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Nociception Monitoring Techniques for Intraoperative Opioid Analgesia in Adults Undergoing General Anesthesia: A Protocol for a Systematic Review and Network Meta-Analysis of Randomized Clinical Trials

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - The review has not yet started.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 23 July 2024 and was last updated on 24 November 2024.

INTRODUCTION

Review question / Objective The objective of this meta-analysis is to compare and analyze the effectiveness of different intraoperative nociception monitoring techniques in optimizing perioperative pain management in adult patients. The primary outcome is intraoperative opioid dosage in adult patients. Secondary outcomes may include postoperative analgesic consumption, postoperative pain scores, intraoperative movement, intraoperative hemodynamic events, extubation time, incidence of nausea and vomiting, and length of hospital stay.

Rationale The primary goals of anesthesia are to provide adequate hypnosis and analgesia, promote rapid recovery, minimize postoperative pain, and reduce side effects. Inadequate analgesia can lead to stress reactions and increased postoperative complications, while excessive opioid use can cause hyperalgesia and respiratory depression. Therefore, it is critical to tailor intraoperative opioid administration based on individual patient factors and surgical stimuli, moving beyond the traditional reliance on empirical judgments based on heart rate and blood pressure.

Recent advances in pain monitoring technologies such as the Analgesia Nociception Index (ANI), Pupillometry (PPI), and Index of Consciousness (IoC) have improved the accuracy of intraoperative management. These tools provide a more accurate assessment of patients' responses to noxious stimuli under anesthesia, potentially allowing for better opioid titration, reduced opioid use, stabilized hemodynamics, faster recovery, and less postoperative pain. Despite their promise, the efficacy of these technologies in consistently reducing opioid consumption remains controversial, with uncertainties regarding their impact on postoperative pain management.

This study will conduct a meta-analysis to evaluate the effectiveness of various analgesia monitoring

technologies in the perioperative setting. It will assess their impact on intraoperative opioid dosage, postoperative analgesic use, pain scores, patient movement, hemodynamic stability, extubation time, nausea, vomiting, and length of hospital stay. This analysis aims to fill knowledge gaps and improve clinical practice in the management of perioperative pain.

Condition being studied The condition being studied is the intraoperative use of opioid dosages under different nociception monitoring technologies during general anesthesia. The objective of this research is to determine the effectiveness of various pain monitoring methods in optimizing intraoperative opioid administration. Key aspects of the study include evaluating the impact of these monitoring technologies on reducing intraoperative opioid dosages, postoperative opioid consumption, extubation time, length of stay (PACU or ICU), postoperative nausea and vomiting, and intraoperative hemodynamic events. By comparing different nociception monitoring techniques, the study aims to identify the most effective pain management strategies that enhance patient safety and improve postoperative outcomes.

METHODS

Search strategy The search strategy employed a combination of key terms and Boolean operators to ensure comprehensive coverage of the topic. Key terms included, but were not limited to, "analgesia nociception index," "surgical pleth index," "surgical stress index," pupillometry, "nociceptive flexion reflex threshold," "nociception level index," "consciousness index," "monitoring, physiologic," "analgesics, opioid," "pain, postoperative," nociception monitoring, "randomized controlled trials as topic," and random allocation. This list is illustrative rather than exhaustive, with additional terms potentially included as the search evolved to capture all relevant studies. Furthermore, handsearching was employed to identify additional key studies to supplement the results. The initial search cut-off date was July 31, 2024, with an update planned for December 2024 to ensure the inclusion of the most recent literature.

Participant or population Adult patients undergoing surgery with general anesthesia.

Intervention Intraoperative analgesia guided by nociception monitoring techniques. The study will employ several methods of nociception monitoring, such as the Analgesia Nociception Index (ANI), Index of Consciousness (IoC2), Nociception Level Index (NOL), Pupillometry (PPI), Surgical Pleth Index (SPI), and Surgical Stress Index (SSI). Each technique will be used to tailor analgesic administration during surgery to optimize patient outcomes by continuously assessing and responding to the nociceptive status.

Comparator Intraoperative analgesia guided by standard clinical practice, which relies on traditional clinical indicators such as heart rate and blood pressure. This group will serve as the control to evaluate the effectiveness of advanced nociception monitoring techniques in optimizing analgesic administration and improving patient outcomes during surgery.

Study designs to be included Randomized controlled trials.

Eligibility criteria 1. Study Design: Only randomized controlled trials (RCTs) were included to ensure a high level of evidence.
2. Participants: Studies involving adult patients undergoing surgery were eligible.
3. Interventions: The study compares the effectiveness of nociception monitoring techniques with standard clinical practice or evaluates the differences between different nociception monitoring technologies.
4. Outcomes: Studies must evaluate either or both: (1) Opioid consumption during and/or after surgery. (2) Postoperative pain using any quantitative scoring system.
5. Secondary sources or articles with insufficient data, such as abstracts, review articles, case reports, and conference proceedings, will be excluded to ensure the analysis is based on primary, empirical data.

Information sources PubMed, EMBASE, Web of Science, Cochrane Library.

Main outcome(s) Intraoperative opioid consumption: This will be measured to assess the effectiveness of nociception monitoring techniques in optimizing opioid use during surgery.

Additional outcome(s) 1. Postoperative Opioid Analgesic Consumption: This measures the amount of pain medication required by patients after surgery.
2. Postoperative Pain Scores: Evaluated using standard pain assessment tools to quantify patient pain levels after surgery.
3. Intraoperative Movement: Monitored to assess patient response to surgical stimuli and adequacy of analgesia.

