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REVIEW ARTICLE

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Risks of serious adverse events associated with non-steroidal anti-inflammatory drugs in gastrointestinal surgery. A protocol for a systematic review with meta-analysis and trial sequential analysis

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Abstract

Background: Post-operative pain is frequent following gastrointestinal surgery and may result in prolonged hospitalisation, delayed recovery, and lower quality of life. Non-steroidal anti-inflammatory drugs (NSAIDs) are effective analgesics and recommended by Enhanced Recovery After Surgery guidelines as part of opioid-sparing multimodal treatment. However, perioperative NSAID treatment may be associated with increased risk of harm. We will investigate the risks of serious adverse events associated with perioperative NSAID treatment in patients undergoing gastrointestinal surgery.

Methods: This protocol uses the recommendations of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols. We wish to assess the effects of NSAIDs versus placebo, usual care, or no intervention on the incidence of serious adverse in patients undergoing gastrointestinal surgery. We will include all randomised trials. To identify trials, we will search the medical literature analysis and retrieval system online, excerpta medica database, cochrane central register of controlled trials, web of science core collection, and BIOSIS. Two authors will screen the literature and extract data. We will use the 'Risk of Bias 2 tool' to assess the risks of systematic errors. We will perform meta-analyses using R. We will use Trial Sequential Analysis to account for the risks of random errors. We will create a "Summary of Findings"-table in which we will present our primary and secondary outcome results. We will assess the certainty of the evidence using grading of recommendations assessment, development and evaluation.

Discussion: This systematic review can potentially elucidate the risks of perioperative NSAID treatment in gastrointestinal surgery and inform the already established non-opioid multimodal pain treatment regimen recommended by enhanced recovery after surgery guidelines.

KEYWORDS
anastomotic leak, gastrointestinal, GRADE, non-steroidal anti-inflammatory drugs, perioperative, safety, serious adverse events, trial sequential analysis

1 | BACKGROUND

1.1 | Pain after gastrointestinal surgery

Gastrointestinal surgery includes both open- and laparoscopic surgery. Primary injury in gastrointestinal surgery is direct trauma to the abdominal wall, damage from tissue mobilisation or surgical impact on the organs.[1] Secondary injury includes for example, bleeding, anaesthetic effects, and patient positioning in regards to abdominal pressure of the CO_2 pneumoperitoneum.[1] Major abdominal surgery induces an immuno-inflammatory response.[1] The impairment of vascular permeability together with excessive fluid administration, may lead to interstitial oedema, thus delaying recovery of gastrointestinal function and an increased risk of anastomotic leakage.[2] Pain from internal organs following surgery–arising from hollow organ stretch or distention, traction on the mesentery and organ ischemia–promotes the inflammatory processes of the surgical stress response.[3] All of the aforementioned responses may both individually and in combination lead to prolonged rehabilitation, including delayed mobilisation, muscle atrophy, decreased insulin sensitivity, thromboembolic disease, and atelectasis.[4,5]

1.2 | Gastrointestinal surgery and pain treatment

Post-operative pain following intraabdominal surgery is often insufficiently treated.[6] While laparoscopic surgery has been shown to reduce pain, shorten length of stay, reduce morbidity, and decrease short-term analgesic requirements,[7] long-term outcomes have shown equivalence between laparoscopic and open surgery.[8] Multimodal pain treatment is the leading treatment principle for managing acute post-operative pain to reduce surgical stress response, improve post-operative rehabilitation, and decrease opioid consumption. NSAIDs are an important element in post-operative pain management. The combination of paracetamol and NSAIDs are recommended by Enhanced Recovery After Surgery guidelines in patients undergoing open- and laparoscopic abdominal surgery.[7] The combination has previously been shown to reduce opioid consumption and therefore reduce opioid related adverse events.[9]

1.3 | NSAIDs analgesic profile

NSAIDs have antipyretic, analgesic, and anti-inflammatory properties. Through blockade of the cyclooxygenase (COX) isoenzymes, COX-1 and COX-2, they impair the synthesis of prostaglandins.[10] NSAIDs have shown to affect both central and peripheral nociception.[11] Blocking of the COX enzymes in peripheral nociceptors, inhibits prostaglandin synthesis, which decreases sensitization in response to tissue damage.[11] Furthermore, by inhibiting the COX-2 enzyme in the dorsal horn of the spinal cord, which is involved in central sensitization, medullary and cortical descending inhibition pathways are activated, resulting in reduced pain in the surrounding uninjured tissue.[11]

