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Intraoperative pharmacologic opioid minimisation strategies and patient-centred outcomes after surgery: a scoping review protocol

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ABSTRACT

Introduction For close to a century opioid administration has been a standard of care to complement anaesthesia during surgery. Considering the worldwide opioid epidemic, this practice is now being challenged and there is a growing use of systemic pharmacological opioid minimising strategies. Our aim is to conduct a scoping review that will examine clinical trials that have evaluated the impact of intraoperative opioid minimisation strategies on patient-centred outcomes and identify promising strategies.

Methods and analysis Our scoping review will follow the framework developed by Arksey and O'Malley. We will search MEDLINE, Embase, CENTRAL, Web of Science and CINAHL from their inception approximately in March 2023. We will include randomised controlled trials, assessing the impact of systemic intraoperative pharmacologic opioid minimisation strategies on patient-centred outcomes. We define an opioid minimisation strategy as any non-opioid drug with antinociceptive properties administered during the intraoperative period. Patient-centred outcomes will be defined and classified based on the consensus definitions established by the Standardised Endpoints in Perioperative Medicine initiative (StEP-COMPAC group) and informed by knowledge users and patient partners. We will use a coproduction approach involving interested parties. Our multidisciplinary team includes knowledge users, patient partners, methodologists and knowledge user organisations. Knowledge users will provide input on methods, outcomes, clinical significance of findings, implementation and feasibility. Patient partners will participate in assessing the relevance of our design, methods and outcomes and help to facilitate evidence translation. We will provide a thorough description of available clinical trials, compare their reported patient-centred outcome measures with established recommendations and identify promising strategies.

Ethics and dissemination Ethics approval is not required for the review. Our scoping review will inform future research including clinical trials and systematic reviews through identification of important intraoperative interventions. Results will be disseminated through a peer-reviewed publication, presentation at conferences and through our network of knowledge user collaborators.

Registration Open Science Foundation (currently embargoed)

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This review will identify existing and promising pharmacologic intraoperative strategies that can be used as alternatives to opioids.
⇒ It will assess patient-centred outcomes that are meaningful for patients and decision-makers in perioperative medicine.
⇒ Identification of relevant citations will be searched through five databases, namely MEDLINE, Embase, CENTRAL, Web of Science and CINAHL.
⇒ We are using an integrated knowledge translation approach including patients, knowledge user organisations and clinicians as partners in all the phases of this review.
⇒ The scope of this review will not include non-pharmacologic opioid minimisation strategies.

INTRODUCTION

Opioid administration is recognised as a standard of care to complement general anaesthesia in order to reduce pain and maintain overall physiological stability (heart rate, blood pressure and metabolic) during surgery.[1] However, potential disadvantages of opioids (ie, risk of tolerance, nausea, confusion, dependence, etc),[2–20] as well as the worldwide opioid crisis, have led to a re-evaluation

of their routine intraoperative use.[21] Multiple national and international societies[22 23] have advised that opioid minimisation strategies (eg, pharmacologic opioid alternatives) be developed and carefully assessed using a patient-oriented approach. In addition, intraoperative opioid minimisation strategies and practices have been identified as patient and caregiver priorities by the recent James Lind Alliance-led Canadian Anaesthesia Research Priority Setting Partnership exercise.[24]

Over the last two decades, more than 20 non-opioid alternative strategies have been developed to complement general anaesthesia, with most being used 'off-label' (ie, use of drug for an indication that has not been approved by regulatory agencies for this specific purpose).[25] Of note, pharmacologic opioid minimisation strategies during the intraoperative period are being adopted despite limited evidence to inform best practice and with large variation in practices.[25–27] While the results of previous reviews and randomised controlled trials (RCTs) suggest that opioid alternatives can reduce short-term opioid use during and after surgery, they have focused primarily on the effect of pharmacologic opioid minimising strategies on surrogate outcome measures, such as short-term quantity of opioids administered, haemodynamic stability or unidimensional instruments (eg, pain intensity assessment).[6–18 28–46] There is a paucity of evidence regarding the impact of opioid minimisation strategies on long-term opioid use and outcomes that are the most meaningful to patients. Importantly, patients were not engaged or consulted on their preferences in previous reviews. Thus, while some pharmacologic strategies have been identified as potentially beneficial, a global perspective that maps all potential pharmacologic opioid alternatives during the intraoperative period, including their potential impact on clinically relevant outcomes most meaningful to patients, is noticeably lacking.[28–34] Furthermore, there is a need to integrate guidance provided by the Standardised Endpoints in Perioperative Medicine initiative (StEP-COMPAC), a group that established recommendations for patient-centred outcome measures to be assessed in perioperative trials to better inform future research and priorities.[47]

