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Assessing the relative efficacy of components of opioid-free anaesthesia in adult surgical patients: protocol for a systematic review and component network meta-analysis

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ABSTRACT

Introduction The rise of opioid-free anaesthesia (OFA) aims to reduce postoperative pain while reducing opioid-related side effects during surgery. However, the various adjuvant agents used in OFA complicate the evaluation of their effectiveness and risks. Recent reviews question the clinical benefits of OFA, highlighting the need for thorough evaluation. This protocol describes a network meta-analysis to compare the effectiveness of OFA with opioid-based anaesthesia and will identify key components for optimal postoperative outcomes.

Methods and analysis We will perform a systematic search of literature published in English without time restriction in Embase, The Cochrane Library, MEDLINE (via PubMed) and CINAHL, along with Google Scholar for grey literature. The final search will be performed on 1 October 2024. We will include randomised controlled trials with adult patients undergoing surgery with general anaesthesia, excluding preclinical, observational, regional anaesthesia-only and prolonged anaesthesia outside the operating room studies. The primary outcome is postsurgical pain scores, with secondary outcomes including quality of recovery, opioid consumption, adverse effects and long-term events. We will assess bias using the Cochrane risk of bias 2 tool and conduct Bayesian network meta-analyses for pooled estimates. We will report effect estimates as ORs and standardised mean differences with 95% credible intervals and assess certainty using GRADE methodology.

Ethics and dissemination Ethics approval is not required for this systematic review. Results will be published in a peer-reviewed journal and presented at national and international anaesthesia and pain management conferences.

PROSPERO registration number CRD42024505853.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ We will use network meta-analysis (NMA) and component network meta-analysis (cNMA) to integrate both direct and indirect evidence, offering a more robust comparison of multiple opioid-free anaesthetic (OFA) strategies with a standardised and transparent approach.
⇒ We will include a wide range of adult surgical patients, enhancing the generalisability of the findings across different surgical contexts employing standardised tools for data extraction and risk of bias assessment, therefore improving the reliability and validity of the synthesised evidence.
⇒ We will use Bayesian models and multiple sensitivity analyses to ensure the robustness of the findings and to assess the influence of study quality and various model assumptions.
⇒ Given the wide variety of OFA strategies, maintaining the transitivity assumption across all outcomes may be challenging, potentially affecting the validity of the indirect comparisons.
⇒ Some OFA strategies are specific to types of surgery, such as abdominal surgery, which could limit the symmetry and applicability of the network to all surgical contexts.

INTRODUCTION

In the last few years, there has been a surge in opioid-free anaesthetic (OFA) regimes that could allegedly provide a beneficial effect leading to a reduction in opioid-related adverse effects such as respiratory depression, hypoxaemia, ileus, nausea and vomiting as well as better control of intraoperative nociception.[1] The concept of OFA relies on the additive or synergistic pharmacological effects of multiple non-opioid analgesics and regional analgesia. Therefore, discerning the contribution of each drug to the overall effect of OFA is difficult.[2] On the other hand, adjuvant agents and their combinations are not devoid of their own perilous side effects that should be considered.[3 4] Recent non-systematic and systematic reviews even bring

into question the clinical benefit of such strategies, concluding that there is scarce evidence to support intraoperative opioid avoidance.[5 6] Moreover, regardless of whether one favours OFA[7] or not,[8] there is a consensus that opioids should be given with caution and, therefore, multimodal analgesia techniques should be encouraged.[9]

In a context where different therapies have been studied but not always head-to-head compared, a network meta-analysis (NMA) can help to gain further insight.[10] This is especially valuable when the interventions of interest are only compared with placebo or standard care.[11] In addition, NMAs can provide a ranking of all competing interventions[12] and reduce the uncertainty in input parameters in cost-effectiveness models.[13] NMA is an extension of the classic pairwise meta-analysis to a scenario where three or more interventions have been tested.[14] It encompasses both direct evidence, obtained from trials that directly compare two or more treatments, and indirect evidence, which emerges when both treatments are separately compared with a common third treatment. NMA uses a single statistical model to combine both the direct and the indirect evidence within a network to estimate intervention effects for every treatment combination, regardless of the comparison type.

