPERO registration: CRD42021284175.

KEYWORDS

chronic opioid therapy, chronic pain, clinical diversity in meta-analyses, persistent postoperative pain, persistent postsurgical pain, protocol, systematic review, trial sequential analysis

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1 | INTRODUCTION

As health-care availability, life expectancy and activity levels amongst the elderly increase, more patients are offered total hip and knee arthroplasties (THA and TKAs).^{1,2} In Denmark alone, around 10 000 primary TKAs and 11 000 primary THAs were performed in 2020 and these numbers are increasing.^{3,4} THA and TKA are associated with immediate moderate to severe postoperative pain and numerous analgesic interventions have been investigated in randomised trials.^{5,6} However, very limited evidence exists regarding the effects of perioperative interventions on reduction of persistent postoperative pain,^{7,8} defined by the International Statistical Classification of Diseases and Related Health Problems ICD-11 as pain lasting ≥ 3 months postoperatively.⁹

The lack of knowledge in this field is highly problematic as current evidence suggests that 9%–20% of THA and TKA patients experience persistent moderate to severe pain.^{10,11} Moreover, whilst no evidence of efficacy and safety exists for long-term opioid therapy,¹² opioids are often initiated during the acute pain phase and not tapered successfully in patients with persistent pain.¹³ This is problematic because opioid use has repeatedly been associated with worse outcomes, including increased mortality rate and decreased quality of life, physical capacity and cognitive abilities.^{14–16} Persistent pain is an immense clinical challenge¹⁷ with major economic and health-related consequences for both patients and society.¹⁴

It may be desirable to refrain from surgery in selected patients with high risk of chronic pain, such as patients with anxiety or depression,^{18,19} but due to lack of alternative treatments, it can be difficult in clinical practice. Avoiding collateral tissue damage during surgery, commonly referred to as ‘minimally invasive surgery’, is the most obvious preventive measure but is difficult to achieve in joint arthroplasty surgeries.²⁰ High pain levels in the immediate postoperative phase limit rehabilitation and have been associated with persistent pain, possibly due to central sensitisation or persistent peripheral inflammation.²¹ Central sensitisation is a dysfunction in the central nervous system typically induced by previous painful stimuli, which cause amplified sensation of pain (hyperalgesia) and perception of tactile stimuli as painful (allodynia).²² Central sensitisation is a well-established contributor to chronic pain conditions, including persistent postoperative pain, and it has been suggested that better perioperative care, comprising multimodal analgesia, physiotherapy and psychological interventions may prevent the development of persistent pain.^{21,23}

In two systematic reviews with identical methodology, we aim to investigate the effects of (a) perioperative analgesic interventions and (b) physiotherapeutic interventions in preventing and reducing persistent pain after total hip and knee arthroplasty.

2 | METHODS

The protocol was written following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols 2015 checklist

(Appendix S1).²⁴ The review was submitted to PROSPERO on 19 October 2021 (identifier CRD42021284175).

2.1 | Eligibility criteria

2.1.1 | Trials

We will include trials that randomly assign participants to a perioperative analgesic or physiotherapeutic intervention versus an inactive control group (i.e. placebo, sham or no intervention). Cluster-randomised trials will also be included. We will exclude conference abstracts and quasi-randomised trials. Cross-over trials are also excluded because all participants will likely have received both interventions within the 3–24 months.

2.1.2 | Participants

Adults aged 18 years or more scheduled for primary THA or TKA for osteoarthritis were included.

2.1.3 | Interventions

We will assess and separately report (a) perioperative analgesic interventions (e.g., systemic analgesics, central or regional nerve blocks and local infiltration analgesia) and (b) physiotherapeutic interventions (e.g., mobilisation regimens, acupuncture, transcutaneous electrical nerve stimulation and cryotherapy).

2.1.4 | Outcomes

We will only include trials that report pain or opioid use at 3–24 months postoperatively. If pain scores or opioid use at 3–24 months postoperatively have not been reported in otherwise includable trials, we will contact authors for additional data.

2.2 | Information sources

Cochrane Central Register of Controlled Trials, MEDLINE and Embase will be searched for eligible trials. The search strategy is presented in Appendix S2. Because we will contact authors of trials matching our other inclusion criteria for unpublished outcome data, no search words related to the outcomes will be used.

