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Intraoperative pharmacologic opioid minimization 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 anesthesia during surgery. Considering the worldwide opioid epidemic, this practice is now being challenged. There is a growing use of systemic pharmacological opioid minimizing strategies to reduce opioid use and potentially improve patient-centred surgical outcomes. Our aim is to conduct a scoping review that will examine clinical trials that have evaluated the impact of intraoperative opioid minimization 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 as well as recommendations from the JBI. We will search MEDLINE, EMBASE, CENTRAL, Web of Science, and CINAHL, from their inception without limitation for language of publication. We will include randomized controlled trials, assessing the impact of systemic intraoperative pharmacologic opioid minimization strategies on patient-centred outcomes. We define an opioid minimization 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 co-production approach involving interested parties. Our multidisciplinary team includes knowledge users (surgeons, nurses, anesthesiologists, critical care physicians), patient partners, methodologists and knowledge user organizations. 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: Our scoping review will inform future research including clinical trials and systematic reviews through identification of important intraoperative interventions.

Registration: Open Science Foundation (currently embargoed, https://osf.io/7kea3/?view_only=49946e5dc46c41a59911d247191c9049)

Article Summary

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 outcomes that are meaningful for patients and decision makers in perioperative medicine.
- Interested parties including patients, knowledge user organizations and clinicians will be involved in all the phases of this review.
- Results from this review will inform future research but inferences to directly guide clinical practices will be limited by the lack of risk of bias assessment and the absence of quantitative synthesis of the results.

INTRODUCTION

Opioid administration is recognized as a standard of care to complement general anesthesia in order to reduce pain and maintain overall physiological stability (heart rate, blood pressure, 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 minimization strategies (eg. pharmacologic opioid alternatives) be developed and carefully assessed using a patient-oriented approach. In addition, intraoperative opioid minimization strategies and practices have been identified as patient and caregiver priorities by the recent James Lind Alliance-led Canadian Anesthesia Research Priority Setting Partnership exercise.[24]

Over the last two decades, more than twenty non-opioid alternative strategies have been developed to complement general anesthesia, 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 minimization 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 randomized 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 minimizing strategies on surrogate outcome measures, such as short-term quantity of opioids administered, hemodynamic stability, or unidimensional instruments (eg. pain intensity assessment).[6-18 28-46] There is a paucity of evidence regarding the impact of opioid minimization 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] Further, 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 minimization strategies. Our primary aim is to map and characterize the RCT evidence assessing the patient-centred effectiveness of pharmacologic intraoperative opioid minimization 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 synthesize the reported patient-centred outcomes in RCTs evaluating pharmacologic intraoperative opioid minimization strategies by mapping and characterizing the trial reported outcomes.

METHODS AND ANALYSIS

Review question

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

Design

Our scoping review will follow best practices including the methodological framework developed by Arksey and O'Malley[49 50 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.

Eligibility criteria

Participants

Our target population will be adult (≥ 18 years old) surgical patients considering significant differences for patient-centred outcome measures between adult 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 anesthesia. 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 minimization strategy compared with one or more control groups consisting of systemic opioids, routine care, or systemic placebo on patient-centred outcomes (see Appendix 1 for definitions). A systemic opioid minimization strategy is defined as any non-opioid drug with anti-nociceptive properties administered orally, or using intramuscular, subcutaneous or intravenous injection during the intraoperative period (see 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 categorized 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 (Appendix 3). First, we ran the pilot search strategy (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.[58] 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 pre-identified 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).[59 60]

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.).[61] 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 & 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).[62] 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 exclusions 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.[63] For stage 1, we will use Distiller SR's artificial intelligence (AI) active-machine learning feature to prioritize title and abstract screening of citations.[64 65] This method has been validated.[65] This active-machine learning feature will allow us to perform prioritized 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.[66] 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 (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 standardized data extraction form in the insightScope platform.[67] Authors will be contacted if relevant data or information is missing.

Data items

To address our primary aim of characterizing the RCT evidence assessing pharmacologic intraoperative opioid minimization strategies and identify promising strategies, we will extract data on the publication (author, year of publication, country), the intervention; including the category of opioid minimization strategy (N-Methyl-D-aspartate receptor antagonists, anticonvulsant, acetaminophen, corticosteroids, alpha-2 adrenergic agonists, beta-adrenergic antagonists, and other),[68 69] whether the intervention involved multiple medications (combination) vs. 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 randomization (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.[70]

To address our secondary aim of synthesizing the reported patient-centred outcomes, we will categorize each patient-centred outcome measure according to the Standardised Endpoints in Perioperative Medicine initiative (StEP-COMPAC group perioperative framework) domains (i.e. well-being, functional outcomes, patient satisfaction, quality of life, and life impact).[71] 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 prioritization

The analysis of our primary aim of characterizing the RCT evidence assessing patient-centred effectiveness of pharmacologic intraoperative opioid minimization 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 minimization strategy identified, as well as important methods and design characteristics of those RCTs. Second, we will further describe the pharmacologic opioid minimization 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 minimization strategies (y-axis) as a function of the reported domain of patient-centred outcome (x-axis) using bubble plots. Third, we will characterize the significance of the patient-centred results from each of the RCTs. More specifically, we will classify each RCT and its pharmacologic opioid minimization 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 (Appendix 3, Steering committee) to determine which pharmacologic strategies are the most promising.[75] Our a priori prioritization of

patient-centred outcome measure instruments will help guide reporting and interpreting of findings (Table 1).[76 77]