1.4 | Serious adverse events from NSAID treatment

In spite of the extensive therapeutic utilities of NSAIDs, many studies advocate caution in the use of perioperative NSAIDs, due to risk of adverse events, including gastrointestinal injury,[12] cardiovascular morbidity and mortality,[13] and renal impairment.[14] Specific risks of serious injuries related to the gastrointestinal tract include gastric and duodenal ulcers, and complications hereof: perforation, haemorrhage, and obstruction; and risk of anastomotic leakage.[15]

1.5 | Gastrointestinal ulcers and bleeding

The pathophysiological basis for NSAID-induced upper gastrointestinal injury, is relative deficiency of gastroduodenal mucosal prostaglandins, resulting in weakening of the epithelial barrier function and secondary acid-related ulceration.[12] Mucosal repair in response to injury is also prostaglandin dependant.[12] NSAIDs can therefore increase the risk of ulcers and due to the antiplatelet action of COX-1 inhibition, promote bleeding.[12]

1.6 | Anastomotic leakage

In terms of surgery related complications, the possible association between NSAID use and anastomotic leaks in colorectal surgery is

primarily based on experimental, retrospective and case-series studies, and lacks definitive studies.[16] However, NSAID use in colorectal surgery with anastomosis is generally cautioned, especially for subgroups of non-selective NSAIDs with high COX-2 affinity, for example, diclofenac, and COX-2 inhibitors.[17,18]

1.7 | Renal impairment

Prostaglandin synthesis is important for renal function through regulation of a variety of physiological kidney processes. NSAID treatment is cautioned in individuals suffering from renal impairment and underlying diseases affecting kidney function.[19]

1.8 | Cardiovascular events

One of the proposed mechanisms for cardiovascular risk of NSAIDs is the observed shift in the prothrombotic-antithrombotic balance on endothelial surfaces, towards thrombosis.[20] NSAIDs have been found to impact renal function and the regulation of fluid balance, accentuating heart failure[21] and together with the pro-thromboembolic effect, contribute to the risk of myocardial infarction and stroke.[22]

1.9 | Why is this review important

Previous reviews assessing the adverse events associated with perioperative NSAID treatment in patients undergoing gastrointestinal surgery have focused on individual serious and non-serious adverse events across surgical specialities (See 'Table S1' in appendix). Further, previous reviews have generally addressed short-term follow up and shown little information regarding long-term events.[23]

An updated systematic review in gastrointestinal surgery, that include meta-analyses, evaluation of risk of systematic error (risk of bias), risk of random errors (trial sequential analysis), and rating certainty of evidence (GRADE) is lacking (See 'Table S2' in appendix). Focus on gastrointestinal surgery could highlight safety specific to this patient population, as well as examining if there are procedure-related correlations for serious adverse events following perioperative NSAID treatment. This study's importance lies in a needed update of existing literature with a scope specific to gastrointestinal surgery.

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

2 | METHODS

This protocol for a systematic review has been reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis protocols (PRISMA-P) guidelines.[24] This protocol is registered on PROSPERO.[25]

2.1 | Design

Systematic review of randomised trials with meta-analysis, trial sequential analysis, and grading of recommendations assessment, development and evaluation.

3 | ELIGIBILITY CRITERIA

3.1 | 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 during our search 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.

3.2 | Types of participants

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

3.3 | Types of interventions

Experimental intervention: NSAIDs in any form, dose, or duration.

Control intervention: placebo, usual care, or no intervention.

3.4 | Co-interventions

We will accept any co-intervention if these are delivered similarly in both the experimental and control group.

4 | OUTCOME MEASURES

4.1 | Primary outcome

1. Proportion of participants with one or more serious adverse events according to the International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use – Good Clinical Practice (ICH-GCP) definition.
   ICH-GCP is defined as any untoward medical occurrence that resulted in death, was life-threatening, required hospitalisation or prolonging of existing hospitalisation, and resulted in persistent or significant disability.[26] If the trialists do not use the ICH-GCP definition, we will include data hierarchically based on the trialists reported "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.

