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Evaluating respiratory depression after methadone administration in surgical patients: protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction Methadone has emerged as a promising option for perioperative pain management, primarily due to its rapid onset of action and prolonged duration of effect, which provides sustained analgesic benefits. Despite its clinical advantages and minimal reported risks for postoperative respiratory depression, concerns about its potential respiratory complications persist. This protocol outlines a meta-analysis aimed at evaluating the risk of respiratory depression associated with methadone administration in the perioperative setting compared with other opioids or placebo.

Methods and analysis We will perform a systematic review of literature published in English from 1 January 1970 to the present using Ovid MEDLINE, Ovid Embase and Cochrane CENTRAL. Eligible studies will consist of randomised controlled trials, cohort studies and case–control studies reporting respiratory depression in surgical patients receiving intravenous methadone. Case reports, reviews and non-English studies will be excluded. The primary outcome is respiratory depression, defined as naloxone administration, a respiratory rate of fewer than 8 breaths per minute, or an arterial oxygen saturation below 90%. Secondary outcomes include the timing and dose–response effect of methadone on respiratory depression. Bias will be evaluated using the Cochrane Risk of Bias Assessment 2 and ROBINS-I tools. Meta-analyses will be performed, and effect estimates will be presented as relative risks or ORs with 95% CIs. The certainty of the evidence will be assessed using Grading of Recommendations Assessment, Development and Evaluation methodology.

Ethics and dissemination Ethics approval is not necessary for this systematic review and meta-analysis. The results will be published in a peer-reviewed journal and presented at national and international conferences focused on perioperative medicine and pain management.

PROSPERO registration number CRD42025630383.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ To enhance the generalisability of our findings, we will include diverse populations, surgical procedures and anaesthesia types.
⇒ We will employ artificial intelligence tools to improve reliability and validity during the study screening and selection process.
⇒ We will include different ways of identifying opioid-induced respiratory depression to achieve comprehensive primary outcome identification.
⇒ We will characterise and analyse respiratory depression risk by methadone dose and timing to provide insights into potential high-risk doses or periods.
⇒ The detection and reporting of respiratory depression may be influenced by the small sample sizes and insufficient monitoring protocols across the individual studies, potentially affecting the consistency and precision of included studies. Differences and variability in definitions and thresholds for respiratory depression may introduce variability and heterogenicity to the meta-analysis.

INTRODUCTION

Inadequately treated surgical pain impacts multiple physiological systems and is associated with prolonged hospital stay, decreased patient satisfaction and increased risk for surgical complications.[1–4] Therefore, pain management is crucial to improve clinical outcomes. Despite clinical recommendations for opioid-sparing strategies for treatment of acute pain, opioids remain an essential part in the management of moderate and severe postoperative pain.[5] Furthermore, recent evidence suggests that intraoperative opioid-sparing techniques may in fact be associated with poor clinical outcomes.[6]

Methadone, a synthetic opioid with multimodal activity (μ-receptor agonism and partial N-methyl-D-aspartate receptor (NMDA) antagonism), has emerged as a valuable option in perioperative pain management.[7 8] It offers rapid onset of effect and the advantage of sustained analgesia due to its slow elimination and extended duration of action, particularly in comparison with other opioids. For instance, Murphy *et al* found decreased requirements of postoperative

intravenous and oral opioids in patients undergoing cardiac surgery and major spine surgery who received methadone compared with those who received hydromorphone or fentanyl.[9 10] A recent systematic review in patients undergoing spine surgery reported clinically relevant lower pain scores in those treated with methadone than comparator cohorts.[8] Additionally, in spine surgeries, postoperative opioid requirements at 48 and 72 hours were decreased by the administration of methadone compared with sufentanil.[11] Long-term (3 months) benefits of intraoperative methadone have also been reported.[12 13] Despite the unique pharmacological attributes and clinical evidence regarding perioperative methadone, and evidence for lack of postoperative respiratory depression,[13] there is worry about perioperative administration of methadone and the risk of respiratory depression.[14 15]

Respiratory depression is a significant and potentially fatal complication associated with opioid use in surgical patients. Its incidence varies from 0.08% to 2% depending on the definition and patient population.[16–18] However, the PRODIGY observational study showed that of all enrolled patients (n=1282), 655 were adjudicated as having at least one episode of respiratory depression during their 48 hours monitoring period.[19] Several groups have investigated the association between perioperative methadone use and postoperative respiratory depression.[20–23] Bova *et al* reported that respiratory depression occurred in 14.8% of patients who received perioperative methadone during the week after surgery. In methadone-naive patients, the incidence was as high as 48%.[20] Conversely, Carle *et al* demonstrated in a large cohort that less than 1% of patients who received methadone required naloxone administration, and there was no significant difference compared with patients who received morphine.[21]

Objective data on the safety profile of methadone concerning the risk of respiratory depression during the perioperative period remains inconclusive. To address this gap, we designed a protocol for a meta-analysis to systematically evaluate whether there is an association between the use of methadone in the perioperative setting and respiratory depression compared with other opioids or placebo.

