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Opioid versus opioid-free analgesia after surgical discharge: protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction Excessive prescribing after surgery has contributed to a public health crisis of opioid addiction and overdose in North America. However, the value of prescribing opioids to manage postoperative pain after surgical discharge remains unclear. We propose a systematic review and meta-analysis to assess the extent to which opioid analgesia impact postoperative pain intensity and adverse events in comparison to opioid-free analgesia in patients discharged after surgery.

Methods and analysis Major electronic databases (MEDLINE, Embase, Cochrane Library, Scopus, AMED, BIOSIS, CINAHL and PsycINFO) will be searched for multi-dose randomised-trials examining the comparative effectiveness of opioid versus opioid-free analgesia after surgical discharge. Studies published from January 1990 to July 2019 will be targeted, with no language restrictions. The search will be re-run before manuscript submission to include most recent literature. We will consider studies involving patients undergoing minor and major surgery. Teams of reviewers will, independently and in duplicate, assess eligibility, extract data and evaluate risk of bias. Our main outcomes of interest are pain intensity and postoperative vomiting. Study results will be pooled using random effects models. When trials report outcomes for a common domain (eg, pain intensity) using different scales, we will convert effect sizes to a common standard metric (eg, Visual Analogue Scale). Minimally important clinical differences reported in previous literature will be considered when interpreting results. Subgroup analyses defined a priori will be conducted to explore heterogeneity. Risk of bias will be assessed according to the Cochrane Collaboration's Risk of Bias Tool 2.0. The quality of evidence for all outcomes will be evaluated using the GRADE rating system.

Ethics and dissemination Ethical approval is not required since this is a systematic review of published studies. Our results will be published in a peer-reviewed journal and presented at relevant conferences. Further knowledge dissemination will be sought via public and patient organisations focussed on pain and opioid-related harms.

Strengths and limitations of this study

- This will be the first systematic review to synthesise the evidence on the comparative effectiveness of opioid versus opioid-free analgesia after postoperative discharge.
- This review will address a major knowledge gap that hinders the use of evidence-based prescribing as a strategy to mitigate postoperative opioid-related harms.
- We will use robust statistical methods to meta-analyse data from randomised controlled trials, but these methods are not free from limitations when outcome reporting is heterogeneous.
- The quality and strength of evidence will be evaluated using the Cochrane Collaboration's Risk of Bias Tool 2.0 and the GRADE framework.

INTRODUCTION

North America is facing a devastating opioid crisis exacerbated by excessive prescribing.[1 2] Surgery often serves as a gateway for opioid-naïve patients to obtain an opioid prescription,[3] and spiral into misuse and addiction.[4–8] Reports from Canada and the USA suggest that 6% to 14% of patients who are prescribed opioids after surgical discharge become persistent opioid users, that is, they continue to take the drug for more than 3 months after surgery.[5 9–12] Interestingly, rates of persistent opioid use are similar among patients undergoing major,[5 10 11] and minor surgeries.[12] Patients who do not become persistent users postoperatively may also contribute to the opioid crisis by diverting unused tablets for non-medical use by others—up to 70% of all opioid tablets prescribed to surgical patients go unused and may become a source for diversion.[13] Given these factors, recent literature suggests that postoperative opioid prescribing should be judicious and based on the best available evidence regarding benefits and harms.[14 15]

Studies have shown that postoperative pain management using only non-opioid drugs is

common internationally but not in Canada nor in the USA, where opioid tablets are often prescribed instead of, or in addition to, non-opioid analgesics.[16–20] In countries such as the Netherlands,[21] China[22] and Chile,[23] reported rates of opioid prescribing after surgical discharge range from 0% to 5%, while in North America, 80% to 95% of patients receive an opioid prescription to manage postoperative pain at home.[16–20] A recent study indicates that surgical patients in Canada and the USA fill opioid prescriptions at a rate that is seven times higher than those in Sweden.[24] Remarkably, in countries where opioids are not a mainstay for postoperative analgesia, pain-related outcomes (ie, satisfaction with pain management) after surgery are often superior to North America.[16–18] This may, in part, reflect a potential therapeutic superiority of non-opioid drugs or increased opioid-related adverse events such as postoperative vomiting. Although these findings bring into question the value of prescribing opioids to manage acute pain after surgical discharge, the decision to prescribe opioids must be informed by robust systematic reviews and meta-analyses focussed on the comparative effectiveness of opioid versus opioid-free postoperative analgesia. These, however, are currently non-existent in the literature.[25]