Table 1. StEP-COMPAC group recommendations for patient-centred outcome assessments in perioperative clinical trials[47] and our prioritization 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 prioritized based on StEP-COMPAC recommendations	Quality of recovery-15 [78]	EuroQol 5 Dimension, five-level version with visual analogue scale [79]	WHO Disability Assessment Schedule version 2.0 [80]	Bauer patient-satisfaction measure [81]	Days alive and out of hospital after surgery (at 30 days and one year) and discharge destination
Prioritization by our team (Steering committee)[1]	1	2	3	4	5

[1]Prioritization based on a) Plausibility for effect between intraoperative pharmacologic intervention and outcome b) Patient and knowledge user priority

For our secondary aim of synthesising reported patient-centred outcomes in RCTs evaluating pharmacologic intraoperative opioid minimization strategies, we will categorize RCTs based on 7 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 genetic were accounted for in the analyses and outcome assessments.[70]

Patient and public involvement

Recognizing 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 at optimizing collaborative partnerships between researchers and lay people or organizations.[82] In line with these principles of inclusiveness, support, mutual respect, and co-building, 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 co-developed 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 (manuscript accepted, publication pending).

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 national grant application. We anticipate ongoing collaboration to assist with the prioritization of outcomes and interventions as well as interpretation of results and facilitating evidence translation and dissemination of our findings (interaction with other interested parties, co-developing 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 [PPEET] survey administered to ensure satisfaction and obtain feedback).[83]

We are also engaging several organizations 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), Strategy for Patient-Oriented Research (https://ossu.ca), the Canadian Anesthesia 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 organizations following a presentation and discussion with each of them as well as through a survey sent to each organization. Our scoping review is developed with the Canadian Perioperative Anesthesia Clinical Trials (PACT) group (https://canadianpact.ca), a collaborative research network in anesthesiology and perioperative care.

Conclusion

Our scoping review will help identify knowledge gaps to be addressed to inform clinical practice guidelines and future research regarding intraoperative opioid minimization strategies. Specifically, it will help identify promising opioid minimization strategies that warrant systematic reviews and future clinical trials. Although influential international perioperative guidelines such as the *Enhanced Recovery After Surgery guideline* do encourage perioperative opioid minimization strategies in general,[84-86] recommendations specifically regarding the intraoperative period are non-existent.[87] Lastly, we will identify whether important patient-centred outcomes are underrepresented in published trials, which will guide future research for improving patient-oriented research and, ultimately, clinical 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 journals. We will work with our knowledge user organizations and their networks to facilitate dissemination through websites, conference presentations, and social media platforms.

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Appendix 1. Definitions

Intraoperative period: The moment between patient entrance in the operating room (OR) and the moment they leave the operating room. For our research program, pharmacologic interventions administered the same day of surgery and before patient's extubation will be considered as intraoperative based on mechanism of action and effect duration properties.

Intraoperative opioid minimization strategy: Any non-opioid drug with antinociceptive properties administered during the intraoperative period.

Intraoperative opioid-free anesthesia: A type of opioid minimization strategy with complete avoidance of opioids during surgery.

Multimodal strategies: The use of different classes of drugs, combining different action mechanisms aiming to reduce adverse effects and improving benefits.

Patient centred outcome domains: well-being, functional outcomes, patient satisfaction, quality of life, life impact, opioid-related, and pain-related.

Perioperative opioid free analgesia: A type of opioid minimization strategy with complete avoidance of opioids for pain management.
Systemic administration: Oral, intravenous, intramuscular or subcutaneous administration.

Appendix 2. List of class of drugs included and specific pharmacologic opioid minimization strategies examples

Class of drugs	Examples
Anticonvulsants	Pregabalin Gabapentin Carbamazepine
Beta-adrenergic antagonist	Esmolol Metoprolol Labetolol
Alpha-2 receptor agonist	Clonidine Dexmedetomidine
Methylxanthine	Caffeine
NMDA Receptor Antagonists	Ketamine Dextromethorphan Magnesium
Corticosteroid/Glucocorticoid	Dexamethasone Methylprednisolone Hydrocortisone Prednisone
Antidepressants	Amitriptyline Duloxetine Tryptophan Bicifadine Fluoxetine Venlafaxine Citalopram
Local Anesthetic	Lidocaine
Anti-inflammatory (non-NSAID)	Acetaminophen Nefopam Metamizol
Non opioid central analgesic	Acetaminophen Nefopam
Ampyrone	Metamizole

Nonsteroidal Anti-inflammatory Drugs	Aspirin Ketorolac Diclofenac Naproxen Ibuprofen Nabumetone Indomethacin Piroxicam
COX-2 specific inhibitor (COXIB)	Celecoxib Rofecoxib Valdecoxib Etoricoxib Lumiracoxib
Cannabinoid	Nabilone Cannabidiol

Appendix 3. Interested parties

Type of knowledge user	Interested parties identified	Role in our scoping review
Practitioners and researchers	Anesthesiologists Surgeons Nurses Pain expert Psychologist Researcher Trainee	Steering committee and stakeholder group
Patients	Patient panel	Steering committee and stakeholder group
Patient organization	Strategy for Patient-Oriented Research (SPOR)	Stakeholder group
Policy makers	Health Canada Choosing Wisely	Stakeholder group
Institutions	Department of Anesthesia and Pain Medicine (University of Ottawa)	Stakeholder group
Interdisciplinary organization	Pain BC Solving Pain Réseau Québécois de Recherche sur la Douleur Chronic Pain Network	Stakeholder group
Researcher and practitioner organization	Perioperative Anesthesia Clinical Trials group Canadian Anesthesia Society	Stakeholder group