To address this knowledge gap, we have assembled a multidisciplinary team of knowledge users, a patient panel, clinicians, policy-makers, trainees and methodologists, to conduct a patient-oriented scoping review to examine the current evidence of RCTs assessing intraoperative pharmacologic opioid minimisation strategies. Our primary aim is to map and characterise the RCT evidence assessing the patient-centred effectiveness of pharmacologic intraoperative opioid minimisation strategies in adult surgical patients. This will include a description of the pharmacologic strategies assessed and identification of promising pharmacologic strategies. Our secondary aim is to synthesise the reported patient-centred outcomes in RCTs evaluating pharmacologic intraoperative opioid minimisation strategies by mapping and characterising the reported outcomes.

METHODS AND ANALYSIS

Review question

Our main research question aims to identify and describe pharmacologic opioid minimisation strategies for use during the intraoperative period that are tailored to the needs of surgical patients undergoing general anaesthesia. We have defined our eligibility criteria according to the Participant, Concept, Context and Source framework.[48] The eligibility criteria have been informed through discussions with interested parties including patient partners. Important definitions are detailed in online supplemental appendix 1.

Design

Our scoping review will follow best practices including the methodological framework developed by Arksey and O'Malley[49–51] and recommendations from the Joanna Briggs Institute (JBI).[48] We have chosen a scoping review design over other approaches to knowledge synthesis considering the large number of strategies available, the complexity of the field, as well as established recommendations for choosing the most appropriate knowledge synthesis research design.[52 53] Our protocol is reported in accordance with JBI guidance,[54 55] and our final review will be reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Extension for Scoping Review guidelines.[56] We will be using the Guidance for Reporting Involvement of Patients and Public (GRIPP2) checklist to report patient involvement in our review.[57] Our study is registered with the Open Science Foundation and all modifications will be posted.[58] We started this study in February 2022 by assembling our team of investigators and partners and applying for Canadian Institutes of Health Research funding. The study will end with dissemination of results planned by December 2023.

Eligibility criteria

Participants

Our target population will be adult (≥18 years old) surgical patients considering significant differences for patient-centred outcome measures between adults and children. We will include studies involving any type of surgery (elective vs emergent, cardiac vs non-cardiac) and any surgical patient population (opioid naïve, opioid user, parturient, etc) undergoing general anaesthesia. The total sample size will need to be at least 30 participants considering statistical and clinical limitations of small sample size studies for pragmatism research question.

Concept

We will include RCTs and cluster RCTs assessing the impact of a systemic intraoperative pharmacologic opioid minimisation strategy compared with one or more control groups consisting of systemic opioids, routine care or systemic placebo on patient-centred outcomes (see online supplemental appendix 1 for definitions). A systemic opioid minimisation strategy is defined as any non-opioid drug with

Table 1 StEP-COMPAC group recommendations for patient-centred outcome assessments in perioperative clinical trials[47] and our prioritisation order tailored to pharmacologic interventions

	Patient-centred outcome domains				
	Patient well-being	**Health-related quality of life**	**Functional outcome**	**Patient satisfaction**	**Life impact**
Instruments to be prioritised based on StEP-COMPAC recommendations	Quality of recovery-15[81]	EuroQol 5 Dimension, five-level version with visual analogue scale[82]	WHO Disability Assessment Schedule version 2.0[83]	Bauer patient-satisfaction measure[84]	Days alive and out of hospital after surgery (at 30 days and 1 year) and discharge destination
Prioritisation by our team (Steering committee)*	1	2	3	4	5

*Prioritisation based on (a) plausibility for effect between intraoperative pharmacologic intervention and outcome (b) patient panel and knowledge users priority.

antinociceptive properties administered orally, or using intramuscular, subcutaneous or intravenous route during the intraoperative period (see online supplemental appendix 2 for the list of classes of drugs included).[13] The intervention must be started during the intraoperative period, and there is no limitation for the duration of the intervention.

