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REVIEW ARTICLE

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Risk of serious adverse events associated with non-steroidal anti-inflammatory drugs in orthopaedic surgery. A protocol for a systematic review

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Abstract

Background: Postoperative pain is a common condition following orthopaedic surgeries and causes prolonged hospitalisation, delayed rehabilitation and hamper the quality of life. Non-steroidal anti-inflammatory drugs (NSAIDs) are effective analgesics and anti-inflammatory mediators in the treatment of postoperative pain. The association of NSAIDs with serious adverse events may however keep some clinicians and clinical decision makers from using NSAIDs perioperatively. The evidence regarding the risks of serious adverse events following perioperative use of NSAIDs in orthopaedic surgery is sparse and needs to be assessed in a systematic review. This is a protocol for a systematic review that aims to identify the risks of serious adverse events from perioperative use of NSAIDs in orthopaedic patients.

Methods: Our methodology is based on the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols and the eight-step assessment procedure suggested by Jakobsen and colleagues. We wish to assess if NSAIDs versus placebo, usual care or no intervention, will influence the risks of serious adverse events in patients undergoing orthopaedic surgery. We will include all randomised trials assessing the use of NSAIDs perioperatively. To identify trials we will search the Medical Literature Analysis and Retrieval System Online, Excerpta Medica database, Cochrane Central Register, Science Citation Index Expanded on Web of Science and BIOSIS. Two authors will screen the literature and extract data. We will use the 'Risk of Bias 2 tool' to assess trials. Extracted data will be analysed using RStudio and Trial Sequential Analysis. We will create a 'Summary of Findings' table in which we will present our primary and secondary outcomes. We will assess the quality of evidence using Grading of Recommendations Assessment, Development and Evaluation (GRADE).

Discussion: This systematic review can potentially aid clinicians and clinical decision makers in the use of NSAIDs for treatment of postoperative pain following orthopaedic surgeries.

KEYWORDS
NSAID, serious adverse events, systematic review

1 | BACKGROUND

1.1 | Orthopaedic surgery

More than 300 million surgeries are performed annually worldwide.[1] Orthopaedic procedures are amongst the most frequent procedures,[2] including major planned procedures as total hip and knee arthroplasty that are being performed in more than 1.5 million patients annually.[3] Orthopaedic surgery consists of both planned and acute surgery involving damage to bones and surrounding tissue, and is associated with moderate to severe postoperative pain, which often is insufficiently treated.[4]

NSAIDs are recommended for the treatment of acute pain in general,[5] and to treat postoperative pain for a range of orthopaedic procedures including total hip and knee arthroplasty.[6]

1.2 | Postoperative pain

Postoperative pain is mediated by nociceptors in the skin, viscera, muscles, joints and meninges, which are stimulated by noxious stimuli including prostaglandins.[7] Primary nerve fibres transmit the signal to the dorsal horn of the spinal cord. This signal ascends through the spinal cord to the pain matrix and parts of the somatosensory cortex.[7] The central nervous system has multiple ways of regulating these pathways.[8] The excitability of the central neurons can be decreased and peptides can be regulated so the experienced pain is less intense.[8] Additionally, the surgical stress creates an inflammatory response which leads to increased pain.[9] Given that the pain mechanisms are complex, and use a variety of signalling systems, a multimodal analgesic treatment approach is recommended to achieve optimal pain relief.[8]

Postoperative pain treatment aims to improve patient comfort, postoperative morbidity, rehabilitation, early mobilisation, quality of life and discharge readiness. Consequently, effective postoperative analgesia is a vital part of the postoperative care.[10–12] Opioids are a cornerstone in the treatment of acute pain, including postoperative pain, but are also associated with adverse effects such as nausea, vomiting and sedation, as well as the risk of addiction.[13] Treatment regimens that limit the need of opioids are therefore important for postoperative rehabilitation.