Appendix 4. Search strategy for MEDLINE/Ovid

1 exp Surgical Procedures, Operative/
2 su.fs. or (surger* or surgical*).tw,kf.
3 (curettage or debridement or electrosurger* or fasciotom* or Keratectom* or laparotom* or lymph node excision or mastectom* or metastasectom* or microsurger* or myotom* or neurosurgical procedure* or orthopedic procedure* or amputation or Osteotom* or pelvic exenteration or pneumonectom* or prosthesis implantation or reoperation or splenectom* or symphysiotom* or transplantation).tw,kf.
4 or/1-3
5 ((opioid* or opiate*) adj3 (sparing or minimi?ation or free)).tw,kf.
6 (multimodal adj5 (an?esthes* or analges*)).tw,kf.
7 5 or 6
8 analgesics/ or exp analgesics, non-narcotic/
9 exp Adrenergic alpha-2 Receptor Agonists/
10 Caffeine/
11 exp anti-inflammatory agents/
12 exp Adrenal Cortex Hormones/
13 exp Cyclooxygenase 2 Inhibitors/
14 exp Adrenergic beta-Antagonists/
15 Receptors, N-Methyl-D-Aspartate/ai [Antagonists & Inhibitors]
16 magnesium compounds/ or magnesium sulfate/
17 exp Anticonvulsants/
18 (Lidocaine or Alpha-2 Receptor Agonist* or Caffeine or Corticosteroid* or Beta block* or NMDA receptor antagonist* or Magnesium or Acetaminophen or NSAID* or Anti-convulsant* or anticonvulsant* or Antidepressant* or gabapentinoid* or cox-2 inhibitor*).tw,kf.
19 Dexmedetomidine/ or lidocaine/ or ketamine/ or Propanolamines/ or Clonidine/
20 (Pregabalin or Gabapentin or Carbamazepine or Carbazepin or Esmolol or Propanolamine* or Metoprolol or Labetolol or Clonidine or Dexmedetomidine or Catapressan or Caffeine or Ketamine or Dextromethorphan or Dexamethasone or Methylprednisolone or hydrocortison* or Prednisone or magnesium or Amitriptyline or Duloxetine or Tryptophan or Bicifadine or Desipramine or fluoxetine or Venlafaxine or Citalopram).ti.
21 or/8-20
22 perioperative period/ or intraoperative period/ or exp Administration, Intravenous/ or Combined Modality Therapy/
23 (perioperat* or peri operat* or intra operat* or intraoperat*).tw,kf.
24 (an?esthes* adj2 induction).tw,kf.
25 or/22-24
26 21 and 25
27 7 or 26
28 4 and 27
29 randomized controlled trial.pt.
30 controlled clinical trial.pt.
31 random*.tw.
32 placebo.ab.

33 clinical trials as topic.sh.
34 trial.ti.
35 or/29-34
36 exp animals/ not humans/
37 35 not 36
38 28 and 37
39 38 use medall

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Intraoperative pharmacologic opioid minimization 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 anesthesia during surgery. Considering the worldwide opioid epidemic, this practice is now being challenged and there is a growing use of systemic pharmacological opioid minimizing strategies. Our aim is to conduct a scoping review that will examine clinical trials that have evaluated the impact of intraoperative opioid minimization 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 randomized controlled trials, assessing the impact of systemic intraoperative pharmacologic opioid minimization strategies on patient-centred outcomes. We define an opioid minimization 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 co-production approach involving interested parties. Our multidisciplinary team includes knowledge users, patient partners, methodologists and knowledge user organizations. 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, https://osf.io/7kea3/?view_only=49946e5dc46c41a59911d247191c9049)

Article Summary

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 organizations and clinicians as partners in all the phases of this review.
- The scope of this review will not include non pharmacologic opioid minimization strategies.

INTRODUCTION

Opioid administration is recognized as a standard of care to complement general anesthesia in order to reduce pain and maintain overall physiological stability (heart rate, blood pressure, 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 minimization strategies (eg. pharmacologic opioid alternatives) be developed and carefully assessed using a patient-oriented approach. In addition, intraoperative opioid minimization strategies and practices have been identified as patient and caregiver priorities by the recent James Lind Alliance-led Canadian Anesthesia Research Priority Setting Partnership exercise.[24]

Over the last two decades, more than twenty non-opioid alternative strategies have been developed to complement general anesthesia, 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 minimization 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 randomized 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 minimizing strategies on surrogate outcome measures, such as short-term quantity of opioids administered, hemodynamic stability, or unidimensional instruments (eg. pain intensity assessment).[6-18, 28-46] There is a paucity of evidence regarding the impact of opioid minimization 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] Further, 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 minimization strategies. Our primary aim is to map and characterize the RCT evidence assessing the patient-centred effectiveness of pharmacologic intraoperative opioid minimization 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 synthesize the reported patient-centred outcomes in RCTs evaluating pharmacologic intraoperative opioid minimization strategies by mapping and characterizing the trial reported outcomes.

METHODS AND ANALYSIS

Review question

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

Design

Our scoping review will follow best practices including the methodological framework developed by Arksey and O'Malley[49] [50] [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. 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 adult 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 anesthesia. 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 minimization strategy compared with one or more control groups consisting of systemic opioids, routine care, or systemic placebo on patient-centred outcomes (see Appendix 1 for definitions). A systemic opioid minimization strategy is defined as any non-opioid drug with anti-nociceptive properties administered orally, or using intramuscular, subcutaneous or intravenous injection during the intraoperative period (see 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 categorized 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 (Appendix 3). First, we ran the pilot search strategy (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.[58] 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 pre-identified 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).[59, 60]

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.).[61] 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 & 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).[62] 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 exclusions 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.[63] For stage 1, we will use Distiller SR's artificial intelligence (AI) active-machine learning feature to prioritize title and abstract screening of citations.[64, 65] This method has been validated.[65] This active-machine learning feature will allow us to perform prioritized 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.[66] 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 (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 standardized data extraction form in the insightScope platform.[67] Authors will be contacted if relevant data or information is missing.