Context

At least one patient-centred outcome must be assessed and reported in the study based on StEP-COMPAC recommendations (well-being, functional outcomes, patient satisfaction, quality of life and life impact).[47] Any instruments that could be categorised in one of these domains will be included. Based on discussions with patient partners, we will also include within the scope of patient-centred outcomes long-term opioid use (≥1 month), opioid-related adverse effects (multidimensional assessment), acute pain (multidimensional assessment, <3 months) and postoperative chronic pain (≥3 months).[24] Studies assessing patient-centred outcome measures only during the time in recovery room will not be included as this time point was judged to be less meaningful by both the patient partners and knowledge users.

Information sources

We will only include RCTs as it is the gold standard study design to address the potential effect of an intervention. We anticipate to retrieve a large number of RCTs meeting our eligibility criteria. Only articles published in peer-reviewed journals will be included.

Search strategy

Our search strategy was developed using a three-step approach in collaboration with method experts, patients, anesthesiologists, surgeons, pain experts and an information specialist.[48] Key terms to be included were informed by discussion with our stakeholder group (online supplemental appendix 3). First, we ran the pilot search strategy (online supplemental appendix 4) in two databases (MEDLINE and CINAHL). This search strategy was developed following the Peer Review of Electronic Search Strategies (PRESS) recommendations and it was peer-reviewed independently by one information specialist.[59] Text terms contained in the title and abstract of relevant citations as well as index terms were collected based on our pilot search strategy. Second, we added those text terms and index terms to the search strategy, which we then ran through MEDLINE, Embase, CENTRAL, Web of Science and CINAHL from inception. To ensure the sensitivity of the search strategy, we verified that the strategy returned a set of 25 preidentified RCT publications meeting our eligibility criteria. We did not limit language of publication and we plan to translate relevant studies using DeepL (https://www.deepl.com/translator).[60 61]

Study records

Data management

Applicability, reproducibility and impact will be increased by following the Canadian Roadmap for Open Science (registering the review, publishing the protocol, accessible and reproducible data and results, etc).[62] Any deviations from our protocol will be noted, with rationale, in the completed review and on our Open Science Framework project file.

Selection process

Screening will be performed in two stages. In stage 1, we will screen titles and abstracts identified by the search strategy, followed in stage 2 by the screening of the full-text articles which were deemed potentially relevant or of uncertain relevance during stage 1 screening. The screening will be performed independently by two reviewers, and disagreements resolved with a third reviewer when necessary. We will use Distiller SR (a cloud-based, audit ready software for knowledge synthesis) to collect citations, remove duplicates and screen titles and abstracts (stage 1).[63] Outcome measure relevance (at least one patient-centred outcome) will be used as an inclusion criterion at full-text screening only (stage 2) and not during title and abstract screening, as this information is believed to be incompletely reported in the abstract. We will collect reasons for exclusion at the full-text screening stage. We will conduct pilot testing of the screening process on a set of 100 random citations for the title and abstract screening. We will report the results of the search and the study inclusion process in the manuscript reporting the results in a Preferred Reporting Items for

Systematic Reviews and Meta-analyses extension for scoping review (PRISMA-ScR) flow diagram.[56]

We will integrate innovative strategies to increase the efficiency of the screening process considering the large number of expected citations and trials.[64] For stage 1, we will use Distiller SR's artificial intelligence (AI) active-machine learning feature to prioritise title and abstract screening of citations.[65 66] This method has been validated.[66] This active-machine learning feature will allow us to perform prioritised screening, as a relevance score will be generated for each citation during an initial training exercise on a sample of approximately 200 citations; this feature will continue to learn throughout the stage 1 screening process, presenting reviewers with the most relevant citations first. Once we have reached a predicted recall rate of 90% (meaning that the active machine learning predicts we will have identified approximately 90% of included RCTs), the AI tool will replace one of the reviewers in our duplicate screening process, and will be instructed to exclude all remaining citations. These citations will still be inspected by a human reviewer, and when there is a disagreement for a citation between the reviewer and the AI tool, a second human reviewer will participate to reach consensus. We will conduct ongoing conflict resolution throughout stage 1 screening to maintain strong performance of the AI tool. For full-text screening (stage 2), we will use the insightScope platform (www.insightscope.ca), a web-based application that allows creation of a large online team to facilitate screening.[67] Prior to beginning full-text screening, each incoming reviewer will need to complete a test set (n=50 citations) and achieve at least 80% sensitivity for included articles compared with a gold standard. The gold standard will be established a priori by two expert reviewers.