1.3 | Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) are a group of agents with analgesic, antipyretic and anti-inflammatory properties.[14] NSAIDs inhibit the prostaglandin G/H synthase via two isozymes, known as cyclooxygenase (COX)-1 and COX-2.[14] COX-1 catalyses the production of prostaglandins which regulate the gastrointestinal cytoprotection and platelet function.[15] COX-2 catalyses the production of prostaglandins primarily responsible for the inflammatory response.[15] NSAIDs can be subdivided in two groups, the non-selective NSAIDs (i.e. ibuprofen) and the selective COX-2 NSAIDs (coxibs, i.e. celecoxib).[15] NSAIDs inhibition of the COX-enzymes takes place both peripherally and centrally, and activates the medullary and cortical regions in the brain involved in the descending inhibitory pain cascade, inducing the analgesic effects of NSAIDs.[16]

NSAIDs are one of the most frequently used medications worldwide accounting for almost 5% of all prescriptions,[17] as well as being widely used as over-the-counter medication.[18] NSAIDs are regularly used in patients with inflammatory, acute, or chronic pain conditions such as, osteoarthritis, rheumatoid arthritis, menstrual cramps and for postoperative pain.[19]

1.4 | NSAID efficacy in treating postoperative pain

Multiple studies have shown NSAIDs to be effective analgesics in the treatment of postoperative pain. Furthermore, systematic reviews have shown that NSAIDs reduce opioid consumption, and thereby opioid-related adverse effects.[20–25] A recent Cochrane review showed that NSAIDs generally have a low number needed to treat (NNT) of NNT 2–3 for the treatment of acute pain.[26]

1.5 | Adverse effects of NSAIDs

Despite the well-documented beneficial effects of NSAIDs in pain treatment, multiple reviews advise caution in the use of NSAIDs due to the risk of both serious and non-serious adverse events.[27,28] However, another review acknowledges the presence of long-term adverse events associated with NSAIDs but concludes that this has yet to be shown with short-term usage.[29] Some of the most concerning adverse events are cardiovascular events, perioperative bleeding, renal impairment, gastrointestinal complications and impaired bone healing.[27,29]

NSAIDs have been shown to increase the risk of thrombosis, especially through the inhibition of COX-2.[30] One of the proposed mechanisms is prostacyclin having a restraining effect on several prothrombotic stimuli.[30] The inhibition of COX-2 results in less prostacyclin and therefore less restrain on the prothrombotic mediators.[30] Previously, this concern was primarily related to patients with known cardiac risk factors,[31] but a recent cohort study has shown that this risk also was found in healthy individuals using NSAIDs for nine to 34 days, though the number needed to harm (NNH) varied depending on the type of NSAID, with ibuprofen: NNH 432-446, diclofenac:

NNH 77-104, rofecoxib: NNH 14-24, celecoxib: NNH 20-24.[31] Furthermore, a recent review showed that a short-term treatment of less than 7 days, also increased the risk of thromboembolic events in patients with pre-existing cardiac risk factors.[30] However, the risks seem to be dose-dependent and differ amongst the types of NSAIDs.[32] Cardiovascular events are amongst the most frequently reported supposed adverse effects of NSAID usage, with cerebrovascular events being the most reported supposed adverse effect of NSAID usage in Denmark.[33]

NSAIDs are thought to increase the risk of postoperative bleeding by a COX-1-mediated inhibition of thromboxane formation. A review from 2005 found a statistical significant increase in the risk of serious postoperative blood loss from 0.2% to 1.7%, with an odds ratio of 4.54 and NNH of 65.[24] The review does not specify the duration of NSAID use.[24] In contrast, another recent review found no significant association between NSAIDs and postoperative bleeding.[34]

NSAIDs have both acute and long-term effect on renal function.[35] The acute effect arises from the inhibition of prostaglandins, these take part in keeping the renal blood flow high.[35] The acute impairment is typically seen in patients with predisposing conditions, and is reversible after cessation of the NSAID.[35] Additionally, a Cochrane review found the reduction in renal function to be clinically irrelevant in patients with normal preoperative renal function.[36] The long-term effect is more poorly understood but the use of NSAIDs may lead to permanent irreversible renal impairment after multiple years of NSAID use.[35]

In orthopaedic surgery, there is a concern that the usage of NSAIDs will lead to delayed bone healing or non-union, which could result in additional surgical procedures, prolonged immobilisation and pain.[37] COX-1 and COX-2 regulate prostaglandin E_2 that is believed to regulate osteoblast activity, resulting in NSAIDs increasing the risk of impaired bone healing.[37] A recent review found an odds ratio of 2.07 (CI: 1.19–3.61) for non-union or delayed union in patients prescribed NSAID.[37] However, for a subgroup of low-dose or short duration of NSAID use, the review found no difference between NSAID and placebo (odds ratio: 1.68, CI: 0.63–4.46).[37]

1.6 | Why is this review important?