Furthermore, OFA regimes often combine various drugs. For instance, lidocaine and ketamine can both be co-administered as part of an OFA protocol. In this context, a component network meta-analysis (cNMA) can help estimate each component's effect, for instance, ketamine and lidocaine, and the effect of a specific combination of interests.[15–17]

We designed a protocol for a cNMA to assess whether OFA is effective compared with usual opioid-based practice. Moreover, we aim to determine which OFA components are associated with the greatest benefit on postoperative outcomes, including postoperative pain and side effects, patient-reported recovery, chronic pain and chronic opioid medication use, and cancer recurrence.

METHODS AND ANALYSIS

This protocol is reported following the Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines.[18 19] The analysis is registered at PROSPERO (CRD42024505853).

Study design

Patients

We will include studies of adults, that is, >17 years old, without a history of chronic pain or chronic opioid medication prescription, who underwent surgery under general anaesthesia.

Intervention

We will consider as OFA strategies the intraoperative administration of one or a combination of the agents reported in table 1. The intervention component will be further defined by its route of administration. Table 2

Table 1 PubMed search strategy

1	Opioid(tiab)
2	Analgesic, Opioid/
3	Alfentanil/
4	Buprenorphine/
5	Butorphanol/
6	Codeine/
7	Dextropropoxyphene/
8	Fentanyl/
9	Hydrocodone/
10	Hydromorphone/
11	Meperidine/
12	Methadone/
13	Morphine/
14	Morphine Derivatives/
15	Nalbuphine/
16	Oxycodone/
17	Pentazocine/
18	Pirinitramide/
19	Remifentanil/
20	Sufentanil/
21	OR/1–20 (Opioid related terms)
22	free(tiab))
23	'opioid free'(tiab)
24	'opioid less'(tiab)
25	'Opioid spar*'
26	OR/22–25 (opioid regime related term)
27	21 AND 26
28	Adaptive Clinical Trial/
29	Adaptive Clinical Trials as Topic/
30	Controlled Clinical Trial/
31	Pragmatic Clinical Trial/
32	Pragmatic Clinical Trial as Topic/
33	Trials, Randomised Clinical/
34	Randomised Controlled Trials as Topic/
35	quasirandom*.mp.
36	randomi*.mp.
37	semiquantitative.mp.
38	OR/28–37(Randomised Controlled Trials & related terms)
39	(animal or animals or ape or apes or baboon or baboons or bat or bats or bird or birds or boar or boars or bonobo or bonobos or bovine or camel or camels or canine or canines or cat or cats or cattle or chicken or chickens or chimpanzee or chimpanzees or dog or dogs or dromedary or dromedaries or duck or ducks or equine or equines or feline or felines or ferret or ferrets or frog or frogs or fowl or fowls or goat or goats or hare or hares or hen or hens or horse or horses or lamb or lambs or livestock or macaque or macaques or mandrill or mandrills or mice or mink or minks or monkey or monkeys or mouse or murine or pig or pigs or piglet or piglets or poultry or porcine or orangutan or orangutans or rabbit or rabbits or rat or rats or rodent or rodents or sheep or swine or tamarin or tamarins or tiger or tigers or veterinary or veterinarian or veterinarians or waterfowl or waterfowls or weasel or weasels or veterinar*).ti. or (veterinar* or fish or shellfish).jw.

Continued

Table 1 Continued

40	(adolescence or adolescent or adolescents or babies or baby or boy or boys or child or childhood or children or childrens or children's or fetus or fetal or fetus or foetal or girl or girls or infancy or infant or infants or neonatal or neonatally or neonate or neonates or newborn or newborns or paediatric or paediatrician or paediatricians or paediatrics or paediatric or paediatrician or paediatricians or paediatrics or teen or teenage or teenagers or teens or toddler or toddlers or youth or youths).ti,jw.
41	38 NOT 39 NOT 40

summarises the pharmacological components and their combinations. If a single dose of opioid is given for intubation with no additional opioid administration afterwards, the strategy will still be considered OFA.

Comparison

The comparator will be the intraoperative intravenous administration of opioids.