We therefore propose to undertake a systematic review and meta-analysis to summarise the evidence regarding the comparative effectiveness of opioid versus opioid-free analgesia after discharge following surgery. Our study will follow the principles of the PICO framework,[26] and aims to respond to the following research questions: (1) in patients discharged after surgery, to what extent does opioid analgesia impact postoperative pain intensity in comparison to opioid-free analgesia? and (2) in patients discharged after surgery, to what extent does opioid analgesia impact the risk of postoperative vomiting in comparison to opioid-free analgesia?

METHODS AND ANALYSIS

Design

This protocol was designed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols statement.[27] A draft protocol was circulated among our knowledge synthesis team (composed of synthesis leaders (JF, GB and LF), synthesis managers (CEK and UD), a patient partner (AD) and collaborators) and adjustments were made according to their feedback. Any future amendments to this protocol and corresponding rationale will be tracked and dated.

Literature search

A comprehensive search of major electronic databases (MEDLINE (via Ovid), Embase (via Ovid), The Cochrane Library (via Wiley), Scopus (via Elsevier), AMED (via Ovid), BIOSIS (via Clarivate), CINAHL (via Ebsco) and PsycINFO (via Ovid)) will be conducted to identify relevant studies. The main strategy (MEDLINE) was developed by an experienced medical librarian and information specialist (TL) with input from the synthesis team (see online supplementary 1). Subsequently, a second medical librarian peer-reviewed this search strategy according to Peer Review of Electronic Search Strategies standards,[28] and changes were made as required. The vocabulary and syntax of the MEDLINE strategy was tailored to allow adaptation and optimal electronic searching of the other databases. Searches will target articles published after January 1990, as earlier publications do not reflect current standards of surgical care with the widespread use of minimally invasive surgery and perioperative care pathways.[29–32] The initial search was conducted in July 2019 and will be re-run prior to manuscript submission to ensure the inclusion of most recent literature. No language limitation will be applied. A combined library of the retrieved articles will be created using Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia; https://www.covidence.org/).[33] Duplicates will be excluded. To ensure literature saturation, we will also search trial registries (ClinicalTrials.gov and the WHO's International Clinical Trials Registry Platform), conference proceedings (identified via Scopus, Embase, BIOSIS and Cochrane Library), articles cited by the included articles (identified via Scopus) and articles that cited the included articles (identified via Scopus). Furthermore, we will contact authors to obtain aggregated data from trials that were completed but not published.

Eligibility criteria

We will include studies that: (1) are parallel randomised controlled trials (RCTs), (2) enrolled youth and/or adults patients (>15 years old) undergoing minor or major surgeries according to the WHO definition,[34 35] (table 1) (3) compared a post-discharge analgesia regimen including opioids (analgesic drugs that act on opioid receptors, such as codeine, oxycodone, hydromorphone, tramadol and morphine) versus an analgesia

Table 1 Definition of surgery (minor and major) according to the WHO

Surgery	Any intervention involving the incision, excision, manipulation or suturing of tissue and requiring regional or general anaesthesia or sedation.
Minor surgery	A surgical intervention occurring in a physician's office or clinic (eg, tooth extraction, cataract surgery, skin tumour excision).
Major surgery	A surgical intervention occurring in a hospital operating theatre (eg, cesarean section, appendectomy, open fracture repair).

regimen including only non-opioid drugs (such as acetaminophen, non-steroidalanti-inflammatory drugs, gabapentinoids) and (4) involved a multiple-dose design focussed on the overall effect of repeated doses of the prescribed analgesics. Our age cut-off was chosen based on data showing fast-growing rates of opioid poisoning in youths over 15 years old.[36 37] Studies involving any non-invasive route of analgesic administration (ie, oral, transmucosal, transdermal and rectal) will be considered for inclusion. Studies where opioids were offered to the opioid-free group as rescue analgesia for breakthrough pain (ie, pain that erupts while a patient is already medicated) will be included only if the opioid drugs were not readily available to patients (ie, a new prescription was required via contact with a healthcare provider). Studies where patients received opioids while in the hospital or clinic will be included if the post-discharge analgesia was according to our inclusion criteria.