4. Intraoperative hemodynamic events: Includes episodes of hypertension/tachycardia or hypotension/bradycardia, which may indicate patient stress or insufficient analgesia.
5. Extubation time: This is an indicator of the speed of recovery from anesthesia.
6. Postoperative nausea and vomiting: Monitored as a common postoperative complication.
7. Length of stay (PACU or ICU): Duration of patient stay in the Post-Anesthesia Care Unit (PACU) or Intensive Care Unit (ICU), measured to evaluate the impact of anesthesia management on recovery and healthcare resource utilization.

Data management Data for this meta-analysis will be extracted from published studies identified through a systematic search of relevant databases. A standardized data extraction form will be used to ensure consistency in gathering information on study characteristics, interventions, outcomes, and other relevant variables. All extracted data will be stored in a secure, electronic spreadsheet with access limited to the research team.
Data verification will be performed by a second reviewer to ensure accuracy and to minimize the risk of extraction errors. Discrepancies between reviewers will be resolved through consensus or by consulting a third researcher. The meta-data (data about data) including information about search strategies, inclusion/exclusion criteria, and quality assessment tools used will also be meticulously recorded to enhance reproducibility and transparency.
The R statistical software package will beused for analysis. The final dataset along with the code used for statistical analyses will be archived in an institutional repository to facilitate future updates or reviews of the meta-analysis.

Quality assessment / Risk of bias analysis The quality of studies included in this network meta-analysis will be evaluated using the Cochrane Collaboration's Risk of Bias Too. Each study will be independently assessed by two reviewers, with disagreements resolved through discussion or consultation with a third reviewer.
In addition to standard risk of bias assessments, this analysis will incorporate evaluations of transitivity and inconsistency across different study comparisons within the network. Inconsistency will be assessed using statistical methods such as the node-splitting approach and inconsistency plots.
The results of the quality assessments, including the risk of bias, transitivity, and inconsistency findings, will be summarized in detailed tables and will be taken into account when interpreting the results of the network meta-analysis. Additionally, the quality of evidence for each comparison and outcome will be rated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach to provide a clear understanding of the strength of the evidence.

Strategy of data synthesis Data from included studies will be synthesized through a network meta-analysis conducted in R using the netmeta package, which facilitates both direct and indirect comparisons across interventions.
Due to variations in drug types, formulations, and measurement units, the standardized mean difference (SMD) will be employed as the effect measure for continuous outcomes. This metric will standardize the results across studies, facilitating comparisons despite the differences in scales.
The network's consistency will be checked using node-splitting methods to assess the agreement between direct and indirect evidence within the network. If inconsistency is detected, further exploration will be conducted through sensitivity analyses or meta-regression to investigate potential sources of heterogeneity.
Graphical representations, including network plots and forest plots, will be generated to visually depict the relationships and comparative efficacy of the interventions. Ranking probabilities will be calculated to provide a hierarchy of the treatments based on their effectiveness.
All analyses will include 95% confidence intervals to quantify the uncertainty of the estimated effects. This structured approach ensures a rigorous and transparent synthesis of the available evidence, providing clear insights into the comparative effectiveness of the included interventions.

Subgroup analysis Subgroup analyses will be conducted to explore the differential effects of treatments in specific patient populations, specifically distinguishing between patients undergoing cardiac and non-cardiac surgery. This stratification is due to the different physiological effects and complexities associated with these two types of surgery.
Patients will be categorized based on the type of surgery they undergo - cardiac or non-cardiac - as reported in the individual studies. The network meta-analysis will be performed separately for each subgroup. This will allow direct and indirect comparisons of interventions within each surgical category, providing tailored evidence for each subgroup.
Interaction tests will be performed to statistically assess whether the differences between subgroups are significant. This will help determine whether the effects of interventions are consistent across surgical types, or whether specific

interventions are more or less effective in one subgroup compared to another. Results will be reported separately for each subgroup, along with a discussion of the clinical implications of the findings. Differences in effect sizes, confidence intervals, and statistical significance are highlighted to aid clinical decision making.

Sensitivity analysis Sensitivity analyses will be conducted to evaluate the robustness of the main findings of the network meta-analysis. The sensitivity analyses will include:
1. Exclusion of studies with high risk of bias: Studies identified as having a high risk of bias based on the Cochrane Risk of Bias tool will be excluded to assess the effect on the overall treatment effect estimates.
2. Alternative effect measures: While the primary analysis will use standardized mean differences (SMD) for continuous outcomes, sensitivity analyses may employ other effect measures such as mean differences or ratio of means to check if the conclusions are dependent on the chosen effect measure.
3. Statistical methods: The primary analysis will assume a random-effects model. Sensitivity analyses will be conducted using a fixed-effects model to compare results and assess the influence of between-study heterogeneity.
4. Subgroup analyses: If data permit, subgroup analyses based on patient characteristics or study quality will be performed to explore potential moderators of treatment effects.

Language restriction No language restrictions will be applied to the search.

Country(ies) involved The study will be conducted exclusively in China.

Other relevant information None

Keywords nociception monitoring; intraoperative analgesia; opioid consumption; postoperative pain.

Dissemination plans We plan to submit the results for publication in a peer-reviewed journal specializing in anesthesia or pain management.

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