4.2 | Secondary outcomes

1. Specific serious adverse events
   a. Acute myocardial infarction (as defined by trialist)
   b. Stroke (as defined by trialist)
   c. Gastrointestinal ulcer (as defined by trialist)
   d. Renal impairment (as defined by trialist)
   e. Anastomotic leakage (as defined by trialist)

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

5 | SEARCH METHODS

5.1 | Electronic searches

We will search the Medical Literature Analysis and Retrieval System Online, Excerpta Medica database, Cochrane Central Register of Controlled Trials, Science Web of Science Core Collection, and BIOSIS.

5.2 | Searching other resources

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

5.3 | Data collection and analysis

We will conduct data collection and analysis according to the recommendations in the *Cochrane Handbook Systematic Reviews of Interventions*,[27] and assess if thresholds for clinical and statistical significance are crossed according to the eight-step procedure as described by Jakobsen and colleagues.[28]

5.4 | Selection of studies

Two review 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. Trial selection will be displayed in an adapted flow diagram.

5.5 | Data extraction and management

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

- Methods: date of publication and duration of trial
- Participants: estimated sample size, number randomised, number analysed, number lost to follow-up/withdrawn, type of surgery, mean age, sex, inclusion and exclusion criteria
- 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
- Outcomes: primary and secondary outcomes specified in the trials, serious adverse events and specific serious adverse events
- Other: bias risk components (defined in assessment of bias paragraph), trial funding, and conflict of interest of the trialists

5.6 | Trial characteristics

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.

6 | ASSESSMENT OF RISK OF BIAS

We will use the instructions given in the 'Revised Cochrane risk-of-bias tool for randomized trials' in our assessment of the risks of systematic errors in included trials.[29] Furthermore, we will assess the risk of for-profit bias. Two authors will independently and in pairs assess the risk of bias according to the following domains:

- Randomisation process
- Deviations from the intended interventions
- Missing outcome data
- Measurements of the outcome
- Selection of the reported results
- For-profit bias

Disagreements between the two authors will be resolved by discussion or by consulting a senior co-author if needed. Assessing all the above enables a classification of the included trials' results as being at an overall 'low risk of bias' or 'high risk of bias'. Trial results will be classified as being at an overall "high risk of bias" if any of the domains are classified as "unclear" or "high risk of bias". Trial results with an overall "high risk of bias" tends to overestimate positive intervention effects and underestimate negative effects.[30–36] Trial results will be classified as being at overall "low risk of bias" if all the domains are judged to be at low risk of bias. 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 as these may differ between outcomes).

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

7 | MEASURES OF TREATMENT EFFECT

7.1 | 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.

We will calculate risk ratios with 95% confidence intervals (CI) for all the dichotomous outcomes, as well as Trial Sequential Analysis (TSA)-adjusted CIs (see below).

7.2 | Dealing with missing data

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

7.3 | Assessment of heterogeneity

We will primarily visually investigate forest plots for signs of heterogeneity. Secondly, we will assess statistical heterogeneity by chi^2-test (threshold $p < .10$), I^2-statistics, and τ^2 statistics.[27,37,38] 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.[27]

To assess reporting bias, we will use funnel plots if 10 or more trials are included. We will visually inspect the funnel plots for signs of small study bias. For our dichotomous outcomes, we will test asymmetry using the Harbord test[39] if τ^2 is less than 0.1, or with the arcsine-transformed Thompson test if τ^2 is greater than 0.1.[27]

7.4 | Unit of analysis issues

For trials using a cross-over design, only data from the first period will be included.[27] 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.[27] 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.[27] These measures will eliminate unit of analysis issues.

8 | DATA SYNTHESIS

8.1 | Meta-analysis

We will conduct our meta-analyses according to the recommendations of the Cochrane Handbook for Systematic Reviews of interventions[27] and an eight-step assessment procedure for assessing if thresholds for statistical and clinical significance as crossed.[28] We will use the statistical software RStudio[40] to analyse data. We will perform both random-effects meta-analysis[41] and fixed-effect meta-analysis[42] 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 outcomes, we will consider a p value of .05. Our secondary outcomes will only be considered hypothesis generating, and therefore we will not be adjusting the p value for the assessment of our secondary outcomes.