Data items

To address our primary aim of characterizing the RCT evidence assessing pharmacologic intraoperative opioid minimization strategies and identify promising strategies, we will extract data on the publication (author, year of publication, country), the intervention; including the category of opioid minimization strategy (N-Methyl-D-aspartate receptor antagonists, anticonvulsant, acetaminophen, corticosteroids, alpha-2 adrenergic agonists, beta-adrenergic antagonists, and other),[68, 69] whether the intervention involved multiple medications (combination) vs. 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 randomization (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.[70]

To address our secondary aim of synthesizing the reported patient-centred outcomes, we will categorize each patient-centred outcome measure according to the Standardised Endpoints in Perioperative Medicine initiative (StEP-COMPAC group perioperative framework) domains (i.e. well-being, functional outcomes, patient satisfaction, quality of life, and life impact).[71] 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 prioritization

The analysis of our primary aim of characterizing the RCT evidence assessing patient-centred effectiveness of pharmacologic intraoperative opioid minimization 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 minimization strategy identified, as well as important methods and design characteristics of those RCTs. Second, we will further describe the pharmacologic opioid minimization 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 minimization strategies (y-axis) as a function of the reported domain of patient-centred outcome (x-axis) using bubble plots. Third, we will characterize the significance of the patient-centred results from each of the RCTs. More specifically, we will classify each RCT and its pharmacologic opioid minimization 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 (Appendix 3, Steering committee) to determine which pharmacologic strategies are the most promising.[75] Our a priori prioritization of patient-centred outcome measure instruments will help guide reporting and interpreting of findings (Table 1).[76, 77]

Table 1. StEP-COMPAC group recommendations for patient-centred outcome assessments in perioperative clinical trials[47] and our prioritization 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 prioritized based on StEP-COMPAC recommendations	Quality of recovery-15 [78]	EuroQol 5 Dimension, five-level version with visual analogue scale [79]	WHO Disability Assessment Schedule version 2.0 [80]	Bauer patient-satisfaction measure [81]	Days alive and out of hospital after surgery (at 30 days and one year) and discharge destination
Prioritization by our team (Steering committee)[1]	1	2	3	4	5

[1]Prioritization based on a) Plausibility for effect between intraoperative pharmacologic intervention and outcome b) Patient and knowledge user priority

For our secondary aim of synthesising reported patient-centred outcomes in RCTs evaluating pharmacologic intraoperative opioid minimization strategies, we will categorize RCTs based on 7 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 genetic were accounted for in the analyses and outcome assessments.[70]

Patient and public involvement

Recognizing 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 at optimizing collaborative partnerships between researchers and lay people or organizations.[82] In line with these principles of inclusiveness, support, mutual respect, and co-building, 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 co-developed 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 (manuscript accepted, publication pending).

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 national grant application. We anticipate ongoing collaboration to assist with the prioritization of outcomes and interventions as well as interpretation of results and facilitating evidence translation and dissemination of our findings (interaction with other interested parties, co-developing 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 [PPEET] survey administered to ensure satisfaction and obtain feedback).[83]

We are also engaging several organizations 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), Strategy for Patient-Oriented Research (https://ossu.ca), the Canadian Anesthesia 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 organizations following a presentation and discussion with each of them as well as through a survey sent to each organization. Our scoping review is developed with the Canadian Perioperative Anesthesia 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 journals. We will work with our knowledge user organizations and their networks to facilitate dissemination through websites, conference presentations, and social media platforms.

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Lead patient engagement activities: MV, SN

Lead knowledge user partnership activities: MV, DF, ML

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All authors reviewed the content of the protocol and approved the final version.

Data statement:

Technical appendix and meta-data will be publicly available on Open Science Foundation (OSF) in our project file following the publication of the manuscript reporting the results.

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Competing interest statement: Dr Ian Gilron has received consulting fees from GW Research, Eupraxia, Biogen, and Novaremed.

Patient and public involvement: Patients were involved in the design, conduct, and reporting plans of this research. Refer to the Methods and patient and public involvement sections for further details.

Provenance and peer review: This study was peer reviewed by the Canadian Institute Health and Research (CIHR) organization.

Appendix 1. Definitions

Intraoperative period: The moment between patient entrance in the operating room (OR) and the moment they leave the operating room. For our research program, pharmacologic interventions administered the same day of surgery and before patient's extubation will be considered as intraoperative based on mechanism of action and effect duration properties.

Intraoperative opioid minimization strategy: Any non-opioid drug with antinociceptive properties administered during the intraoperative period.

Intraoperative opioid-free anesthesia: A type of opioid minimization strategy with complete avoidance of opioids during surgery.

Multimodal strategies: The use of different classes of drugs, combining different action mechanisms aiming to reduce adverse effects and improving benefits.

Patient centred outcome domains: well-being, functional outcomes, patient satisfaction, quality of life, life impact, opioid-related, and pain-related.

Perioperative opioid free analgesia: A type of opioid minimization strategy with complete avoidance of opioids for pain management.
Systemic administration: Oral, intravenous, intramuscular or subcutaneous administration.