We will exclude single-dose trials as they do not reflect 'real-world' practices where analgesia regimens span several days postoperatively.[38] Besides, postoperative analgesia trials with a single-dose design have been extensively systematically reviewed in previous literature.[38 39] We will also exclude: (1) placebo-controlled trials where no active analgesic drugs are offered to patients (they do not reflect standard practice), (2) studies where the postoperative analgesia regimen is not clearly described (eg, placebo-controlled trials with unclear description of analgesics given in addition to placebo), (3) studies exclusively focussed on children (≤15 years old), (4) studies with post-discharge analgesia administrated via invasive routes such as intravenous or epidural (rarely prescribed after surgical discharge) and (5) studies evaluating analgesia for chronic postoperative pain (treatment starting beyond 2 months after surgery).[40]

Selection of studies

The titles/abstracts of the articles identified by our search strategy will be evaluated against the review's eligibility criteria by pairs of reviewers. Due to the anticipated large number of articles to be screened, eight reviewers (all with previous training in healthcare research) will be involved in the screening process. Screening will be conducted, independently and in duplicate, using the Covidence software.[33] Two lead reviewers (JF and CEK) will pilot-test the eligibility criteria on the first 100 titles and abstracts identified by the search. To harmonise the rest of the screening process, reviewers will attend a training session and conduct a pilot screening of at least 20 titles/abstracts to prompt clarifications. A screening decision table was created to guide decision-making (see online supplementary 2). To ensure accuracy, all titles/abstracts will be screened by at least one lead member of the synthesis team (JF or CEK). Disagreements regarding eligibility will be resolved by consensus between the reviewers or by consulting an adjudicator (LF).

Articles that are clearly irrelevant will be excluded after examination of titles and abstracts; those that are potentially eligible will have their full-text versions retrieved and evaluated against the eligibility criteria. Publications in non-English language will be translated into English by an ISO certified translation company. Full-text screening will be conducted by two lead members of the synthesis team (JF and CEK) using the Covidence platform.[33] The extent of agreement between reviewers during full-text screening will be assessed using kappa statistics (thresholds:<0.20 slight agreement, 0.21 to 0.40 fair agreement, 0.41 to 0.60 moderate agreement, 0.61 to 0.80 substantial agreement and >0.80 almost perfect agreement).[41] Disagreements will be resolved by consensus or by consulting an adjudicator (LF).

Outcome measures

The primary outcome of interest in this review will be patient self-reported outcomes focussed on postoperative pain intensity (ie, self-perceived magnitude of pain at a given time postoperatively). The secondary a priori outcome of interest will be the risk of postoperative vomiting. These outcomes were chosen based on previous literature that showed good pain relief to be the most desirable outcome in perioperative care according to patient preference, while postoperative vomiting is the least desirable outcome.[42–44] If data are available in the eligible studies, we will also explore the association of the interventions with other endpoints included in core outcome sets for research in perioperative care.[45 46] These include: (1) drug adverse events (other than vomiting), (2) patient satisfaction with pain management, (3) participant disposition (ie, withdrawal due to adverse events or ineffective treatment), (4) self-reported postoperative health status (overall and domain-based scores, vitality (ie, fatigue), physical function, emotional function, social function, role function (ie, work or other daily activities), sleep function), (5) emergency room visits and (6) hospital readmissions.

