INPLASY PROTOCOL

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Corresponding author:
Hyun Kang

roman00@naver.com

Author Affiliation:
Chung-Ang University

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None declared.

Comparison of efficacy and safety of perioperaive sufentanil and remifentanil: a protocol for systematic review and/or meta-analysis

Kim, HJ[1]; Choi, GJ[2]; Kang, H[3].

Review question / Objective: **The objective of this systematic review and meta-analysis of randomized controlled trials (RCTs) was to compare the efficacy and safety of perioperaive sufentanil and remifentanil use in patients receiving elective surgery under general anesthesia.**
Condition being studied: **Patients receiving elective surgery under general anesthesia, and receving sufentanil or remifentanil during the operation.**
Information sources: **We will search articles in MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, and Google Scholar from their inception up to August, 2022. To obtain more comprehensive search results, we will also search the ClinicalTrials.gov and cris.nih.go.kr for ongoing or incomplete clinical trials. We will also conduct a search of gray literature using OpenSIGLE.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 14 July 2022 and was last updated on 21 July 2022 (registration number INPLASY202270070).

INTRODUCTION

Review question / Objective: **The objective of this systematic review and meta-analysis of randomized controlled trials (RCTs) was to compare the efficacy and safety of perioperaive sufentanil and remifentanil use in patients receiving elective surgery under general anesthesia.**

Rationale: **Intravenous opioids are commonly used to provide analgesia during general anesthesia) and are the most widely used agents for treatment of acute pain in the immediate postoperative period. Remifentanil is a type of opioid that is primarily metabolized and degraded by a non-specific esterase in blood plasma and tissues, while sufentanil is another type of**

opioid which is metabolized by the liver and kidneys and therefore has a long action time.

Condition being studied: Patients receiving elective surgery under general anesthesia, and receving sufentanil or remifentanil during the operation.

METHODS

Search strategy: We are going to search MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, and Google Scholar in August 2022. In addition, the reference lists of the retrieved full articles will be searched. A search for registered trials using clinical trial registries to identify RCTs which were completed but not yet published, and grey literature using OpenSIGLE will be conducted.

Participant or population: All patients receiving elective surgery under general anesthesia.

Intervention: Intraoperative administration of sufentanil.

Comparator: Intraoperative administration of remifentanil.

Study designs to be included: Inclusion criteria: Randomized controlled trial. Exclusion criteria: observational study, conference abstracts, posters, case reports, case series, comments or letters to the editor, reviews, and laboratory or animal studies.

Eligibility criteria: We will apply no restriction on language nor date.

Information sources: We will search articles in MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, and Google Scholar from their inception up to August, 2022. To obtain more comprehensive search results, we will also search the ClinicalTrials.gov and cris.nih.go.kr for ongoing or incomplete clinical trials. We will also conduct a search of gray literature using OpenSIGLE.

Main outcome(s): The postoperative pain score measured using visual analogue score (VAS) or numerical rating score (NRS)Post operative pain score (VAS, NRS).

Additional outcome(s): The postoperative analgesic use, time to first analgesic request, hemodynamic variables (SBP, MAP, DBP, HR), the incidence of nausea and vomiting, recovery time and peripheral O2 saturation (SpO2).

Data management: Study selection
Two investigators will independently review the titles and abstracts of the identified studies. If a study was considered eligible on the basis of the title or abstract, the full paper will be retrieved and evaluated. Potentially relevant studies identified by at least one investigator or studies with an abstract that could not provide sufficient information regarding the eligibility criteria will be retrieved and full-text versions will be evaluated. Both investigators will discuss their opinions to arrive at a consensus as to whether a study should be included. In cases where a consensus could not be reached, disagreement over inclusion or exclusion will be resolved with a discussion with a third investigator.
Kappa statistics will be used to measure the degree of agreement for study selection between the two independent investigators. Kappa statistics will be interpreted as follows: 1) less than 0, less than chance agreement; 2) 0.01 to 0.20, slight agreement; 3) 0.21 to 0.40, fair agreement; 4) 0.41 to 0.60, moderate agreement; 5) 0.61 to 0.80, substantial agreement; and 6) 0.8 to 0.99, almost perfect agreement.
Data extraction
Using a standardized data collection form, two independent investigators will extract all interrelated data from the included studies and cross-check them. When the investigators disagreed for data extraction, the article will be re-evaluated by each investigator until a consensus is reached. If consensus was not reached, a third investigator will be consulted.

The following data will be extracted: (1) title, (2) name of the first author, (3) name of the journal, (4) year of publication, (5) study design, (6) country, (7) language, (8) risk of bias, (9) type of surgery, (10) inclusion criteria, (11) exclusion criteria, (12) sex, (13) age, (14) number of subjects, (15) administration methods (continuous infusion, target controlled infusion), and (16) nature of primary and secondary outcomes investigated.