Appendix 2. List of class of drugs included and specific pharmacologic opioid minimization strategies examples

Class of drugs	Examples
Anticonvulsants	Pregabalin Gabapentin Carbamazepine
Beta-adrenergic antagonist	Esmolol Metoprolol Labetolol
Alpha-2 receptor agonist	Clonidine Dexmedetomidine
Methylxanthine	Caffeine
NMDA Receptor Antagonists	Ketamine Dextromethorphan Magnesium
Corticosteroid/Glucocorticoid	Dexamethasone Methylprednisolone Hydrocortisone Prednisone
Antidepressants	Amitriptyline Duloxetine Tryptophan Bicifadine Fluoxetine Venlafaxine Citalopram
Local Anesthetic	Lidocaine
Anti-inflammatory (non-NSAID)	Acetaminophen Nefopam Metamizol
Non opioid central analgesic	Acetaminophen Nefopam
Ampyrone	Metamizole
Nonsteroidal Anti-inflammatory Drugs	Aspirin

	Ketorolac Diclofenac Naproxen Ibuprofen Nabumetone Indomethacin Piroxicam
COX-2 specific inhibitor (COXIB)	Celecoxib Rofecoxib Valdecoxib Etoricoxib Lumiracoxib
Cannabinoid	Nabilone Cannabidiol

Appendix 3. Interested parties

Type of knowledge user	Interested parties identified	Role in our scoping review
Practitioners and researchers	Anesthesiologists Surgeons Nurses Pain expert Psychologist Researcher Trainee	Steering committee and stakeholder group
Patients	Patient panel	Steering committee and stakeholder group
Patient organization	Strategy for Patient-Oriented Research (SPOR)	Stakeholder group
Policy makers	Health Canada Choosing Wisely	Stakeholder group
Institutions	Department of Anesthesia and Pain Medicine (University of Ottawa)	Stakeholder group
Interdisciplinary organization	Pain BC Solving Pain Réseau Québécois de Recherche sur la Douleur Chronic Pain Network	Stakeholder group
Researcher and practitioner organization	Perioperative Anesthesia Clinical Trials group Canadian Anesthesia Society	Stakeholder group

Appendix 4. Search strategy for MEDLINE/Ovid

1	exp Surgical Procedures, Operative/
2	su.fs. or (surger* or surgical*).tw,kf.
3	(curettage or debridement or electrosurger* or fasciotom* or Keratectom* or laparotom* or lymph node excision or mastectom* or metastasectom* or microsurger* or myotom* or neurosurgical procedure* or orthopedic procedure* or amputation or Osteotom* or pelvic exenteration or pneumonectom* or prosthesis implantation or reoperation or splenectom* or symphysiotom* or transplantation).tw,kf.
4	or/1-3
5	((opioid* or opiate*) adj3 (sparing or minimi?ation or free)).tw,kf.
6	(multimodal adj5 (an?esthes* or analges*)).tw,kf.
7	5 or 6
8	analgesics/ or exp analgesics, non-narcotic/
9	exp Adrenergic alpha-2 Receptor Agonists/
10	Caffeine/
11	exp anti-inflammatory agents/
12	exp Adrenal Cortex Hormones/
13	exp Cyclooxygenase 2 Inhibitors/
14	exp Adrenergic beta-Antagonists/
15	Receptors, N-Methyl-D-Aspartate/ai [Antagonists & Inhibitors]
16	magnesium compounds/ or magnesium sulfate/
17	exp Anticonvulsants/
18	(Lidocaine or Alpha-2 Receptor Agonist* or Caffeine or Corticosteroid* or Beta block* or NMDA receptor antagonist* or Magnesium or Acetaminophen or NSAID* or Anti-convulsant* or anticonvulsant* or Antidepressant* or gabapentinoid* or cox-2 inhibitor*).tw,kf.
19	Dexmedetomidine/ or lidocaine/ or ketamine/ or Propanolamines/ or Clonidine/
20	(Pregabalin or Gabapentin or Carbamazepine or Carbazepin or Esmolol or Propanolamine* or Metoprolol or Labetolol or Clonidine or Dexmedetomidine or Catapressan or Caffeine or Ketamine or Dextromethorphan or Dexamethasone or Methylprednisolone or hydrocortison* or Prednisone or magnesium or Amitriptyline or Duloxetine or Tryptophan or Bicifadine or Desipramine or fluoxetine or Venlafaxine or Citalopram).ti.
21	or/8-20
22	perioperative period/ or intraoperative period/ or exp Administration, Intravenous/ or Combined Modality Therapy/
23	(perioperat* or peri operat* or intra operat* or intraoperat*).tw,kf.
24	(an?esthes* adj2 induction).tw,kf.
25	or/22-24
26	21 and 25
27	7 or 26
28	4 and 27
29	randomized controlled trial.pt.
30	controlled clinical trial.pt.
31	random*.tw.

32 placebo.ab.
33 clinical trials as topic.sh.
34 trial.ti.
35 or/29-34
36 exp animals/ not humans/
37 35 not 36
38 28 and 37
39 38 use medall

Search strategy for Embase

40 exp *surgery/

41 (surg* or surgical*).tw.

42 (curettage or debridement or electrosurger* or fasciotom* or Keratectom* or laparotom* or lymph node excision or mastectom* or metastasectom* or microsurger* or myotom* or neurosurgical procedure* or orthopedic procedure* or amputation or Osteotom* or pelvic exenteration or pneumonectom* or prosthesis implantation or reoperation or splenectom* or symphysiotom* or transplantation).tw.

43 40 or 41 or 42

44 ((opioid* or opiate*) adj3 (sparing or minimi?ation or free)).tw.

45 (multimodal adj5 (an?esthes* or analges*)).tw.