Data collection process

We reviewed important concepts to be included in data charting with our patient panel and our knowledge users (online supplemental appendix 3, Steering committee and Stakeholder group) and developed a draft data abstraction form with our patient panel, methodological and clinical experts. It will be pilot tested by two reviewers using a sample of five reports, prior to initiation of data collection for the full set of included studies. Two reviewers will abstract the data independently using a standardised data extraction form in the insightScope platform.[68] Authors will be contacted if relevant data or information is missing.

Data items

To address our primary aim of characterising the RCT evidence assessing pharmacologic intraoperative opioid minimisation strategies and identify promising strategies, we will extract data on the publication (author, year of publication and country), the intervention; including the category of opioid minimisation strategy (N-Methyl-D-aspartate receptor antagonists, anticonvulsant, acetaminophen, corticosteroids, alpha-2 adrenergic agonists, beta-adrenergic antagonists and others),[69 70] whether the intervention involved multiple medications (combination) versus only one medication, the timing of administration (intraoperative vs intraoperative and postoperative period) and the reported patient-centred outcome measures (domains and instruments). Other data to be extracted will include the type of randomisation (group unit vs individual unit) and method (type of comparator, type of surgery, multicentre vs one centre, registered protocol, sample size, adverse events reported, funding source, sex, gender and genetic considerations), study population characteristics (age group, opioid use or chronic pain history), as well as implementation barriers previously identified, such as the mode of administration of the pharmacologic strategy.[71]

To address our secondary aim of synthesising the reported patient-centred outcomes, we will categorise each patient-centred outcome measure according to the Standardised Endpoints in Perioperative Medicine initiative (StEP-COMPAC group perioperative framework) domains (ie, well-being, functional outcomes, patient satisfaction, quality of life and life impact).[47] We will also capture long-term opioid use, opioid-related adverse effects (multidimensional assessment), acute pain (multidimensional assessment) and postoperative chronic pain separately.[72 73]

Data synthesis and outcome prioritisation

The analysis of our primary aim of characterising the RCT evidence assessing patient-centred effectiveness of pharmacologic intraoperative opioid minimisation strategies will be descriptive and will include the use of summary figures, tables and charts. First, we will collate and present in tables the number of RCTs assessing each pharmacologic opioid minimisation strategy identified, as well as important methods and design characteristics of those RCTs. Second, we will further describe the pharmacologic opioid minimisation strategies including the category of pharmacologic agent involved, the timing of administration of the intervention and the number of pharmacologic agents involved in each strategy. We will report the number of trials (bubble size) assessing each class of opioid minimisation strategies (y-axis) as a function of the reported domain of patient-centred outcome (x-axis) using bubble plots. Third, we will characterise the significance of the patient-centred results from each of the RCTs. More specifically, we will classify each RCT and its pharmacologic opioid minimisation strategy as being beneficial (eg, promising), equivocal, not effective or potentially deleterious based on patient-centred outcomes reported and author's conclusion.[74] In cases of inconsistency in results, we will hold nominal group discussions with our identified interested parties (online supplemental appendix 3, Steering committee) to determine which pharmacologic strategies are the most promising.[75] Our a priori prioritisation of patient-centred outcome measure instruments will help guide reporting and interpreting of findings (table 1).[76 77]