Outcomes

The primary outcome is postsurgical pain scores measured on a Numerical Rating or Visual Analogue Scale (NRS, VAS). If the pain scores are presented on multiple time points after surgery, the pain scores on the time point closest to 24 hours after surgery will be used for meta-analyses. Secondary outcomes will include the quality of recovery measured via the QoR-40 or Qor-15 whichever was collected (timepoint closest to 24 hours after surgery), postoperative cumulative opiate consumption converted to morphine milligram equivalents, and adverse effects such as bradycardia, hypotension and postoperative nausea and vomiting and long-term events such as chronic pain after 3 months from surgery, chronic pain opioid medication and disease-free survival in oncologic patients.

Inclusion and exclusion criteria

We will include randomised controlled trials carried out in adult patients undergoing surgery with general anaesthesia. We will exclude preclinical, human observational studies and those in which the anaesthetic management was carried out under regional anaesthesia exclusively or those studies in which the patient was not extubated in the operating room.

Literature search

We will search the following electronic databases: Embase (via Ovid), The Cochrane Library (via CENTRAL), MEDLINE (via PubMed) and the Cumulative Index to Nursing and Allied Health Literature (CINAHL). Details of the search are reported in tables 1–3 and eTable 1 in the online supplemental file 1. Additionally, we will search the grey literature through Google Scholar. We will examine the reference compilations of incorporated studies or pertinent reviews discovered during the search to guarantee a comprehensive coverage of the literature.

Table 2 Embase search strategy

1	narcotic analgesic agent/exp
2	alfentanil/
3	buprenorphine/
4	butorphanol/
5	codeine/
6	dextropropoxyphene/
7	Fentanyl/
8	Hydrocodone/
9	Hydromorphone/
10	Meperidine/
11	Methadone/
12	Morphine/
13	Morphine Derivatives/
14	Nalbuphine/
15	Oxycodone/
16	Pentazocine/
17	Piritramide/
18	Remifentanil/
19	Sufentanil/
20	OR/1–20 (Opioid related terms)
21	free:ti,ab
22	'opiat* free':ti,ab OR 'opiat* less':ti,ab OR 'opiat* spar*':ti,ab OR 'opioid* free':ti,ab OR 'opioid* less':ti,ab OR 'opioid* spar*':ti,ab,kw
23	21 OR 22 (opioid regime related term)
24	20 AND 23
25	'randomised controlled trial'/exp
26	'controlled clinical trial'/de
27	random*:ti,ab,tt
28	'randomization'/de
29	'intermethod comparison'/de
30	placebo:ti,ab,tt
31	(compare:ti,tt OR compared:ti,tt OR comparison:ti,tt)
32	((evaluated:ab OR evaluate:ab OR evaluating:ab OR assessed:ab OR assess:ab) AND (compare:ab OR compared:ab OR comparing:ab OR comparison:ab))
33	(open NEXT/1 label):ti,ab,tt
34	((double OR single OR doubly OR singly) NEXT/1 (blind OR blinded OR blindly)):ti,ab,tt
35	'double blind procedure'/de
36	(parallel NEXT/1 group*):ti,ab,tt
37	(crossover:ti,ab,tt OR 'cross over':ti,ab,tt)
38	((assign* OR match OR matched OR allocation) NEAR/6 (alternate OR group OR groups OR intervention OR interventions OR patient OR patients OR subject OR subjects OR participant OR participants)):ti,ab,tt
39	(assigned:ti,ab,tt OR allocated:ti,ab,tt)