46 44 or 45

47 exp *analgesic agent/

48 exp *alpha 2 adrenergic receptor stimulating agent/

49 *caffeine/

50 exp *antiinflammatory agent/

51 exp *corticosteroid/

52 exp *cyclooxygenase 2 inhibitor/

53 exp *beta adrenergic receptor blocking agent/

54 exp *n methyl dextro aspartic acid receptor stimulating agent/

55 *magnesium/

56 *magnesium sulfate/

57 exp *anticonvulsive agent/

58 (Lidocaine or Alpha-2 Receptor Agonist* or Caffeine or Corticosteroid* or Beta block* or NMDA receptor antagonist* or Magnesium or Acetaminophen or NSAID* or Anti-convulsant* or anticonvulsant* or Antidepressant* or gabapentinoid* or cox-2 inhibitor*).tw.

59 *dexmedetomidine/

60 *lidocaine/

61 *ketamine/

62 *propanolamine derivative/

63 *clonidine/

64 (Pregabalin or Gabapentin or Carbamazepine or Carbazepin or Esmolol or Propanolamine* or Metoprolol or Labetolol or Clonidine or Dexmedetomidine or Catapressan or Caffeine or Ketamine or Dextromethorphan or Dexamethasone or Methylprednisolone or hydrocortison* or Prednisone or magnesium or Amitriptyline or Duloxetine or Tryptophan or Bicifadine or Desipramine or fluoxetine or Venlafaxine or Citalopram).ti.

65 or/47-64

66 *perioperative period/

67 intraoperative period/

68 (perioperat* or peri operat* or intra operat* or intraoperat*).tw.

69 anesthesia induction/

70 *intravenous drug administration/

71 (an?esthes* adj1 induction).tw.

72 or/66-71

73 65 and 72

74 46 or 73

75 43 and 74

76 random*.tw. or placebo*.mp. or double-blind*.tw. or trial.ti.

77 75 and 76

78 (exp animal/ or nonhuman/) not exp human/

79 77 not 78

80 79 use emczd

Search strategy for CENTRAL

81 exp Surgical Procedures, Operative/

82 su.fs. or (surger* or surgical*).tw,kw.

83 (curettage or debridement or electrosurger* or fasciotom* or Keratectom* or laparotom* or lymph node excision or mastectom* or metastasectom* or microsurger* or myotom* or neurosurgical procedure* or orthopedic procedure* or amputation or Osteotom* or pelvic exenteration or pneumonectom* or prosthesis implantation or reoperation or splenectom* or symphysiotom* or transplantation).tw,kw.

84 or/81-83

85 ((opioid* or opiate*) adj3 (sparing or minimi?ation or free)).tw,kw.

86 (multimodal adj5 (an?esthes* or analges*)).tw,kw.

87 85 or 86

88 analgesics/ or exp analgesics, non-narcotic/

89 exp Adrenergic alpha-2 Receptor Agonists/

90 Caffeine/

91 exp anti-inflammatory agents/

92 exp Adrenal Cortex Hormones/

93 exp Cyclooxygenase 2 Inhibitors/

94 exp Adrenergic beta-Antagonists/

95 Receptors, N-Methyl-D-Aspartate/ai [Antagonists & Inhibitors]

96 magnesium compounds/ or magnesium sulfate/

97 exp Anticonvulsants/

98 (Lidocaine or Alpha-2 Receptor Agonist* or Caffeine or Corticosteroid* or Beta block* or NMDA receptor antagonist* or Magnesium or Acetaminophen or NSAID* or Anti-convulsant* or anticonvulsant* or Antidepressant* or gabapentinoid* or cox-2 inhibitor*).tw,kw.

99 Dexmedetomidine/ or lidocaine/ or ketamine/ or Propanolamines/ or Clonidine/

100 (Pregabalin or Gabapentin or Carbamazepine or Carbazepin or Esmolol or Propanolamine* or Metoprolol or Labetolol or Clonidine or Dexmedetomidine or Catapressan or Caffeine or Ketamine or Dextromethorphan or Dexamethasone or Methylprednisolone or hydrocortison* or Prednisone or magnesium or Amitriptyline or

Duloxetine or Tryptophan or Bicifadine or Desipramine or fluoxetine or Venlafaxine or Citalopram).ti.

101 or/88-100

102 perioperative period/ or intraoperative period/ or exp Administration, Intravenous/ or Combined Modality Therapy/

103 (perioperat* or peri operat* or intra operat* or intraoperat*).tw,kw.

104 (an?esthes* adj2 induction).tw,kw.

105 or/102-104

106 101 and 105

107 87 or 106

108 84 and 107

109 108 use cctr

110 39 or 80 or 109

Search strategy for Web of science

1. (TS=(surg*)) OR TS=((curettage or debridement or electrosurger* or fasciotom* or Keratectom* or laparotom* or lymph node excision or mastectom* or metastasectom* or microsurger* or myotom* or neurosurgical procedure* or orthopedic procedure* or amputation or Osteotom* or pelvic exenteration or pneumonectom* or prosthesis implantation or reoperation or splenectom* or symphysiotom* or transplantation))

2. TS=(((opioid* or opiate*) NEAR/3 (sparing or minimi?ation or free)))

3. (TS=(multimodal NEAR/5 (an$esthes* or analges*)))

4. (#2) OR #3

5. (TS=(nonnarcotic analges*)) OR TS=(non narcotic analges*)

6. TS=((Pregabalin or Gabapentin or Carbamazepine or Carbazepin or Esmolol or Propanolamine* or Metoprolol or Labetolol or Clonidine or Dexmedetomidine or Catapressan or Caffeine or Ketamine or Dextromethorphan or Dexamethasone or Methylprednisolone or hydrocortison* or Prednisone or magnesium or Amitriptyline or Duloxetine or Tryptophan or Bicifadine or Desipramine or fluoxetine or Venlafaxine or Citalopram))