No date or language limitations will be imposed, although only journal articles that can be properly translated to English using Google Translate (translate.google.com) will be assessed. To ensure literature saturation, the reference lists of relevant trials and reviews will be screened for additional eligible trials. Prior to publication, an updated search will be carried out to ensure the inclusion of new eligible trials.

Authors of included trials will be contacted per email to elaborate on unclear bias domains and, if necessary, on details of interventions, outcomes and study results.

2.3 | Study records

All study records will be assessed by two independent reviewers (JL, AK and/or MM) in all stages of the reviewing process (screening, eligibility, extraction of data and risk of bias evaluation). A senior author will solve disagreements (SO or OM).

Screening will be performed using Endnote X9 (Clarivate Analytics). Data from included trials will be extracted in duplicate into two identical, predesigned spreadsheets and exported to the most recent version of R (<https://www.r-project.org/>) for meta-analysis.

2.4 | Data items

If a trial presents multiple data analyses, the data set with the highest number of included participants (i.e., the intention-to-treat analysis) will be used. When necessary, data will be approximated from figures. For continuous outcomes, if standard deviations are not reported, we will attempt to calculate the standard deviations using the available trial data.

Aside from outcome data, which are specified below, data on trials (country and year of conduct), participants (age, sex, inclusion of opioid users, preoperative pain score and control group analgesia) and interventions (dose, intensity, duration and timing) will be extracted.

2.4.1 | Primary outcome

Participants' mean pain scores at 3–24 months after THA or TKA (shortest follow-up time favoured). Both pain assessed at rest and pain during mobilisation will be used. To avoid unnecessary interference from concurrent pain conditions, outcomes will be assessed no later than 24 months postoperatively.

Pain scores assessed with 11-point and 101-point pain scales will be converted to millimetres on the 0–100 mm visual analogue scale (VAS) for analysis. Data from trials using incompatible pain scales will not be assessed. In the published literature, a minimal clinically important difference as low as 10 mm on the VAS scale has been suggested in studies on chronic pain.^{25,26} Because we will mostly investigate short-term interventions' effects on long-term outcomes, we will accept 10 mm as clinically important.

2.4.2 | Secondary outcomes

1. Number of participants with persistent pain or treated with opioid therapy 3–24 months after surgery. An arbitrary relative risk reduction of 10% will be considered clinically important.²⁶

2. Number of participants experiencing one or more serious adverse events (SAE) within 24 months after surgery. If the specific term 'SAE' is not used, but adverse events are systematically reported, these will be assessed as SAEs according to the International Conference on Harmonisation–Good Clinical Practice (ICH GCP) consensus guideline.²⁷ An arbitrary relative risk difference of 10% will be considered clinically important.

2.5 | Risk of bias

The risk of bias is assessed on outcome level using the RoB 2 tool adhering to the Cochrane Handbook for Systematic Reviews of Interventions' recommendations.^{28,29} Thus, bias from the randomisation process, deviations from intended interventions, missing outcome data, outcome measurement and selection of the reported results will be evaluated with help from the signalling questions and assigned 'low risk of bias', 'some concerns' or 'high risk of bias'. We will judge the overall risk of bias for an outcome to be high, if one or more domains are judged to be at 'some concerns' or 'high risk of bias'. We will judge the overall risk of bias for an outcome to be low if all domains are judged to be at 'low risk of bias'.

Conclusions will be based primarily on results at overall low risk of bias.

2.5.1 | Trial heterogeneity

Statistical heterogeneity will be evaluated by visual inspection of forest plots, by chi-square tests and quantified with the I^2 or τ^2 .

Clinical heterogeneity between trials combined in each meta-analysis will be assessed using the newly developed Clinical Diversity In Meta-analyses (CDIM) tool.³⁰ The clinical heterogeneity will guide further non-protocolised, subgroup analyses. Anticipated sources of clinical diversity will be evaluated through the planned subgroup analyses.

2.5.2 | Non-reporting bias

If 10 or more trials are synthesised in a meta-analysis, potential small study effects will be examined visually using funnel plots and quantitatively using relevant statistical tests (Egger, Harbord, Rücker).²⁸

2.5.3 | Sensitivity analyses

All outcomes will be assessed with best-worst case and worst-best case analyses.³¹ These analyses are used to assess the impact of missing data.

The primary outcome will be investigated with subgroup analyses based on.