Continued

Table 2 Continued

40	(controlled NEAR/8 (study OR design OR trial)):ti,ab,tt
41	(volunteer:ti,ab,tt OR volunteers:ti,ab,tt)
42	'human experiment'/de
43	trial:ti,tt
44	OR/25–43
45	(((random* NEXT/1 sampl* NEAR/8 ('cross section*' OR questionnaire* OR survey OR surveys OR database or databases)):ti,ab,tt) NOT ('comparative study'/de OR 'controlled study'/de OR 'randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt OR 'randomly assigned':ti,ab,tt))
46	('cross-sectional study'/de NOT ('randomized controlled trial'/exp OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt OR 'control group':ti,ab,tt OR 'control groups':ti,ab,tt))
47	('case control*':ti,ab,tt AND random*:ti,ab,tt NOT ('randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt))
48	('systematic review':ti,tt NOT (trial:ti,tt OR study:ti,tt))
49	(nonrandom*:ti,ab,tt NOT random*:ti,ab,tt)
50	'random field*':ti,ab,tt
51	('random cluster' NEAR/4 sampl*):ti,ab,tt
52	(review:ab AND review:it) NOT trial:ti,tt
53	('we searched':ab AND (review:ti,tt OR review:it))
54	'update review':ab
55	(databases NEAR/5 searched):ab
56	((rat:ti,tt OR rats:ti,tt OR mouse:ti,tt OR mice:ti,tt OR swine:ti,tt OR porcine:ti,tt OR murine:ti,tt OR sheep:ti,tt OR lambs:ti,tt OR pigs:ti,tt OR piglets:ti,tt OR rabbit:ti,tt OR rabbits:ti,tt OR cat:ti,tt OR cats:ti,tt OR dog:ti,tt OR dogs:ti,tt OR cattle:ti,tt OR bovine:ti,tt OR monkey:ti,tt OR monkeys:ti,tt OR trout:ti,tt OR marmoset*:ti,tt) AND 'animal experiment'/de)
57	('animal experiment'/de NOT ('human experiment'/de OR 'human'/de))
58	OR/45–57
59	44 NOT 58
60	teen OR youth OR adolescent OR juvenile OR child
61	59 NOT 60
62	24 AND 61

Additionally, we will explore the personal archives of the authors to confirm the inclusion of all pertinent materials. We will include articles reported in English with no time restriction. The last search will be performed on 1 October 2024.

Study review and selection

Two reviewers (AB and GM) will independently screen the titles and abstracts retrieved from the search strategy and the additional sources to identify those meeting the mentioned eligibility criteria. Study review and selection

Table 3 Cochrane search strategy

1	((narcotic* near/1 free) or (narcotic* near/1 less) or (narcotic* near/1 spar*) or (non near/1 narcotic*) or (non near/1 opioid*)):ti,ab,kw
2	alfentanil/
3	buprenorphine/
4	butorphanol/
5	codeine/
6	dextropropoxyphene/
7	Fentanyl/
8	Hydrocodone/
9	Hydromorphone/
10	Meperidine/
11	Methadone/
12	Morphine/
13	Morphine Derivatives/
14	Nalbuphine/
15	Oxycodone/
16	Pentazocine/
17	Piritramide/
18	Remifentanil/
19	Sufentanil/
20	OR/1–20 (Opioid related terms)
21	((narcotic* near/1 free) or (narcotic* near/1 less) or (narcotic* near/1 spar*) or (non near/1 narcotic*) or (non near/1 opioid*)):ti,ab,kw
22	((opiat* near/1 free) or (opiat* near/1 less) or (opiat* near/1 spar*) or (opioid* near/1 free) or (opioid* near/1 less) or (opioid* near/1 spar*)):ti,ab,kw
23	21 OR 22 (opioid regime related term)
24	20 AND 23
25	(Adaptive Clinical Trial):ti,ab,kw (Word variations have been searched)
26	('adaptive clinical trial (topic)'):ti,ab,kw (Word variations have been searched)
27	Adaptive Clinical Trials as Topic
28	ct.fs.
29	controlled clinical trial or 'controlled clinical trial (topic)'
30	double blind procedure
31	Double-Blind Method
32	multicenter study or 'multicenter study (topic)'
33	placebo or placebo effect
34	pragmatic trial
35	exp randomized controlled trial or 'randomized controlled trial (topic)'
36	('quasirandomised controlled trial'):ti,ab,kw (Word variations have been searched)
37	OR/25–36
38	24 AND 37

Continued

Table 3 Continued

39	(newborn* or new-born* or neonat* or neo-nat* or infan* or baby* or babies* or toddler* or kid or kids or boy* or girl* or pubescen* or preadolesc* or prepubesc* or preteen or tween):ti,so
40	((exp animals or exp animal experimentation or nonhuman) not ((exp animals or exp animal experimentation or nonhuman) and exp human))
41	38 NOT (38 OR 39)

will be carried out in Rayann, which is a free software tool for literature screening that provides similar features to those offered by pay software alternatives.[20] Subsequently, we will obtain full texts of the articles meeting these prespecified criteria and review them again. Any disagreement between the reviewers will be discussed and referred to a third investigator (MWH).