METHODS AND ANALYSIS

This protocol is reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[24] A Measurement Tool to Assess Systematic Reviews 2[25] and the Patient-Centered Outcomes Research Institute Methodology Standard checklist will be used in this research. The analysis is registered at PROSPERO (CRD42025630383). Any modifications to our PROSPERO registration or the existing protocol will be recorded, accompanied by an explanation of the reasons for each change. Our team consists of methodological experts in evidence synthesis and clinical specialists from different anaesthesiology subspecialties.

Study design

Patients

Our study will involve adult and paediatric surgical patients undergoing cardiac and non-cardiac procedures with general or regional anaesthesia.

Intervention

We will consider intravenous methadone given during the intraoperative or postoperative period (during post-anaesthesia care unit or nursing floors). The intervention component will be further defined by dosage.

Comparison

The comparator will be the intraoperative or postoperative (during post-anaesthesia care unit or nursing floors) intravenous or oral administration of opioids (excluding methadone) or placebo.

Outcomes

The primary outcome is respiratory depression, which is defined as any of the following: the administration of naloxone, a respiratory rate of fewer than 8 breaths per minute or arterial oxygen saturation below 90%. Secondary outcomes will include the dose–response effect of methadone on respiratory depression and the time of respiratory depression. We will define early and late respiratory depression episodes as those occurring 0–24 hours and >24 hours after the end of anaesthesia (or surgery, as reported), respectively. If the postoperative timing of respiratory depression is unclear, we will use the longest time interval that the study reported for methadone administration as the postoperative interval.

Inclusion and exclusion criteria

We will include randomised clinical trials, retrospective studies, controlled studies, cohort analyses, case–control studies, involving patients undergoing general or regional anaesthesia who received intravenous methadone and reported events or the incidence of respiratory depression. We will exclude case reports and review articles, articles in any language other than English and methadone use in the context of addiction treatment.

Literature search

We will perform a comprehensive systematic search of the literature adhering to the PRISMA-S1 for Searching checklist.[26] We will search Ovid MEDLINE, Ovid Embase, Cochrane Library (CDSR and CENTRAL) and Scopus from 1970 to the current date. A medical librarian specialising in systematic reviews will create the search strings using subject headings and keywords in consultation with coauthors. We will manually deduplicate records in EndNote. We will search the references of the included articles and reviews. The full search strings for all databases are provided in tables 1 and 2, as well as in online supplemental etables 1, 2.

Table 1 Cochrane Library search strategy

1	MeSH descriptor: [Surgical Procedures, Operative] explode all trees
2	MeSH descriptor: [Perioperative Care] explode all trees
3	MeSH descriptor: [Pain, Postoperative] explode all trees
4	surgery or surgical or intraoperative or intra-operative or perioperative or postoperative or post-operative or preoperative or pre-operative or "enhanced recovery"
5	#1 or #2 or #3 or #4
6	MeSH descriptor: [Methadone] explode all trees
7	Methadone or Methadyl Acetate or Diskets or Dolophine or Intensol or Methadose or Methatab
8	#6 or #7
9	MeSH descriptor: [Respiration Disorders] explode all trees
10	MeSH descriptor: [Respiration, Artificial] explode all trees
11	respiratory or respiration or breath or breathing or hypoventilate or hypoventilation or ventilate or ventilation
12	MeSH descriptor: [Naloxone] explode all trees
13	Naloxone or Narcan or Kloxxado or Nalone or Evzio or Prenoxad or Narcanti or Nacotan or Zimhi
14	#9 or #10 or #11 or #12 or #13
15	#5 and #8 and #14
16	MeSH descriptor: [Substance-Related Disorders] explode all trees
17	MeSH descriptor: [Substance Abuse, Intravenous] explode all trees
18	MeSH descriptor: [Opioid-Related Disorders] explode all trees
19	(opioid or heroin or methadone) and (abuse or addicted or addiction or dependence or disorder* or misuse)
20	#20 #16 or #17 or #18 or #19
21	#15 not #20

MeSH, Medical Subject Headings.

We will search ClinicalTrials.gov to identify relevant completed studies not published in the published literature yet. This will allow us to assess publication and reporting bias and identify and track ongoing studies that might answer our research questions in the future.