Previous reviews concerning the adverse effects associated with perioperative NSAID treatment have primarily been conducted with a focus on a single specific serious adverse events, single NSAIDs, or adverse events across surgical specialities. These reviews did not apply an updated methodology using risk of bias, trial sequential analysis and GRADE (see Tables S1 and S2). Furthermore, previous reviews have generally only included a short-term follow-up, and shown little information regarding long-term effects.[29]

An updated systematic review in orthopaedic surgery, which include meta-analysis, evaluation of systematic errors (risk of bias), evaluation of risks of random errors (trial sequential analysis) and rating of certainty of evidence, (GRADE) is lacking (see Table S3). Focusing on orthopaedic surgery, could highlight safety concerns specific to the unique patient population, as well as examining if there is a procedure-related correlation in serious adverse events following NSAID treatment.

This study's importance lies in a needed update on existing literature, with a scope specific to a single surgical speciality and its unique patient population.

The aim of this study is to assess the harmful effects of NSAIDs versus placebo, no intervention, or usual care in patients undergoing orthopaedic surgery. We expect the results from this review to elucidate the risks of NSAID administration perioperatively.

2 | METHODS

This protocol for a systematic review is developed and written in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines.[38,39]

2.1 | Criteria for considering studies for this review

2.1.1 | Types of studies

We will include all randomised clinical trials irrespective of trial design, publication year, publication type, publication status, setting and language. We will include cluster-randomised trials. We will exclude quasi-randomised trials. Large observational studies identified in our search strategy for randomised clinical trials, will be included for a narrative description of rare and long-term serious adverse events. Observational studies will not be included in any meta-analysis of intervention effects.

2.1.2 | Types of participants

We will include adults (≥18 years old) undergoing orthopaedic surgery. We will include trials on both acute and elective surgeries.

2.1.3 | Types of interventions

We will include any trial allocating participants to receive any NSAID compared with placebo, usual care or no intervention perioperatively. We will include trials with any duration of treatment. We will accept any co-intervention, if the co-intervention is intended to be delivered similarly to both the intervention and control groups.

2.2 | Outcome measures

2.2.1 | Primary outcome

Proportion of participants with one or more serious adverse events. The ICH-GCP defines a serious adverse event as any untoward

medical occurrence that resulted in death, was life-threatening, required hospitalisation or prolonging of existing hospitalisation, resulted in persistent or significant disability, or jeopardised the participant.[40] If the trialists do not use the ICH-GCP definition, we will include the data if the trialists use the term 'serious adverse event'. If the trialists do not use the ICH-GCP definition nor use the term serious adverse event, then we will also include the data if we judge the event to fulfil the ICH-GCP definition for a serious adverse event. We will as exploratory analyses assess each single specific serious adverse event separately.

2.2.2 | Secondary outcomes

1. Specific serious adverse events
   a. Acute myocardial infarction, as defined by trialists
   b. Stroke, as defined by trialists
   c. Gastrointestinal ulcers, as defined by trialists
   d. Renal impairment, as defined by trialists
   e. Non-union or delayed bone healing, as defined by trialists

For all outcomes, we will use the trial results reported at maximal follow-up. All dichotomous outcomes will be assessed as proportions.

2.3 | Search methods

2.3.1 | Electronic searches

We will search the Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica database (EMBASE), Cochrane Central Register of Controlled Trials (CENTRAL), Science Citation Index Expanded on Web of Science and BIOSIS to identify relevant trials. We will search all databases from their inception to the present.

2.3.2 | Searching other resources

The reference lists of relevant publications will be checked for any potential relevant unidentified trials.

2.4 | Data collection and analysis

We will conduct data collection and analysis according to the recommendations in the *Cochrane Handbook Systematic Reviews of Interventions*,[41] and according to the eight-step procedure as described by Jakobsen and colleagues.[42]

2.4.1 | Selection of studies

Two authors will independently and in pairs screen titles and abstracts. Relevant full-text study reports will be retrieved and assessed for eligibility by two review authors independently and in pairs. Disagreements will be resolved through discussion or by consulting a third co-author.

2.4.2 | Data extraction and management

Two authors will independently and in pairs extract data from included trials unto a standardised extraction sheet. Disagreements will be resolved through discussion or by consulting a third author. The following trial characteristics will be extracted.