Data extraction

We will extract the generic and the trade name of the experimental medication, the type of control used and administered intraoperative dose; patient characteristics (average age, gender, comorbidities, body mass index, American Society of Anesthesiology (ASA), ASA physical status risk score), surgery characteristics (type and duration) perioperative anaesthetic management (fluids administered, neuromuscular block agents, monitoring and reversal agents, postoperative analgesic medication). We will collect each trial sample size, type, source of financial support and publication status from trial reports.

For binary outcomes, we will collect cell counts from contingency tables, event rates and/or effect estimates (ie, ORs or risk ratios) along with a measure of uncertainty (eg, 95% CIs, p values). For continuous outcomes, we will collect means and SD and/or effect estimates such as mean differences with their 95% CIs and p values. If outcome measures are not reported as means and SD, we will estimate them from reported measures such as medians and IQR or overall ranges.[21] Effect estimates derived from cluster randomised trials will be pooled using the reported effect adjusted for clustering, or if not available, a corrected estimate accounting for an estimated design.[22] Any missing data or effect sizes will be sought directly from the study authors. Whenever possible, we will use results from an intention-to-treat analysis.

Risk of bias

We will assess the within-study bias with the Cochrane risk of bias 2 tool.[22] We will assess for the presence of publication bias by examining the asymmetry of the comparison-adjusted funnel plot and carrying out Begg's test.

Data synthesis

We will summarise the selected studies based on trial and patients' characteristics, outcome effect estimates and risk of bias. Whenever we will not be able to retrieve sufficient data to perform a quantitative analysis, we will report and summarise the results in a narrative way. If studies are too diverse to combine, we will summarise the results through graphical displays following current recommendations.[23–25] We will analyse the data using a methodology consistent with previous suggestions. This involves employing a series of interconnected and complementary techniques to assess the combined impacts of OFA and its individual elements. The concepts of the components to be compared and their combinations are shown in tables 4 and 5.

First, we will conduct a pairwise network meta-analysis, considered a full interaction cNMA. The head-to-head comparison will be reported graphically in a network with nodes representing treatment strategies, connected by edges depicting direct head-to-head comparisons. Node size will be proportional to participant count, whereas edges' thickness will reflect the number of randomised clinical trials in each comparison. The network geometry will be evaluated with quantitative metrics.[26] We will then fit Bayesian models as previously suggested. We will use minimally informative priors for the treatment effect and heterogeneity estimates as previously derived in simulation studies.[27 28] We will run four chains of 30 000 samples with 15 000 run-in samples for all analyses. We will evaluate the convergence of the model by examining trace plots and evaluating the Potential Scale Reduction Factor with Gelman-Rubin plot. We will assess the transitivity assumption both visually and statistically. The visual assessment will involve examining tabular and graphical representations to analyse and compare the distribution of the following influencing factors: surgical procedure type and duration, patient age, initial functional status, comorbidities or ASA score and presence of cancer. The statistical assessment of transitivity will involve a global assessment of consistency using the design-by-treatment interaction model and a local assessment through the node-splitting approach.[29] We will also report ORs, calculated standardised mean differences (SMDs) and Hedge's g, with relative 95% CIs for dichotomous and continuous outcomes. We will also report treatment ranking using the Surface Under the Cumulative RAnking curve (SUCRA).[30]

We plan to carry out the following sensitivity analysis: (1) we will evaluate the potential influence of the quality of individual studies on the observed effect estimates by conducting a sensitivity analysis that excludes studies with a high risk of bias; (2) we will carry out the analysis by using frequentist methods; (3) we will revise the network effect estimates for this specific group in comparison to the other categories, incorporating enthusiastic, sceptical and pessimistic priors; (4) we will evaluate the model with a different geometry defining nodes with different administered doses for the same drugs; (5) to examine potential effect moderators we will fit the model with the following covariable: mean age of participants, the duration and the type of surgery, use of a single dose of opioids at intubation time.