For our secondary aim of synthesising reported patient-centred outcomes in RCTs evaluating pharmacologic intraoperative opioid minimisation strategies, we will categorise RCTs based on seven outcome domains (five from StEOP-COMPAC initiative and two from our Steering committee), namely: well-being, functional outcomes, patient satisfaction,

quality of life, life impact, opioid-related (long-term opioid use and multidimensional assessment of opioid-related adverse effects) and pain-related (multidimensional acute pain and postoperative chronic pain). We will present results for individual RCTs and the number of RCTs that reported each outcome measure classified by domain. We will report the proportion of published RCTs that reported on instruments deemed to be important by the StEP-COMPAC group recommendations (table 1). We will also report if sex, gender and genetics were accounted for in the analyses and outcome assessments.[71]

Patient and public involvement

Recognising the need to have the patient voice on the investigative team, our study team includes a patient panel of four individuals with lived perioperative experience. For this collaborative work, we are following the principles laid out in the Strategy for Patient-Oriented Research (SPOR) Patient Engagement Framework which aims to optimize collaborative partnerships between researchers and people with lived experience or organisations.[78] In line with these principles of inclusiveness, support, mutual respect and cobuilding, we (the patient panel and research leads) have met numerous times. Each meeting is co-led with a patient-oriented research facilitator (Nicholls), and we are using first names to facilitate communication and reduce power imbalance. We have also codeveloped terms of reference for the patient panel to inform and guide the ongoing engagement (https://osf.io/afm3z/). Our patient engagement approach and work are described in another publication.[79]

To date, we have developed the protocol through discussions and written comments, including assessment of the relevance of the scope of the review, the outcomes, the plain language abstract, the planned items for extraction and a national grant application. We anticipate ongoing collaboration to assist with the prioritisation of outcomes and interventions as well as interpretation of results and facilitating evidence translation and dissemination of our findings (interaction with other interested parties, codeveloping an abstract, advertisements on social media, etc). We have sought to build strong and sustainable relationships through transparency (mutual goals agreed on), commitment, regular communication and feedback (email updates, group discussion) and ongoing evaluation (Public and Patient Engagement Evaluation tool survey administered to ensure satisfaction and obtain feedback).[80]

We are also engaging several organisations as knowledge users, namely SolvingPain (https://www.solvingpain.ca), Pain BC (https://painbc.ca), Health Canada (https://www.canada.ca/en/health-canada.html), Réseau Québécois de Recherche sur la Douleur (https://qprn.ca/fr/), Choosing Wisely (https://choosingwiselycanada.org), SPOR (https://ossu.ca), the Canadian Anaesthesia Society (https://www.cas.ca/en/home) and the Canadian Chronic Pain Network (https://cpn.mcmaster.ca). We have defined roles of our knowledge user organisations following a presentation and discussion with each of them as well as through a survey sent to each organisation. Our scoping review is developed with the Canadian Perioperative Anaesthesia Clinical Trials (PACT) group (https://canadianpact.ca), a collaborative research network in anesthesiology and perioperative care.

ETHICS AND DISSEMINATION

Our review does not require research ethics committee approval. To increase dissemination, our final manuscript reporting the results will be submitted for publication in open access, peer-reviewed journal. We will work with our knowledge user organisations and their networks to facilitate dissemination through websites, conference presentations, and social media platforms.

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Contributors Study question: MV, DAF, ML, AFT, FZ, MG, MML and AG. Design and methodology: MV, DAF, ML, AFT, FZ, MG, MML, AG and NHL. Develop search strategy: MV, DAF, ML, AFT, NHL and RS. Drafting the manuscript: MV, DF, ML and NHL. Revise the manuscript: MV, DAF, ML, AFT, FZ, MG, ML, AG, NHL, SC, MH, ALM, NF, SN, DIM, IG, BH, MB, PP, GM, JM, HM, RS and HD. Guide artificial intelligence feature for screening titles and abstracts: BH. Design data extraction form: MV, DAF, ML, AFT, BL, FZ, MG, MML, AG and NHL. Lead patient engagement activities: MV and SN. Lead knowledge user partnership activities: MV, DAF and ML. Screening, data abstraction and data charting: MV, NHL, SS, MH, AA-M and NAF. All authors reviewed the content of the protocol and approved the final version.

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Competing interests IG has received consulting fees from GW Research, Eupraxia, Biogen and Novaremed.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting or dissemination plans of this research. Refer to the Methods section for further details.

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