1. type of surgery (THA vs. TKA)
2. type of anaesthesia (general vs. regional)
3. risk of bias assessment (low risk of bias trials vs. high risk of bias trials)

Further, regression analyses on the timing of outcome assessment will be performed. To avoid testing inter-trial differences, only trials with multiple pain score registrations at 3–24 months are included.

2.6 | Data synthesis

2.6.1 | Meta-analysis

In coherence with the Cochrane Handbook,²⁸ meta-analyses will be performed for all interventions investigated in two or more trials. Interventions may be administered with different frequency, dosage, mode of administration and timing in relation to surgery. The reviewing team will decide whether these differences allow for meta-analysis or not.

Meta-analyses will be conducted using the most recent version of R (<https://www.r-project.org/>). The continuous outcomes will be presented as mean differences with 95% confidence intervals (CI). Dichotomous outcomes will be presented as risk ratios (RR) with 95% CI.

We will compare the fixed effect estimate to the random effects estimate and primarily report the most conservative estimate.³¹

2.6.2 | Unit of analysis errors

Cluster-randomised trials are prone to the unit of analysis errors. When this is inadequately accounted for in the trial, we will perform approximate analyses using effective sample sizes.^{28,32}

2.6.3 | Trial sequential analysis

Previous reviews have evaluated the effect of some of the included interventions on similar outcomes. Repeated meta-analyses increase the risk of type 1 errors. To control the risk of random errors, trial sequential analyses (TSA) will be performed for all outcomes.^{33,34} For the primary (continuous) outcome, we will use an alpha of 5%, beta of 20%, difference of 10 mm on the VAS scale, variance and diversity as suggested by the meta-analysis. For the secondary (dichotomous) outcomes, an alpha of 5%, beta of 20%, relative risk difference of 10%, proportion at risk in the control group and diversity as suggested by the meta-analysis.

2.7 | Confidence in cumulative evidence

Grading of Recommendations, Assessment, Development and Evaluation (GRADE)^{35,36} ratings will be assigned by two authors

(JL, AK and/or MM) independently. GRADE assessments of certainty are determined through consideration of five domains: risk of bias, inconsistency, indirectness, imprecision and publication bias. Discrepancies will be discussed to arrive at consensus and if this is not possible, the disagreement will be solved by consulting a fourth reviewer (SO).

The overall certainty of evidence will be rated as high (further research is very unlikely to change our confidence in the estimate of effect), moderate (further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate), low (further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate) or very low (very uncertain about the estimate of effect).

3 | DISCUSSION

Although THA and TKA are frequently performed, knowledge on how to prevent persistent postoperative pain is lacking. With the two reviews outlined in this protocol, we aim to estimate the effect of perioperative analgesic and physiotherapeutic interventions on persistent pain after these surgical procedures.

We will pool data from THA and TKA trials because these procedures are relatively similar in terms of pain and rehabilitation,^{37–39} whereas inclusion of all types of surgery would create too much heterogeneity, though it would increase the amount of data.⁷ We have divided interventions into two reviews to increase the clinical relevance of results for anaesthesiologists and physiotherapists, respectively.

We have chosen patient-reported pain score as our primary outcome because it is the most direct measure of patient-experienced pain. Moreover, pain scores reflect both functional ability and quality of life⁴⁰ and are a frequently reported outcome.⁵ We expect more trials to report pain scores as continuous data. Therefore, we have chosen to use the continuous pain scores for our primary outcome. Dichotomising outcomes (secondary outcome) using scale-derived cut-offs are controversial.⁴¹ However, we find that a frequency outcome will be more intuitively understood by clinicians. Moreover, it allows us to combine multiple different outcome measures, which may be beneficial when aggregating data.

Because we investigate perioperative interventions with little or no long-term systemic effect, we expect most SAEs to appear shortly after surgery. Further, we know from a previous review that SAEs are sparsely reported in this research field.⁵ Therefore, we will include registered SAEs regardless of the postoperative follow-up period.

Overall, we believe that these reviews will provide interesting and important contributions on the long-term effects of perioperative interventions and optimally improve patient care.

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None.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS


Jens Laigaard, Troels Haxholdt Lunn, Ole Mathiesen and Søren Overgaard conceived the idea for the protocol. Jens Laigaard, Anders Karlsen, Mathias Maagaard and Søren Overgaard drafted the first version of the protocol. Andreas Creutzburg and Lukas Kristian Rosenberg helped finalising the draft with questions and corrections for the protocol. All authors critically revised the manuscript and take responsibility for the content.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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