Table 4 List of included components

Agent	Route of administration	Abbreviation
Opioid	Intravenous	p-iv
Halogenated	Inhalated	ha
Propofol	Intravenous	prop-iv
Lidocaine	Intravenous	l-iv
Ketamine	Intravenous	k-iv
Dexmedetomidine	Intravenous	dxm-iv
Clonidine	Intravenous	cl-iv
Adenosine	Intravenous	ad-iv
Magnesium	Intravenous	mg-iv
Esketamine	Intravenous	sk-iv
Beta-Blockers	Intravenous	bb-iv
Gabapentinoids	Ral	gaba
NSAIDs	Intravenous	nsaid-iv
Calcium channel blockers	Intravenous	cabl-iv
Local anaesthetic block	Regional	la-block
Local anaesthetic	Epidural	la-epi
Local anaesthetic	Subarachnoid	la-intra
Local anaesthetic	Subcutaneous	la-w
Opioid	Epidural	p-epi
Opioid	Intradural	p-intra

Next, we will carry out a cNMA in a Bayesian framework by using a previously described modelisation strategy.[31–33] We will first fit the models by considering the influence of individual components as additive. In other words, the total effect of a combination is assumed to be the sum of the relative individual component effects. The additivity assumption will be tested by previously published methods for Bayesian and frequentist frameworks.[17 33] Furthermore, we will carry out an interaction effect model by considering the interaction between propofol and intravenous lidocaine, propofol and regional anaesthetic block, and propofol and epidural analgesia as clinically meaningful.

Ultimately, any departures from our PROSPERO registration and the existing protocol will be documented in a methodical manner, providing comprehensive explanations and rationale.

Table 5 Combination of included components

op-iv+propi-iv	Opioid-based TIVA
op-iv+ha	Balanced general anaesthesia
(±l-iv±k-iv±dxm-iv±cl-iv±ad-iv±sk-iv±mg-iv±bb-iv±gaba±cabl-iv) + prop-iv	Opioid-free TIVA
(±l-iv±k-iv±dxm-iv±cl-iv±ad-iv±sk-iv±mg-iv±bb-iv±gaba±cabl-iv) + ha	Opioid-free balanced anaesthesia
la-block (±l-iv±k-iv±dxm-iv±cl-iv±ad-iv±sk-iv±mg-iv±bb-iv±gaba±cabl-iv) + prop-iv	Combined TIVA anaesthesia
la-block (±l-iv±k-iv±dxm-iv±cl-iv±ad-iv±sk-iv±mg-iv±bb-iv±gaba±cabl-iv) + ha	Combined balanced anaesthesia
la-epi (±l-iv±k-iv±dxm-iv±cl-iv±ad-iv±sk-iv±mg-iv±bb-iv±gaba±cabl-iv) + prop-iv	Epidural+TIVA anaesthesia
la-epi (±l-iv±k-iv±dxm-iv±cl-iv±ad-iv±sk-iv±mg-iv±bb-iv±gaba±cabl-iv) + ha	Epidural+balanced anaesthesia
la-intra (±l-iv±k-iv±dxm-iv±cl-iv±ad-iv±sk-iv±mg-iv±bb-iv±gaba±cabl-iv) + prop-iv	Intradural+TIVA anaesthesia
la-intra (±l-iv±k-iv±dxm-iv±cl-iv±ad-iv±sk-iv±mg-iv±bb-iv±gaba±cabl-iv) + ha	Intradural+balanced anaesthesia
la-w (±l-iv±k-iv±dxm-iv±cl-iv±ad-iv±sk-iv±mg-iv±bb-iv±gaba±cabl-iv) + prop-iv	Wound infiltration+TIVA anaesthesia
la-w (±l-iv±k-iv±dxm-iv±cl-iv±ad-iv±sk-iv±mg-iv±bb-iv±gaba±cabl-iv) + ha	Wound infiltration+balanced anaesthesia
op-epi | op-intra (±k-iv±dxm-iv±cl-iv±ad-iv±sk iv) + prop-iv	Neuraxial opioids+TIVA
op-epi | op-intra (±k-iv±dxm-iv±cl-iv±ad-iv±sk iv) + ha	Neuraxial opioids+balanced anaesthesia

'+' means AND; '±' means with or without; | means OR.

TIVA, total intravenous anaesthesia.