1. Methods: date of publication and duration of trial
2. Participants: estimated sample size, number randomised, number analysed, number lost to follow-up/withdrawn, type of surgery, mean age, sex, inclusion and exclusion criteria
3. Intervention: intervention (type of drug, duration, dose, mode of administration), co-intervention (type, duration, dose, mode of administration), comparison (type, duration, dose, mode of administration), concomitant medications and excluded medications
4. Outcomes: primary and secondary outcomes as specified under 'outcomes'
5. Other: bias risk components (defined in assessment of bias paragraph), trial funding and conflict of interest of the trialists

We will create a 'Characteristics of included studies' table. In this table, we will note if outcome data were not reported in a usable fashion. Disagreements will be resolved by discussion or by consulting a third co-author if needed.

2.4.3 | Assessment of risk of bias in included studies

We will use the instructions given in the 'Risk of Bias 2 tool'[43] in our assessment of methodology in included trials and thereby the risk of bias in the included trials. Furthermore, we will assess the risk of profit bias. Two authors will independently evaluate the methodology in the included trials in the following aspects.

1. Randomisation process
2. Deviations from the intended interventions
3. Missing outcome data
4. Measurements of the outcome
5. Selection of the reported results
6. For profit bias

Disagreements between the authors will be resolved by discussion or by consulting a third co-author if needed. Assessing all the above enables a classification of the included randomised trials as being at an overall 'low risk of bias' or an overall 'high risk of bias'. Trials will be classified as being at an overall 'high risk of bias'; if any of the trial components are classified as 'some concerns' or 'high risk

of bias'. Trials with an overall 'high risk of bias' tends to overestimate positive intervention effects and underestimate negative effects.[44–50] We will assess risks of bias for each outcome result (bias due to missing outcome data, bias in selection of the reported result and bias in measurement of the outcome may differ between outcomes).

Our primary conclusions will be based on the results of our primary outcomes at an overall 'low risk of bias'. Our conclusions will be presented in a 'Summary of Findings table'.

2.5 | Measures of treatment effect

2.5.1 | Serious adverse events

Two authors will independently categorise serious adverse events from each trial and any disagreement will be resolved by discussion or by consulting a third author, if necessary.

We will calculate risk ratios (RRs) with 95% confidence Interval (CI) for all the dichotomous outcomes, as well as trial sequential analysis (TSA)-adjusted CIs (see below).

2.6 | Dealing with missing data

We will use intention to treat data if provided by the trialists. If any relevant data are missing from the included trials, we will contact the authors to obtain such data. We will not use intention-to-treat data if the original report did not contain such data.

2.7 | Assessment of heterogeneity

We will produce and investigate forest plots to assess any visual signs of heterogeneity. Secondly, we will assess statistical heterogeneity by χ^2-test (threshold $p < .10$), I^2-statistics and τ^2 statistics.[41,51,52] We will investigate possible clinical heterogeneity by performing subgroup analyses. In the event of substantial or unexpected heterogeneity, we may conclude that meta-analysis should be avoided.[41]

To assess reporting bias, we will use funnel plots if 10 or more trials are included. We will visually inspect the funnel plots to assess the risk of publication bias. For our dichotomous outcomes, we will test asymmetry using the Harbord test[53] if τ^2 is less than 0.1 or with the Thompson test[41] if τ^2 is greater than 0.1.

2.8 | Unit of analysis issues

We will include randomised clinical trials. For trials using a cross-over design, only data from the first period will be included.[41] For cluster randomised trials we will adjust the original sample size to the effective sample size using the 'design effect', incorporating the intra-cluster correlation coefficient.[41]

If multiple trial arms are used as a study design, we will only use the relevant arms in our meta-analysis. If two comparisons are combined in the same meta-analysis we will halve the control group to avoid double-counting.[41] These measures will eliminate unit of analysis issues.

2.9 | Data synthesis

2.9.1 | Meta-analysis

We will conduct our meta-analysis in accordance with the recommendations of the Cochrane Handbook for Systematic Reviews of interventions[41] and the eight-step assessment procedure suggested by Jakobsen et al.[42] We will use the statistical software RStudio[54] and the package 'meta'[55] to analyse data. We will assess our results with both random-effects meta-analysis[56] and fixed-effect meta-analysis[57] and primarily report the most conservative results (highest P-value). The less conservative result will be reported and considered as a sensitivity analysis. We use one primary outcome and multiple secondary outcomes. For our primary outcome, we will consider a p value of .05. Our secondary outcomes will be considered hypothesis generating; therefore, we will not be adjusting the p value and still use a p value of .05 as our thresholds for statistical significance. We will use the eight-step procedure to asses if the thresholds for significance are crossed.[42]

2.9.2 | Trial sequential analysis

In order to minimise the risk of random errors resulting from sparse data and repetitive testing for significance in cumulative meta-analysis, we will use TSA. TSA is a method where the required information size (the number of participants needed in a meta-analysis to detect or reject a pre-specified effect of an intervention) is calculated. Using TSA also produces a cumulative Z-curve and detects potential breaches of relevant trial sequential monitoring boundaries with adjusted p values.[58–63]

We will estimate the required information size based on the observed proportion of patients with an outcome in the control group, a relative risk decrease or increase of 25%, an α of 5% for our primary outcome and an α of 5% for our secondary outcomes, a β of 20% and diversity[64] as suggested by our meta-analysis.