Study selection and review

Two reviewers will screen the citations and full-text articles using Covidence. We will use Covidence's machine-learning model, which prioritises studies based on their relevance to the research question, to enhance the efficiency of study selection. After excluding duplicates and titles/abstracts clearly unrelated to the clinical question, in instances of disagreement, a third reviewer will be consulted. We will record the selection process in a PRISMA flow diagram.

Table 2 Scopus search strategy

1	Article title, Abstracts, Keywords: surger* or surgical or intraoperative* or intra-operative* or perioperative* or postoperative* or "post-operative*" or preoperative* or pre-operative* or "enhanced recovery"
2	AND
3	Article title, Abstracts, Keywords: Methadone or Methadyl Acetate or Diskets or Dolophine or Intensol or Methadose or Methatab
4	AND
5	Article title, Abstracts, Keywords: respiratory or respiration or SpO2 or oxygen saturation or breath or breathing or hypoventilat* or ventilat* or Naloxone or Narcan or Kloxxado or Nalone or Evzio or Prenoxad or Narcanti or Nacotan or Zimhi

Data extraction

We will extract the following data from the selected individual studies: (1) study characteristics: first author, year of publication and sample size; (2) patient characteristics: mean age, gender, race/ethnicity study, country of origin, American Society of Anesthesiologists physical status category and mean body mass index; (3) opioid use characteristics among groups: methadone dose (reported in mg or mg/kg, as available)—and its conversion to oral morphine milligram equivalents (OME)—and opioid use in the control group (opioid used, dose in mg or mg/kg, as available, and conversion to OME); (4) type of surgical procedure and (5) outcomes of interest: naloxone use at 24, 48 and 72 hours after surgery, respiratory rate of fewer than 8 breaths per minute, or arterial oxygen saturation below 90%, as well as dose–response effect of methadone on respiratory depression and the time of respiratory depression. For OME conversion, we will use the conversion rates suggested by Nielsen *et al*.[27] One investigator will input data into standardised extraction forms in COVIDENCE, and a second investigator will verify its accuracy through a quality check.

Risk of bias

One investigator independently will evaluate the risk of bias for eligible studies by outcome; a second investigator will review each risk of bias assessment. Disagreements will be resolved through consensus after discussing the reasons for the discrepancies. For randomised trials, the risk of bias will be assessed using the second version of the Cochrane Risk of Bias assessment tool (RoB 2),[28] evaluating five domains for each outcome of the selected studies: (1) bias in the randomisation process; (2) bias due to deviations from intended interventions; (3) bias due to missing data; (4) bias in outcome measurement and (5) bias in the selection of reported results. For retrospective studies, we will employ the ROBINS-I assessment.[29] The risk of bias for each specific trial (either

prospective or retrospective) will be derived from judgements made in individual domains. The overall risk-of-bias assessments for each study outcome will be categorised as low, moderate or high according to the combined risk of bias across components and the confidence that the study results for a specific outcome are credible, given the study's limitations.

Strength of evidence

The overall strength of the evidence for primary and secondary outcomes will be evaluated according to Evidence-based Practice Center programme methods.[30] One author will grade the strength of evidence for each outcome as high, moderate, low or insufficient. A senior investigator will then review the findings. Any discrepancies will be resolved by consensus from all investigators.

Data synthesis

We will summarise the selected studies by type, patient characteristics, effect estimates and risk of bias. When we cannot perform a quantitative analysis, we will report and summarise the results narratively. If the studies are too diverse to combine, we will present the results using graphical displays. For continuous data, we will assume that if the sample mean and SD are provided as summary statistics for a study, then the outcome data are normally distributed. These values will be used to calculate the mean difference (MD) and its 95% CI and will serve as the effect measure in the meta-analyses. In studies where continuous outcomes are reported as median and IQR, we will interpret that the data from those studies are skewed away from normality. When the distribution of outcomes is skewed, estimating the mean (from the median) and SD (from the IQR) becomes impossible. If these studies were included in a meta-analysis for normal data analysis, unreliable or even misleading conclusions may arise.

When a study reports the median and IQR, a skewness statistic and its critical range at the 5% level will be calculated.[31] If the absolute value of the statistic exceeds the critical value, transformation to normality will not be applied. If the skewness test is not rejected, we will then use normal-based transformation methods to recover the sample mean and SD[32 33] If the mean of an outcome is available but the SD is not, the missing SD will be imputed from the average of the SDs reported by those studies that include SDs.