7. (TS=(Nonsteroid* anti-inflammatory)) OR TS=(Nonsteroid* antiinflammatory)

8. TS=((Lidocaine or Alpha-2 Receptor Agonist* or Caffeine or Corticosteroid* or Beta block* or NMDA receptor antagonist* or Magnesium or Acetaminophen or NSAID* or Anti-convulsant* or anticonvulsant* or Antidepressant* or gabapentinoid* or cox-2 inhibitor*))

9. (((#5) OR #6) OR #7) OR #8

10. TS=(intravenous) OR TS=(an$esthes* NEAR/2 induction)

11. ALL=(perioperat* or peri operat* or intra operat* or intraoperat*)

12. (#10) OR #11

13. (#9) AND #12

14. (#13) OR #4

15. (#1) AND #14

16. TS=((randomised OR randomized OR randomisation OR randomisation OR placebo* OR (random* AND (allocat* OR assign*)) OR (blind* AND (single OR double OR treble OR triple))))

17. TS=((animal or animals or pisces or fish or fishes or catfish or catfishes or sheatfish or silurus or arius or heteropneustes or clarias or gariepinus or fathead minnow or fathead minnows

or pimephales or promelas or cichlidae or trout or trouts or char or chars or salvelinus or salmo or oncorhynchus or guppy or guppies or millionfish or poecilia or goldfish or goldfishes or carassius or auratus or mullet or mullets or mugil or curema or shark or sharks or cod or cods or gadus or morhua or carp or carps or cyprinus or carpio or killifish or eel or eels or anguilla or zander or sander or lucioperca or stizostedion or turbot or turbots or psetta or flatfish or flatfishes or plaice or pleuronectes or platessa or tilapia or tilapias or oreochromis or sarotherodon or common sole or dover sole or solea or zebrafish or zebrafishes or danio or rerio or seabass or dicentrarchus or labrax or morone or lamprey or lampreys or petromyzon or pumpkinseed or pumpkinseeds or lepomis or gibbosus or herring or clupea or harengus or amphibia or amphibian or amphibians or anura or salientia or frog or frogs or rana or toad or toads or bufo or xenopus or laevis or bombina or epidalea or calamita or salamander or salamanders or newt or newts or triturus or reptilia or reptile or reptiles or bearded dragon or pogona or vitticeps or iguana or iguanas or lizard or lizards or anguis fragilis or turtle or turtles or snakes or snake or aves or bird or birds or quail or quails or coturnix or bobwhite or colinus or virginianus or poultry or poultries or fowl or fowls or chicken or chickens or gallus or zebra finch or taeniopygia or guttata or canary or canaries or serinus or canaria or parakeet or parakeets or grasskeet or parrot or parrots or psittacine or psittacines or shelduck or tadorna or goose or geese or branta or leucopsis or woodlark or lullula or flycatcher or ficedula or hypoleuca or dove or doves or geopelia or cuneata or duck or ducks or greylag or graylag or anser or harrier or circus pygargus or red knot or great knot or calidris or canutus or godwit or limosa or lapponica or meleagris or gallopavo or jackdaw or corvus or monedula or ruff or philomachus or pugnax or lapwing or peewit or plover or vanellus or swan or cygnus or columbianus or bewickii or gull or chroicocephalus or ridibundus or albifrons or great tit or parus or aythya or fuligula or streptopelia or risoria or spoonbill or platalea or leucorodia or blackbird or turdus or merula or blue tit or cyanistes or pigeon or pigeons or columba or pintail or anas or starling or sturnus or owl or athene noctua or pochard or ferina or cockatiel or nymphicus or hollandicus or skylark or alauda or tern or sterna or teal or crecca or oystercatcher or haematopus or ostralegus or shrew or shrews or sorex or araneus or crocidura or russula or european mole or talpa or chiroptera or bat or bats or eptesicus or serotinus or myotis or dasycneme or daubentonii or pipistrelle or pipistrellus or cat or cats or felis or catus or feline or dog or dogs or canis or canine or canines or otter or otters or lutra or badger or badgers or meles or fitchew or fitch or foumart or foulmart or ferrets or ferret or polecat or polecats or mustela or putorius or weasel or weasels or fox or foxes or vulpes or common seal or phoca or vitulina or grey seal or halichoerus or horse or horses or equus or equine or equidae or donkey or donkeys or mule or mules or pig or pigs or swine or swines or hog or hogs or boar or boars or porcine or piglet or piglets or sus or scrofa or llama or llamas or lama or glama or deer or deers or cervus or elaphus or cow or cows or bos taurus or bos indicus or bovine or bull or bulls or cattle or bison or bisons or sheep or sheeps or ovis aries or ovine or lamb or lambs or mouflon or mouflons or goat or goats or capra or caprine or chamois or rupicapra or leporidae or lagomorpha or lagomorph or rabbit or rabbits or oryctolagus or cuniculus or laprine or hares or lepus or rodentia or rodent or rodents or murinae or mouse or mice or mus or musculus or murine or woodmouse or apodemus or rat or rats or rattus or norvegicus or guinea pig or guinea pigs or cavia or porcellus or hamster or hamsters or mesocricetus or cricetulus or cricetus or gerbil or gerbils or jird or jirds or meriones or