8.2 | Trial sequential analysis

To minimise the risks 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-defined assumed effect of an intervention) is calculated. TSA creates a graph that allows for the visual detection of breaches of relevant trial sequential monitoring boundaries (benefit, harm, futility) with adjusted p values.[43–48]

We will estimate the required information size based on the observed proportion of patients with an outcome in the control group, a relative risk increase of 25%, an alpha of 5% for our primary outcome and secondary outcomes, a beta of 20%, and diversity as suggested by the meta-analysis.[49]

9 | SUBGROUP ANALYSIS AND INVESTIGATION OF HETEROGENEITY

9.1 | Subgroup analysis

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

- Trial results with high risk of bias compared to trial results with low risk of bias.
- Trials including participants undergoing upper gastrointestinal surgeries compared to trials including participants undergoing lower gastrointestinal surgeries compared to trials including participants undergoing other gastrointestinal surgeries.

- According to type of NSAIDs used.
- According to the duration of NSAID use (trials using at or above median duration compared to trials using below median duration).
- According to dose of NSAIDs (trials using at or above median dose compared to trials using below median dose).
- Usage of NSAID prior to surgery, compared with no usage prior to surgery.
- Meta-regression of dose of NSAIDs.
- Meta-regression of duration of NSAIDs.

We will use the formal test for subgroup interactions in RStudio.[40] We expect trials at an overall 'high risk of bias' to underestimate potential harm. We expect a higher risk with longer duration of NASID usage. We expect a higher risk with higher dose of NSAID.

9.2 | Sensitivity analysis

To assess the potential impact of the missing data, we will perform the two following sensitivity analyses for both our primary and secondary outcomes.

- 'Best/worst-case' scenario
- '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.[28]

10 | 'SUMMARY OF FINDINGS' TABLE

We will create a 'Summary of Findings' table presenting our prespecified primary and secondary outcomes. We will use the five GRADE considerations (risk of bias, inconsistency of trial results, 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 being very low, low, moderate, or high.[50] 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.

11 | 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.[24,51] The methodology is pre-defined and follows the recommendations of the Cochrane Handbook for systematic Reviews of Interventions,[27] the eight-step procedure assessment as suggested by Jakobsen et al,[28] TSA,[45] and the GRADE assessment.[52] 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 practice decision makers with reliable evidence adjusted for bias, sparse data, and repetitive testing and inform the already established non-opioid multimodal pain treatment regimen recommended by Enhanced Recovery After Surgery guidelines.

We will conduct a similar systematic review on the risk of serious adverse events associated with NSAIDs in orthopaedic surgery patients.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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REFERENCES

1. Scott MJ, Miller TE. Pathophysiology of major surgery and the role of enhanced recovery pathways and the anesthesiologist to improve outcomes. *Anesthesiol Clin*. 2015;33(1):79-91. doi:10.1016/j.anclin.2014.11.006
2. Chowdhury AH, Lobo DN. Fluids and gastrointestinal function. *Curr Opin Clin Nutr Metab Care*. 2011;14(5):469-476. doi:10.1097/MCO.0b013e328348c084
3. Gebhart GF, Bielefeldt K. Physiology of visceral pain. *Compr Physiol*. 2016;6(4):1609-1633. doi:10.1002/cphy.c150049
4. Brower RG. Consequences of bed rest. *Crit Care Med*. 2009;37(10 Suppl):S422-S428. doi:10.1097/CCM.0b013e3181b6e30a
5. Convertino VA, Bloomfield SA, Greenleaf JE. An overview of the issues: physiological effects of bed rest and restricted physical activity. *Med Sci Sports Exerc*. 1997;29(2):187-190. doi:10.1097/00005768-199702000-00004
6. Gerbershagen HJ, Aduckathil S, van Wijck AJ, et al. Pain intensity on the first day after surgery: a prospective cohort study comparing 179 surgical procedures. *Anesthesiology*. 2013;118(4):934-944. doi:10.1097/ALN.0b013e31828866b3
7. Feldheiser A, Aziz O, Baldini G, et al. Enhanced recovery after surgery (ERAS) for gastrointestinal surgery, part 2: consensus statement for anaesthesia practice. *Acta Anaesthesiol Scand*. 2016;60(3):289-334. doi:10.1111/aas.12651