Data will be initially extracted from tables or text or calculated from the available data, if possible. Data presented only in a graphical format will be derived from the open-source software Plot Digitizer (version 2.6.8; http://plotdigitizer.sourceforge.net). If the values were incomplete or not reported, we will attempt to contact the corresponding author to obtain the relevant information.

Quality assessment / Risk of bias analysis: Two independent investigators will critically appraise the quality of each study using the revised Cochrane risk of bias tool for randomized trials (RoB 2.0 version). Initially, investigators will rate each domain in every study: D1) bias arising from the randomization process, D2) bias due to deviations from the intended interventions, D3) bias due to missing outcome data, D4) bias in measurement of the outcome, and D5) bias in selection of the reported result. The overall risk of bias will also be evaluated. It will be judged as low risk when the risk of bias for all domains was low; high, when the risk of bias for at least one domain was high or the risk of bias for multiple domains was of some concern; and some concern, if the overall judgment was neither low nor high. In cases where a consensus could not be reached, disagreement will be resolved by discussion with a third investigator.

Strategy of data synthesis: Conventional meta-analysis

Conventional meta-analysis will be conducted using Comprehensive Meta-Analysis version 2.0 (Englewood, NJ, USA, 2008). Two investigators will independently input all data into the software. The weighted mean difference (WMD) or risk ratios (RRs) and 95% confidence interval (CI) will be calculated for each outcome. We will use the chi-square and I2 tests to explore the heterogeneity between the studies. A Pchi2 less than 0.1 or an I2 greater than 50% was considered to indicate considerable heterogeneity. A fixed effects model will be selected if Pchi2 ≥ 0.10 and I2 ≤ 50%. In cases of Pchi2 < 0.10 or I2 > 50%, a random effects model will be used.

To explore heterogeneity, we will perform a sensitivity analysis by removing one study at a time and determining whether it altered the results. Subgroup analyses will be performed according to the administration methods. We will calculate the number needed to treat (NNT) based on the absolute risk reduction, as an estimate of the overall clinical impact of the intervention.

Publication bias will be assessed using Begg's funnel plot and Egger's linear regression test, and a p-value < 0.05 will used to identify the presence of a publication bias; otherwise, funnel plots for each data set will be visually assessed for asymmetry. If a publication bias was present, a trim-and-fill analysis will be performed to evaluate its effect [16].

Trial sequential analysis

We will additionally perform a trial sequential analysis (TSA) on the postoperative pain score using TSA software (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Denmark) to assess whether the results of the conventional meta-analysis were conclusive. Conventional meta-analysis runs the risk of overestimation (type I errors) or underestimation (type II errors) owing to sparse data [17]. TSA provides more information on the precision and uncertainty of meta-analysis results, specifically the required information size (RIS) and a threshold for statistical significance, which controls the risk of potential false-positive and false-negative findings of meta-analyses. We will use a fixed or random effects model with the DerSimonian–Laird (DL) method to construct the cumulative Z-curve. TSA was performed to maintain an overall 5% risk of a type I error.

When the cumulative Z-curve crossed the trial sequential monitoring boundary or entered the futility area, a sufficient level of evidence to accept or reject the anticipated intervention effect may have been obtained, and no further studies were needed. If the Z-curve did not cross any boundaries and the RIS was not reached, the evidence to reach a conclusion would be considered insufficient, indicating the need for further studies.
We will use an alpha of 5% for all outcomes, a beta of 10%, and the observed mean difference, variance, and diversity, as suggested by the trials in the meta-analysis.

Subgroup analysis: Subgroup analyses will be performed according to the administration methods.

Sensitivity analysis: To explore heterogeneity, we will perform a sensitivity analysis by removing one study at a time and determining whether it altered the results.

Language: We will not apply restriction on language.

Country(ies) involved: Republic of Korea.

Other relevant information: None.

Keywords: Sufentanil; remifentanil; general anesthesia; randomized controlled trial.

Dissemination plans: Submitting manuscript for peer-reviewed publication.

Contributions of each author:
Author 1 - Geunjoo Choi drafted this protocol, contributed the conceptualization, the development of the selection criteria, and the risk of bias assessment strategy.
Email: pistis23@naver.com
Author 2 - Hyo Jin kim drafted this protocol, contributed the conceptualization, the development of the selection criteria, and the risk of bias assessment strategy.
Email: raphaella.ane@gmail.com
Author 3 - Hyun Kang drafted this protocol, contributed the conceptualization, the development of the selection criteria, and the risk of bias assessment strategy and provide the statistical expertise.
Email: roman00@naver.com