Data charting

A customised data extraction form was collectively developed by the synthesis team (see online supplementary 3). This form will be pilot tested by two independent reviewers (JF and CEK). Subsequently, a team meeting will take place to discuss potential issues and refine the form. Finally, the refined data extraction form will be integrated into the Covidence software.[33] Data extraction will be conducted, independently and in duplicate, by pairs of reviewers. The following data will be extracted from each study: author, publication date, study location, number of participating centres, funding source, inclusion and exclusion criteria, sample size (patients randomised and patients analysed in each group), patient characteristics (age, sex, clinical condition, type of surgery and proportion receiving preoperative opioids, if available), surgery classification (major vs minor), type of anaesthesia, in-hospital analgesia interventions (if applicable), hospital length of stay (if applicable), characteristics of the post-discharge analgesia intervention (drugs, dosage (in

Table 2 Primary outcome data (pain intensity after surgical discharge)

Pain assessment time points	► Multi-dose analgesia trials often involve the assessment of pain intensity at different time points after surgical discharge. ► We will focus on the following time points after surgical discharge: Day 0 (6–12 hours after prescription), Day 1 (13–24 hours), Day 2 (25–48 hours), Day 3 (49–72 hours), Days 4–7 (3–168 hours), Days 8–30 (169 to 720 hours). ► These time points were the most commonly reported in the eligible trials identified by our scoping review and preliminary MEDLINE search. ► We will consider for analysis the last measure obtained within the time point interval (ie, the measure closest to the interval upper bound).
The primary time point of interest	► Our primary time point of interest will be Day 1 after discharge (13–24 hours), as evidence suggests that this is the period after surgery when patients report most severe pain.
Other important considerations	► We will prioritise reports of dynamic pain (during movement) over pain at rest if both are reported. Dynamic pain is deemed more relevant to the process of postoperative recovery. ► We will also prioritise reports of 'worst pain' over 'average pain'. The latter is highly influenced by variations in instructions (eg, should periods without any pain be accounted for when pain is 'averaged'?).

morphine equivalents for opioids[47]), frequency of administration and duration), outcome measures assessed, time points of assessment and duration of follow-up.

The number of reviewers involved in data extraction will depend on the number of RCTs fulfilling our eligibility criteria. To harmonise data extraction, reviewers will attend a training session, conduct at least two pilot extractions and receive a written 'data extraction guide' with detailed instructions. To ensure accuracy, at least one lead member of the synthesis team (JF or CEK) will extract data from each article. Data extracted in duplicate will be cross-checked by an independent third reviewer. Discrepancies in the extracted data will be resolved by consensus between the reviewers after revisiting the full-text article. If discrepancies remain, an adjudicator will be consulted (LF).

As this meta-analysis is focussed on acute pain management after surgery, we will target outcome data collected up to 30 days postoperatively (from the day when the trial analgesia regimens were prescribed). Data regarding pain intensity (primary outcome) will be assessed as described in table 2. Postoperative vomiting (secondary outcome) will be assessed as a dichotomous measure (presence of vomiting: yes/no). The assessment of other outcomes will be exploratory and will depend on whether data is available and how they are reported.

Methodological quality of individual studies

Risk of bias will be assessed independently and in duplicate by two lead members of the synthesis team (JF and CEK) using the Cochrane Collaboration's Risk of Bias Tool 2.0 (RoB 2.0) for randomised trials.[48] Assessments will be conducted using an iterative form available online (www.riskofbias.info/). The RoB 2.0 appraises risk of bias across five domains: (1) bias arising from the randomisation process, (2) bias due to deviations from intended interventions, (3) bias due to missing outcome data, (4) bias in measurement of the outcome and (5) bias in selection of the reported result. The domain concerning missing outcome data will be assessed according to Akl,[49] and Ebrahim.[50] For each domain, risk of bias will be judged as 'low risk', 'some concerns' or 'high risk'. Studies are considered to have an overall 'high risk of bias' if at least one domain is judged as 'high risk'. Disagreements regarding risk of bias will be resolved by consensus or by consulting an adjudicator (LF).