Confidence in cumulative evidence

We will use the GRADE working group classification to assess the certainty of evidence for each outcome, including modifications specific to certainty assessment in network meta-analysis.[34] The evidence will be categorised as high, moderate, low and very-low certainty and reported.

Planned timeline

We already completed the research question formulation and protocol development phase and tentatively estimate for the following project phases that the literature search and study selection phase will take 3 months to complete, the data extraction and risk of bias assessment will take 3 months, the data synthesis and analysis will take an additional 3 months. The writing of the manuscript will overlap whenever possible with the previous phases, and we estimate that will take an additional 2 months before the final approval of all coauthors to proceed to submission. We are currently in the literature search phase and plan to be able to submit during the first half of 2025.

Patient and public involvement

None

ETHICS AND DISSEMINATION

The proposed NMA will use data from published studies. As such, ethical approval is not required for this research. However, we will ensure that all selected studies comply with ethical standards as per the guidelines of their respective journals and institutions. All included studies will have followed ethical guidelines, including obtaining informed consent from participants. Particular attention will be given to the accurate representation of the findings, including potential biases and limitations associated with the included studies. Findings will be published in a peer-reviewed journal and presented at relevant conferences. We will also share results with healthcare professionals, policymakers and through professional networks and social media. Our goal is to contribute to evidence-based practice and support updates to clinical guidelines.

DISCUSSION

Despite the reasoning behind implementing intraoperative OFA strategies, convincing evidence of benefit for both short-term and long-term outcomes is still lacking. This meta-analysis will summarise both direct and indirect evidence of the effect of OFA on improving perioperative outcomes and will try to distinguish which non-opioid alternative, if any, is preferable. The results of this study will also provide guidance for future clinical trials.

This analysis may present several limitations. First, given the substantial number of OFA strategies, we will probably deal with a large network, and thus, the transitivity assumptions may not hold for every analysed outcome. Second, due to the nature of specific techniques, such as epidural or intradural anaesthesia, some OFA strategies may be confined to some particular surgical settings, such as abdominal surgery, thus affecting the network symmetry. Third, exploring potential effect modifiers is limited since we will not have access to individual patient data.

Overall, this analysis may be helpful to identify whether OFA has any benefits and which components of OFA strategies can be particularly beneficial. This will provide useful information for clinicians to guide their daily decision-making process and for trialists to design future research focusing on the most promising intervention.

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Contributors AB, GM, OD-C and MWH conceived the study. ANE, TW, ASN, DS, DJB and JC contributed with the clinical background and expertise. ANE and TW contributed with the analytical plan and bias assessment approach. AB, GM and OD-C drafted the protocol. MWH supervised the study. All authors read, revised and approved the final version. The guarantor is GM.