To provide estimates of intervention effects, a quantitative analysis will be conducted using R (employing fixed-effect or random effects models with the meta and metafor packages). We will conduct a meta-analysis for most outcomes when at least three studies report the same outcome (ie, respiratory depression) at the same time (early vs late episodes). Summary estimates will be computed for each individual outcome, yielding ORs and/or relative risk with a 95% CI. To enhance the interpretability of our findings, we will provide a narrative summary of the proportion of RD events for each individual component of the composite RD definition.

Heterogeneity will be evaluated using I^2 statistics, and if significant heterogeneity is identified (p value<0.1 or $I^2 \geq 25\%$), subgroups will be analysed further to uncover potential baseline differences within the study sample that may account for the heterogeneity. Results will be interpreted in the context of pooled effect estimates while considering the risk of bias, heterogeneity and publication bias for each outcome across the included studies. If meta-analysis is possible, we will summarise the results narratively. The findings, including the quality of evidence and the confidence level in the evidence, will be summarised in a findings table.

A meta-regression analysis will be used to examine the dose–response effect of methadone on respiratory depression. We will use weighted least-squares linear regression to evaluate variation between studies, model the relative risk as a function of methadone dose in mg, test for trends and graph the predicted dose–response curve.[34] The dependent variable for the regression was the natural log of each study-specific relative risk for respiratory depression. The methadone dose for each study will then be treated as a continuous, independent variable. The coefficient of the methadone term in the regression model estimates the slope of the linear methadone-respiratory depression dose–response effect. The results from the regression equation will estimate the percentage risk increase in respiratory depression predicted at any given dose of methadone therapy (in mg).

Planned timeline

We have completed the research question formulation, protocol development phase and literature search phase and are currently working in study selection and review. We estimate that the study screening and selection will take 1 month to complete. Data extraction and risk-of-bias assessment will require an additional 2 months, and data synthesis will take another 2 months. The writing of the manuscript will overlap with these phases, and we estimate it could take an extra month for final approval from all coauthors before submission. We plan to submit by July 2025.

Patient and public involvement

None

ETHICS AND DISSEMINATION

The proposed systematic review and meta-analysis will use data from previously published studies found in peer-reviewed journals or reputable databases. Therefore, ethical approval is not necessary. We will ensure that the included studies demonstrate compliance with the ethical standards set by their respective journals and institutions. We will prioritise accurately representing the findings while addressing potential biases and limitations in the included studies. The results will be published in a peer-reviewed journal, with the aim of advancing the evidence base for methadone use in the perioperative setting.

DISCUSSION

By summarising evidence from existing literature, this meta-analysis will evaluate methadone's perioperative safety profile concerning respiratory depression in surgical patients, compared with other opioids or a placebo. A prior meta-analysis by Machado *et al* reported better pain scores at 24 (MD 1.09; 95% CI 0.72 to 1.47; p<0.00001), 48 (MD 1.47; 95% CI 1.02 to 3.04; p<0.00001) and 72 (MD 1.02; 95% CI 0.39 to 1.65; p<0.001) hours when using methadone instead of other opioids.[35] However, they did not assess the risk of respiratory depression. Souza *et al* indicated that methadone administration was linked to reduced postoperative opioid consumption (MD −15.22 mg oral morphine equivalents; 95% CI −27.05 to −3.38; p=0.01) and did not observe differences in secondary outcomes such as time to extubation (MD 0.02 hours; 95% CI 20.02 to 0.06; p=0.32), time to first analgesia request (MD 37.71 min; 95% CI 275.17 to 150.58; p=0.51), hospital length of stay (MD 20.10 days, 95% CI 20.49 to 0.29; p=0.61) or respiratory depression (OR 1.03; 95% CI 0.20 to 5.25; p=0.97).[36] However, this meta-analysis did not assess the use of naloxone to determine whether patients experienced respiratory depression, and the authors note that included studies may have been limited in their ability to detect respiratory depression.

We anticipate that this study will provide stronger evidence to assist clinicians in making informed decisions about the perioperative administration of methadone and the risk of respiratory depression and ultimately enhance patient care. Additionally, this study may promote the development of perioperative pain management protocols by assessing criteria such as methadone dosing to reduce adverse respiratory outcomes.

The current review may encounter some limitations. First, studies will exhibit variations in the definition, threshold and detection of respiratory depression, which may introduce heterogeneity and affect the reliability of pooled estimates. Second, small sample sizes and insufficient monitoring protocols in individual studies could hinder the detection of respiratory depression. Third, including studies with varied surgical populations, methadone dosages and comparator interventions may challenge the generalisability of the findings.

Despite these limitations, this meta-analysis will enhance the understanding of methadone's role in perioperative care, particularly concerning its respiratory safety profile. Furthermore, the results may promote future research and protocol development aimed at improving patient outcomes in surgical settings.

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