Quality of evidence (ie, confidence in the effect estimates) will be assessed using the GRADE rating system.[51] Assessment will be conducted on an outcome-by-outcome basis by two lead members of the synthesis team (JF and CEK) working independently.[52] Specific guidelines will be followed to improve reliability.[53–74] Disagreements will be resolved by consensus or by consulting an adjudicator (LF). In the GRADE system, RCTs are initially rated as 'high confidence' evidence but may be rated down by one or more of five categories of limitations: (1) risk of bias, (2) inconsistency, (3) indirectness, (4) imprecision and (5) publication bias.[51] After considering these categories, the confidence in estimates for each outcome will be categorised according to table 3. Publication bias will be formally assessed by visual assessment of funnel plot asymmetry,[75] and by Begg's test,[76] when there are at least 10 studies available for meta-analysis. The final results will be summarised in an evidence profile.[51]

Data synthesis

For data synthesis, we will primarily assess the treatment effects of opioid versus opioid-free analgesia across all surgical procedures that are eligible for this review; however, we will also explore potential sources of heterogeneity between trials by assessing treatment effects across specific surgical contexts. Meta-analyses will be conducted using random-effects models, which are conservative in considering that the 'true' effect of an intervention may vary across different trials.[77] Weighted mean differences (WMDs) and 95% CIs will be calculated for pain intensity data reported by more than one RCT. The principle of 'weighting' by the inverse of the variance aims to attribute

Table 3 GRADE certainty ratings

Certainty	Interpretation
Very low	The true effect is probably markedly different from the estimated effect.
Low	The true effect might be markedly different from the estimated effect.
Moderate	The authors believe that the true effect is probably close to the estimated effect.
High	The authors have a lot of confidence that the true effect is similar to the estimated effect.

Adapted from https://bestpractice.bmj.com/info/toolkit/learn-ebm/what-is-grade/.

Table 4 Process of standardisation (rescaling) of pain intensity measures into a common metric

Step 1	► Non-VAS pain intensity scales will be initially converted into standardised mean differences (SMD), by dividing the between-group differences in means (in each trial), by the pooled SD of the two groups. ► The SMD expresses the intervention effect in SD units, rather than the original units of measurement.
Step 2	► Standardisation will be done by multiplying the SMD by the SD of the VAS scale. ► The SD used here will be the pooled SD obtained from the largest trial where pain intensity was assessed via VAS.
Step 3	► Standardised data (now presented as a VAS score) will be meta-analysed with data from other trials (ie, those that used VAS or had pain data converted into VAS) to calculate a pooled WMD in VAS scores.

VAS, Visual Analogue Scale; WMD, weighted mean difference.

more weight to studies that provide more information about the treatment effect.[78] Methods described in the Cochrane Handbook will be used to estimate the mean and SD when median, range and sample size are reported, and to impute the SD if the SE or SD for the differences are not reported.[79] Relative risks (RRs) with associated 95% CIs will be calculated for dichotomous data reported by more than one RCT (ie, secondary outcome: vomiting). Analyses will follow the Hartung-Knapp-Sidik-Jonkman method as evidence supports that this approach outperforms traditional random-effects methods such as DerSimonian-Laird (known to lead to high type I error rates when the number of studies is small and there is moderate or substantial heterogeneity).[80] All analyses will be conducted using Stata statistical software (V.15.1, StataCorp, College Station, Texas, USA). Comparisons will be two-tailed and use a threshold $p \leq 0.05$.

Interpreting effect estimates for pain intensity is challenging as this outcome can be assessed using different scales (eg, Visual Analogue Scale (VAS), Numerical Rating Scale (NRS), SF-36 bodily pain scale or other scales). To address this issue, we will follow specific guidelines to standardise this outcome into a standard metric.[81–83] We chose the 10 cm pain intensity VAS (score range 0 to 10 cm; lower score represents less pain) as this is the pain intensity scale most commonly used in acute pain trials.[84–86] The process of standardisation is described in table 4. Once the WMD between opioid versus opioid-free analgesia is calculated for a given outcome, we will contextualise this value in relation to the corresponding minimally important difference (MID): the smallest change in score that patients perceive as important.[87] Reported MID in VAS pain scores for surgical patients, according to anchor-based methods, is 1/10 cm.[88] As recommended by the OMERACT initiative,[81] we will use pain intensity WMD and MID data to determine the strength of the intervention effect, as described in table 5.