2.10 | Subgroup analysis and investigation of heterogeneity

2.10.1 | Subgroup analysis

By performing subgroup analysis, we will attempt to determine whether the potential effects are influenced by risk of bias, the type

of orthopaedic surgery, type, dose and duration of NSAID, or the usage of NSAIDs prior to surgery.

We will perform the following subgroup analysis when analysing the primary outcome.

1. Trial results with high risk of bias compared to trial results with low risk of bias
2. Trials including participants undergoing arthroplasty surgeries compared to trials including participants undergoing osteosynthesis surgeries compared to trials including participants undergoing other orthopaedic surgeries
3. According to type of NSAIDs used
4. According to the duration of NSAID use (trials using at or above median duration compared to trials using below median duration)
5. According to dose of NSAIDs (trials using at or above median dose compared to trials using below median dose)
6. Usage of NSAID prior to surgery, compared with no usage prior to surgery
7. Meta-regression of dose of NSAIDs
8. Meta-regression of duration of NSAIDs

We will use the formal test for subgroup interactions in RStudio.[54] We expect trials at an overall 'high risk of bias' to underestimate potential harm and overestimate potential benefit. We expect a higher risk with longer duration and higher dose of NASID.

2.11 | Sensitivity analysis

To assess the potential impact of the missing data, we will perform the two following sensitivity analyses on both our primary outcome as well as our secondary outcomes.

1. 'Best/worst-case' scenario
2. 'Worst/best-case' scenario

In the best-case scenario, we will assume that participants lost to follow-up did not experience a serious adverse event. In the worst-case scenario, we will assume that participants lost to follow-up experienced a serious adverse event. Thereby creating two extremes around our primary point-estimate. We will present both results in our review.

Other post hoc sensitivity analysis may be warranted if unexpected clinical or statistical heterogeneity is identified during the analysis of the review results.[42]

3 | 'SUMMARY OF FINDINGS' TABLE

Our 'Summary of Findings' table will be based on our prespecified primary and secondary outcomes. We will use the GRADE considerations (bias risk of the trials, consistency of effect, imprecision [assessed by TSA], indirectness and publication bias) to assess the quality of the body of evidence concerning our prespecified outcomes. Using GRADE will result in the quality of evidence for each outcome as being very low, low, moderate, or high.[42,65–68] We will present two 'Summary of Findings' tables, one based on the results from trials at an overall low risk of bias, and one based on the results from all trials.

4 | DISCUSSION

This protocol for a systematic review on randomised clinical trials has several strengths. The development of the protocol is based on the PRISMA-P guidelines.[38,39] The methodology is pre-defined and generally follows the recommendations of the Cochrane Handbook for systematic Reviews of Interventions,[41] the eight-step procedure assessment as suggested by Jakobsen et al,[42] trial sequential analysis,[60] and the GRADE assessment.[67] Through our predefined methodology, we consider the risk of random as well as systematic errors.

This protocol for a systematic review also has limitations. We expect potential trials to vary in follow-up, as well as duration and dose of NSAIDs, giving rise to clinical heterogeneity. Furthermore, we expect potential trials to not register dose and duration of NSAID usage prior to inclusion.

With this systematic review, we seek to provide clinicians and clinical decision makers with reliable evidence adjusted for bias, sparse data and repetitive testing regarding the potential risks of using NSAID in a perioperative regime.

We will conduct a similar systematic review on NSAID-induced serious adverse events in gastrointestinal surgery patients.

AUTHOR CONTRIBUTIONS

MFL: drafted the protocol. **SB:** aided in the drafting of the protocol and amended the protocol. **CCWL:** amended the protocol. **MEL:** amended the protocol. **AST:** amended the protocol. **JCJ:** amended the protocol and contributed to the design and conception of the study. **MM:** aided in the drafting of the protocol, amended the protocol, and contributed to the design and conception of the study. **OM:** amended the protocol and contributed to the design and conception of the study.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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