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REFERENCES

1 Mulier J, Dekock M. Opioid free general anesthesia, a new paradigm? *Best Pract Res Clin Anaesthesiol* 2017;31:441–3.
2 Salomé A, Harkouk H, Fletcher D. Opioid-Free Anesthesia Benefit-Risk Balance: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *J Clin Med* 2021;10:2069.
3 Verret M, Lauzier F, Zarychanski R, *et al*. Perioperative Use of Gabapentinoids for the Management of Postoperative Acute Pain: A Systematic Review and Meta-analysis. *Anesthesiology* 2020;133:265–79.
4 Beloeil H, Garot M, Lebuffe G, *et al*. Balanced Opioid-free Anesthesia with Dexmedetomidine *versus* Balanced Anesthesia with Remifentanil for Major or Intermediate Noncardiac Surgery . *Anesthesiology* 2021;134:541–51.
5 Shanthanna H, Ladha KS, Kehlet H, *et al*. Perioperative Opioid Administration. *Anesthesiology* 2021;134:645–59.
6 Feenstra ML, Jansen S, Eshuis WJ, *et al*. Opioid-free anesthesia: A systematic review and meta-analysis. *J Clin Anesth* 2023;90:111215.
7 Lavand'homme P. Opioid-free anaesthesia: Pro: damned if you don't use opioids during surgery. *Eur J Anaesth* 2019;36:247–9.
8 Lirk P, Rathmell JP. Opioid-free anaesthesia: Con: it is too early to adopt opioid-free anaesthesia today. *Eur J Anaesth* 2019;36:250–4.
9 Veyckemans F. Opioid-free anaesthesia: Still a debate? *Eur J Anaesth* 2019;36:245–6.
10 Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med* 2004;23:3105–24.
11 Falissard B, Zylberman M, Cucherat M, *et al*. Real medical benefit assessed by indirect comparison. *Therapie* 2009;64:225–32.
12 Salanti G, Ades AE, Ioannidis JPA. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol* 2011;64:163–71.
13 Thorlund K, Zafari Z, Druyts E, *et al*. The impact of incorporating Bayesian network meta-analysis in cost-effectiveness analysis - a case study of pharmacotherapies for moderate to severe COPD. *Cost Eff Resour Alloc* 2014;12:8.
14 Caldwell DM, Ades AE, Higgins JPT. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. *BMJ* 2005;331:897–900.
15 Petropoulou M, Efthimiou O, Rücker G, *et al*. A review of methods for addressing components of interventions in meta-analysis. *PLoS One* 2021;16:e0246631.
16 Rücker G, Schmitz S, Schwarzer G. Component network meta-analysis compared to a matching method in a disconnected network: A case study. *Biom J* 2021;63:447–61.
17 Rücker G, Petropoulou M, Schwarzer G. Network meta-analysis of multicomponent interventions. *Biom J* 2020;62:808–21.
18 Shamseer L, Moher D, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;350:g7647.
19 Hutton B, Salanti G, Caldwell DM, *et al*. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015;162:777–84.
20 Van der Mierden S, Tsaioun K, Bleich A, *et al*. Software tools for literature screening in systematic reviews in biomedical research. *Ann Intern Med* 2015;162:777–84.
21 Wan X, Wang W, Liu J, *et al*. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* 2014;14:135.
22 Higgins JPT, Thomas J, Chandler J, *et al*. *Cochrane handbook for systematic reviews of interventions 6.4*. Cochrane, 2023.
23 Higgins JPT, López-López JA, Becker BJ, *et al*. Synthesising quantitative evidence in systematic reviews of complex health interventions. *BMJ Glob Health* 2019;4:e000858.
24 Ogilvie D, Fayter D, Petticrew M, *et al*. The harvest plot: a method for synthesising evidence about the differential effects of interventions. *BMC Med Res Methodol* 2008;8:8.
25 Harrison S, Jones HE, Martin RM, *et al*. The albatross plot: A novel graphical tool for presenting results of diversely reported studies in a systematic review. *Res Synth Methods* 2017;8:281–9.
26 Salanti G, Kavvoura FK, Ioannidis JPA. Exploring the geometry of treatment networks. *Ann Intern Med* 2008;148:544–53.
27 Turner RM, Jackson D, Wei Y, *et al*. Predictive distributions for between-study heterogeneity and simple methods for their application in Bayesian meta-analysis. *Stat Med* 2015;34:984–98.
28 Turner RM, Davey J, Clarke MJ, *et al*. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. *Int J Epidemiol* 2012;41:818–27.
29 Efthimiou O, Debray TPA, van Valkenhoef G, *et al*. GetReal in network meta-analysis: a review of the methodology. *Res Synth Methods* 2016;7:236–63.
30 Mills EJ, Kanters S, Thorlund K, *et al*. The effects of excluding treatments from network meta-analyses: survey. *BMJ* 2013;347:f5195.
31 Welton NJ, Caldwell DM, Adamopoulos E, *et al*. Mixed treatment comparison meta-analysis of complex interventions: psychological interventions in coronary heart disease. *Am J Epidemiol* 2009;169:1158–65.
32 Freeman SC, Scott NW, Powell R, *et al*. Component network meta-analysis identifies the most effective components of psychological preparation for adults undergoing surgery under general anesthesia. *J Clin Epidemiol* 2018;98:105–16.
33 Pompoli A, Furukawa TA, Efthimiou O. Dismantling cognitive-behaviour therapy for panic disorder: a systematic review and component network meta-analysis. *Psychol Med* 2018;48:1945–53.
34 Brignardello-Petersen R, Florez ID, Izcovich A, *et al*. GRADE approach to drawing conclusions from a network meta-analysis using a minimally contextualised framework. *BMJ* 2020;371:m3900.