unguiculatus or jerboa or jerboas or jaculus or chinchilla or chinchillas or beaver or beavers or castor fiber or castor canadensis or sciuridae or squirrel or squirrels or sciurus or chipmunk or chipmunks or marmot or marmots or marmota or suslik or susliks or spermophilus or cynomys or cottonrat or cottonrats or sigmodon or vole or voles or microtus or myodes or glareolus or primate or primates or prosimian or prosimians or lemur or lemurs or lemuridae or loris or bush baby or bush babies or bushbaby or bushbabies or galago or galagos or anthropoidea or anthropoids or simian or simians or monkey or monkeys or marmoset or marmosets or callithrix or cebuella or tamarin or tamarins or saguinus or leontopithecus or squirrel monkey or squirrel monkeys or saimiri or night monkey or night monkeys or owl monkey or owl monkeys or douroucoulis or aotus or spider monkey or spider monkeys or ateles or baboon or baboons or papio or rhesus monkey or macaque or macaca or mulatta or cynomolgus or fascicularis or green monkey or green monkeys or chlorocebus or vervet or vervets or pygerythrus or hominoidea or ape or apes or hylobatidae or gibbon or gibbons or siamang or siamangs or nomascus or symphalangus or hominidae or orangutan or orangutans or pongo or chimpanzee or chimpanzees or pan troglodytes or bonobo or bonobos or pan paniscus or gorilla or gorillas or troglodytes))

18. (#16) NOT #17

19. (#15) AND #18

Search strategy for CINAHL

S1	(MH "Surgical Patients")
S2	(MH "Surgery, Operative+")
S3	TI ((curettage or debridement or electrosurger* or fasciotom* or Keratectom* or laparotom* or lymph node excision or mastectom* or metastasectom* or microsurger* or myotom* or neurosurgical procedure* or orthopedic procedure* or amputation or Osteotom* or pelvic exenteration or pneumonectom* or prosthesis implantation or reoperation or splenectom* or symphysiotom* or transplantation)) OR AB ((curettage or debridement or electrosurger* or fasciotom* or Keratectom* or laparotom* or lymph node excision or mastectom* or metastasectom* or microsurger* or myotom* or neurosurgical procedure* or orthopedic procedure* or amputation or Osteotom* or pelvic exenteration or pneumonectom* or prosthesis implantation or reoperation or splenectom* or symphysiotom* or transplantation))
S4	TI surger* OR AB surger* OR TI surgical* OR AB surgical*
S5	S1 OR S2 OR S3 OR S4
S6	opioid* N3 sparing OR opioid* N3 minimi* OR opioid* N3 free
S7	opiate* N3 sparing OR opiate* N3 minimi* OR opiate* N3 free
S8	multimodal N5 an*esthes OR multimodal N5 analges*
S9	S6 OR S7 OR S8
S10	(MH "Analgesics") OR (MH "Analgesics, Nonnarcotic+") OR (MH "Anesthesia Adjuvants+")
S11	(MH "Adrenergic Beta-Agonists+")
S12	(MH "Caffeine")
S13	(MH "Antiinflammatory Agents+")

S14	(MH "Adrenal Cortex Hormones+")
S15	(MH "Adrenergic Beta-Antagonists+")
S16	(MH "Magnesium Compounds+")
S17	(MH "Anticonvulsants+")
S18	(MH "Lidocaine")
S19	(MH "Ketamine")
S20	"Dexmedetomidine"
S21	(MH "Propanolamines")
S22	(MH "Clonidine")
S23	TI ((Lidocaine or Alpha-2 Receptor Agonist* or Caffeine or Corticosteroid* or Beta block* or NMDA receptor antagonist* or N-Methyl-D-aspartate receptor antagonist* or Magnesium or Acetaminophen or NSAID* or Anti-convulsant* or anticonvulsant* or Antidepressant* or gabapentinoid* or cox-2 inhibitor* or Nonsteroidal anti-inflammator*)) OR AB ((Lidocaine or Alpha-2 Receptor Agonist* or Caffeine or Corticosteroid* or Beta block* or NMDA receptor antagonist* or N-Methyl-D-aspartate receptor antagonist* or Magnesium or Acetaminophen or NSAID* or Anti-convulsant* or anticonvulsant* or Antidepressant* or gabapentinoid* or cox-2 inhibitor* or Nonsteroidal anti-inflammator*))
S24	TI (Pregabalin or Gabapentin or Carbamazepine or Carbazepin or Esmolol or Propanolamine* or Metoprolol or Labetolol or Clonidine or Dexmedetomidine or Catapressan or Caffeine or Ketamine or Dextromethorphan or Dexamethasone or Methylprednisolone or hydrocortison* or Prednisone or magnesium or Amitriptyline or Duloxetine or Tryptophan or Bicifadine or Desipramine or fluoxetine or Venlafaxine or Citalopram)
S25	S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24
S26	(MH "Intraoperative Period")

S27	(MH "Administration, Intravenous")
S28	(MH "Combined Modality Therapy")
S29	TI ((perioperat* or peri operat* or intra operat* or intraoperat*)) OR AB ((perioperat* or peri operat* or intra operat* or intraoperat*))
S30	TI an*esthes* N2 induction OR AB an?esthes* N2 induction
S31	(MH "Anesthesia Induction")
S32	S26 OR S27 OR S28 OR S29 OR S30 OR S31
S33	S25 AND S32
S34	S9 OR S33
S35	S5 AND S34
S36	(MH "Randomized Controlled Trials+") OR (MH "Double-Blind Studies") OR (MH "Triple-Blind Studies") OR (MH "Clinical Trials")
S37	TI random* OR AB random* OR TI placebo OR AB placebo OR TI trial
S38	(control W5 group)
S39	(MH "Random Assignment")
S40	S36 OR S37 OR S38 OR S39
S41	S35 AND S40
S42	(MH "Animals+")
S43	(MH "Animal Studies")
S44	TI animal model*
S45	S42 OR S43 OR S44

S46 (MH "Human")

S47 S45 NOT S46

S48 S41 NOT S47

S49 S41 NOT S47