When assessing pain intensity data, to further optimise the interpretation of meta-analyses results, we will also calculate the proportion of patients who reported adequate pain control (no more than mild pain, as determined by a pain score <3/10 cm VAS).[88 89] By assuming a normal distribution of postoperative pain scores in both groups, differences in risk of reporting adequate pain control will be derived with its associated 95% CIs.[81–83]

If we identify more than one trial measuring the exploratory outcomes of interest in this knowledge synthesis (eg, patient satisfaction, self-reported postoperative health status, readmissions), data will be meta-analysed and reported as WMDs (continuous measures) or RRs (dichotomous measures), as appropriate. Where relevant, outcome data using different metrics will be converted into a standard metric according to guideline recommendations.[81–83] Focussed literature searches will be conducted to identify anchor-based MIDs.[87]

Heterogeneity between the RCTs included in the meta-analyses will be assessed using the χ^2 test and the I^2 test.[90] To explore potential sources of heterogeneity, we will test the a priori hypothesis that opioid analgesia has a larger effect in trials where patients are expected to feel more pain, such as those involving: (1) major surgery versus minor surgery,[5] (2) day surgery (ie, with same-day discharge) versus in-patient surgery (ie, at least one overnight stay in the hospital)[25] and (3) only women as participants (those reporting sex-specific data or involving sex-specific surgeries (eg, gynaecological, breast)) versus men.[91–93] We also hypothesise that (4) trials with high risk of bias (vs lower risk of bias) will report larger effect sizes.[94 95] Other clustering strategies for subgroup analyses (eg, by surgical speciality (eg, dental surgery, orthopaedic surgery), specific types of surgery (eg, cholecystectomy, molar excision), type of anaesthesia (eg, general, neuraxial, regional anaesthesia), study geographical location (eg, North America)) will be decided based on the characteristics of the trials identified, in consultation with clinicians (ie, knowledge users) who care for the relevant surgical populations. These post hoc subgroup analyses will be planned after data extraction, but prior to analyses of results. All subgroup analyses will be conducted regardless of heterogeneity estimates if there are at least two trials in each subgroup. Tests of interaction will be

Table 5 Interpretation of weighed mean differences (WMDs) in relation to minimal important differences (MIDs)

Very large effect (most patients are likely to benefit)	WMD equal or above 2 MIDs (WMD > 2MIDs)
Large effect (many patients may benefit)	WMD equal or above 1 MID, but below 2 MIDs (1 MID < WMD < 2 MIDs)
Moderate effect (some patients may benefit)	WMD above 0.5 MID, but below 1 MID (0.5 MID < WMD < 1 MIDs)
Small effect (most patients are unlikely to benefit)	WMD equal or below 0.5 MID (0.5 MID < WMD < 1 MIDs)

performed to establish if subgroups differed significantly from one another.[96]

Patient and public involvement

A patient partner (AD) is part of our synthesis team. She brings in her lived experiences with postoperative pain and analgesic requirements after surgical discharge to ensure that our findings are responsive to the needs of patients. She will be actively involved in all stages of this research project and will contribute her experiential knowledge to inform our research design, data interpretation, as well as to optimise strategies for knowledge dissemination and translation. In addition to traditional channels of knowledge dissemination (ie, conference presentations, peer-reviewed publication), further dissemination will be sought via public and patient organisations focussed on pain and opioid-related harms.

SIGNIFICANCE

North America is currently facing a major public health crisis of opioid abuse. Opioid-based postoperative pain management is recognised as one of the driving forces behind this crisis. Given how commonly postoperative overprescription contributes to misuse, diversion, addiction and death, there is an urgent need to address this element of the opioid crisis. Alternatives to opioids are often overlooked, while they should be incorporated as the foundation of postoperative pain management whenever possible. This may prevent more people from becoming addicted in the future (it is impossible to become addicted without exposure) and, also importantly, reduce diversion of unused prescriptions. Our systematic review will provide key information to guide clinical decision-making regarding analgesia prescription after surgery. This work has the potential to contribute practice changing evidence to inform future guidelines aimed to improve analgesia prescribing and mitigate postoperative opioid-related harms.

ETHICS AND DISSEMINATION

The results of this study will be published in an international peer-reviewed journal and presented at relevant conferences. This review will inform future guidelines on postoperative analgesia prescription. Ethical approval is not required since this is a systematic review based on published studies.

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