8. Kuhry E, Schwenk W, Gaupset R, Romild U, Bonjer J. Long-term outcome of laparoscopic surgery for colorectal cancer: a cochrane systematic review of randomised controlled trials. *Cancer Treat Rev*. 2008;34(6):498-504. doi:10.1016/j.ctrv.2008.03.011
9. Stasiowska MK, Ng SC, Gubbay AN, Cregg R. Postoperative pain management. *Br J Hosp Med (Lond)*. 2015;76(10):570-575. doi:10.12968/hmed.2015.76.10.570
10. Arfe A, Scotti L, Varas-Lorenzo C, et al. Non-steroidal anti-inflammatory drugs and risk of heart failure in four European countries: nested case-control study. *BMJ*. 2016;354:i4857. doi:10.1136/bmj.i4857
11. Gupta A, Bah M. NSAIDs in the treatment of postoperative pain. *Curr Pain Headache Rep*. 2016;20(11):62. doi:10.1007/s11916-016-0591-7
12. Scheiman JM. NSAID-induced gastrointestinal injury: a focused update for clinicians. *J Clin Gastroenterol*. 2016;50(1):5-10. doi:10.1097/MCG.0000000000000432
13. Schjerning AM, McGettigan P, Gislason G. Cardiovascular effects and safety of (non-aspirin) NSAIDs. *Nat Rev Cardiol*. 2020;17(9):574-584. doi:10.1038/s41569-020-0366-z
14. Murray MD, Brater DC. Renal toxicity of the nonsteroidal anti-inflammatory drugs. *Annu Rev Pharmacol Toxicol*. 1993;33:435-465. doi:10.1146/annurev.pa.33.040193.002251
15. Coxib, Traditional NTC, Bhala N, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet*. 2013;382(9894):769-779. doi:10.1016/S0140-6736(13)60900-9
16. Van Koughnett JA, Wexner SD. NSAIDs and risk of anastomotic leaks after colorectal surgery. *Nat Rev Gastroenterol Hepatol*. 2014;11(9):523-524. doi:10.1038/nrgastro.2014.130
17. Rushfeldt CF, Sveinbjornsson B, Soreide K, et al. Risk of anastomotic leakage with use of NSAIDs after gastrointestinal surgery. *Int J Colorectal Dis*. 2011;26(12):1501-1509. doi:10.1007/s00384-011-1285-6
18. Fjederholt KT, Okholm C, Svendsen LB, Achiam MP, Kirkegård J, Mortensen FV. Ketorolac and other NSAIDs increase the risk of anastomotic leakage after surgery for GEJ cancers: a cohort study of 557 patients. *J Gastrointest Surg*. 2018;22(4):587-594. doi:10.1007/s11605-017-3623-7
19. Horl WH. Nonsteroidal anti-inflammatory drugs and the kidney. *Pharmaceuticals (Basel)*. 2010;3(7):2291-2321. doi:10.3390/ph3072291
20. Caughey GE, Cleland LG, Penglis PS, Gamble JR, James MJ. Roles of cyclooxygenase (COX)-1 and COX-2 in prostanoid production by human endothelial cells: selective up-regulation of prostacyclin synthesis by COX-2. *J Immunol*. 2001;167(5):2831-2838. doi:10.4049/jimmunol.167.5.2831
21. Varga Z, Sabzwari SRA, Vargova V. Cardiovascular risk of nonsteroidal anti-inflammatory drugs: an under-recognized public health issue. *Cureus*. 2017;9(4):e1144. doi:10.7759/cureus.1144
22. Marsico F, Paolillo S, Filardi PP. NSAIDs and cardiovascular risk. *J Cardiovasc Med (Hagerstown)*. 2017;18(1):e40-e43. doi:10.2459/JCM.0000000000000443
23. Mathiesen O, Wetterslev J, Kontinen VK, et al. Adverse effects of perioperative paracetamol, NSAIDs, glucocorticoids, gabapentinoids and their combinations: a topical review. *Acta Anaesthesiol Scand*. 2014;58(10):1182-1198. doi:10.1111/aas.12380
24. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev*. 2015;4:1. doi:10.1186/2046-4053-4-1
25. International prospective register of systematic reviews: Risks of serious adverse events associated with non-steroidal anti-inflammatory drugs in gastrointestinal surgery. A protocol for a systematic review https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022341810.
26. Agency EM. Guideline for good clinical practice E6(R2) 2016 https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-6-r2-guideline-good-clinical-practice-step-5_en.pdf.
27. Higgins JPT, Thomas J, Chandler J, et al. *Cochrane Handbook for Systematic Reviews of Interventions version 6.3*. Cochrane; 2022:2022 www.training.cochrane.org/handbook
28. Jakobsen JC, Wetterslev J, Winkel P, Lange T, Gluud C. Thresholds for statistical and clinical significance in systematic reviews with meta-analytic methods. *BMC Med Res Methodol*. 2014;14:120. doi:10.1186/1471-2288-14-120
29. Sterne JAC, Savovic J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898. doi:10.1136/bmj.l4898
30. Kjaergard LL, Villumsen J, Gluud C. Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses. *Ann Intern Med*. 2001;135(11):982-989. doi:10.7326/0003-4819-135-11-200112040-00010
31. Lundh A, Lexchin J, Mintzes B, et al. Industry sponsorship and research outcome. *Cochrane Database Syst Rev*. 2017;2:MR000033. doi:10.1002/14651858.MR000033.pub3
32. Moher D, Pham B, Jones A, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? *Lancet*. 1998;352(9128):609-613. doi:10.1016/S0140-6736(98)01085-X
33. Savovic J, Jones H, Altman D, et al. Influence of reported study design characteristics on intervention effect estimates from randomised controlled trials: combined analysis of meta-epidemiological studies. *Health Technol Assess*. 2012;16(35):1-82. doi:10.3310/hta16350
34. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA*. 1995;273(5):408-412. doi:10.1001/jama.273.5.408
35. Wood L, Egger M, Gluud LL, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *BMJ*. 2008;336(7644):601-605. doi:10.1136/bmj.39465.451748.AD
36. Gluud LL. Bias in clinical intervention research. *Am J Epidemiol*. 2006;163(6):493-501. doi:10.1093/aje/kwj069
37. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21(11):1539-1558. doi:10.1002/sim.1186
38. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-560. doi:10.1136/bmj.327.7414.557
39. Harbord RM, Egger M, Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. *Stat Med*. 2006;25(20):3443-3457. doi:10.1002/sim.2380
40. Vascular Events In Noncardiac Surgery Patients Cohort Evaluation Study I, Devereaux PJ, Chan MT, et al. Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. *JAMA*. 2012;307(21):2295-2304. doi:10.1001/jama.2012.5502
41. DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. *Contemp Clin Trials*. 2015;45:139-145. doi:10.1016/j.cct.2015.09.002
42. Demets DL. Methods for combining randomized clinical trials: strengths and limitations. *Stat Med*. 1987;6(3):341-350. doi:10.1002/sim.4780060325
43. Brok J, Thorlund K, Gluud C, Wetterslev J. Trial sequential analysis reveals insufficient information size and potentially false positive results in many meta-analyses. *J Clin Epidemiol*. 2008;61(8):763-769. doi:10.1016/j.jclinepi.2007.10.007
44. Brok J, Thorlund K, Wetterslev J, Gluud C. Apparently conclusive meta-analyses may be inconclusive—trial sequential analysis adjustment of random error risk due to repetitive testing of accumulating data in apparently conclusive neonatal meta-analyses. *Int J Epidemiol*. 2009;38(1):287-298. doi:10.1093/ije/dyn188
45. Wetterslev J, Jakobsen JC, Gluud C. Trial sequential analysis in systematic reviews with meta-analysis. *BMC Med Res Methodol*. 2017;17(1):39. doi:10.1186/s12874-017-0315-7

46. Wetterslev J, Thorlund K, Brok J, Gluud C. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. *J Clin Epidemiol*. 2008;61(1):64-75. doi:10.1016/j.jclinepi.2007.03.013
47. Wetterslev J, Thorlund K, Brok J, Gluud C. Estimating required information size by quantifying diversity in random-effects model meta-analyses. *BMC Med Res Methodol*. 2009;9:86. doi:10.1186/1471-2288-9-86
48. Thorlund K, Engstrøm J, Wetterslev J, et al. User manual for trial sequential analysis (TSA). *Copenhagen Trial Unit, Centre of Clinical Intervention Research* 2011 www.ctu.dk/tsa.
49. Imberger G, Thorlund K, Gluud C, Wetterslev J. False-positive findings in Cochrane meta-analyses with and without application of trial sequential analysis: an empirical review. *BMJ Open*. 2016;6(8):e011890. doi:10.1136/bmjopen-2016-011890
50. Cuello-Garcia CA, Santesso N, Morgan RL, et al. GRADE guidance 24 optimizing the integration of randomized and non-randomized studies of interventions in evidence syntheses and health guidelines. *J Clin Epidemiol*. 2022;142:200-208. doi:10.1016/j.jclinepi.2021.11.026
51. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ*. 2015;350:g7647. doi:10.1136/bmj.g7647
52. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926. doi:10.1136/bmj.39489.470347.AD

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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