INPLASY

Efficacy and safety of ketamine and esketamine for preventing opioid-induced cough: a meta-analysis of randomized controlled trials

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Preliminary searches.

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 24 December 2024 and was last updated on 24 December 2024.

INTRODUCTION

Review question / Objective Can ketamine and esketamine prevent opioid-induced cough?

Rationale Opioid-induced cough (OIC) is a common adverse effect occurring in 30-65% of patients receiving rapid intravenous opioids, particularly during anesthesia induction. While generally self-limiting, OIC can cause significant complications including increased intracranial, intraocular, and intra-abdominal pressures. Various pharmacological interventions have been studied to prevent OIC, including ketamine and its S-enantiomer esketamine. These NMDA receptor antagonists may suppress cough reflexes through central antitussive effects and peripheral mechanisms. While individual randomized controlled trials (RCTs) have evaluated ketamine and esketamine for OIC prevention, their results have been inconsistent, and optimal dosing strategies remain unclear. Additionally, potential hemodynamic effects of these agents warrant careful consideration. Therefore, we conducted this systematic review and meta-analysis to comprehensively evaluate the efficacy and safety of ketamine and esketamine for preventing OIC, aiming to provide evidence-based guidance for clinical practice.

Condition being studied Opioid-induced cough (OIC) is a reflex response characterized by sudden, forceful expiration that occurs shortly after rapid intravenous administration of opioids, particularly during anesthesia induction. This phenomenon affects 30-65% of patients receiving opioids and is especially common with synthetic opioids like fentanyl, remifentanil, and sufentanil. While typically brief and self-limiting, OIC can lead to adverse effects including increased intracranial, intraocular, and intra-abdominal pressures. In vulnerable patients such as those with cerebral aneurysms, recent eye surgery, or severe respiratory disease, these complications can be clinically significant. The exact mechanism of OIC remains unclear but may involve opioid-induced

histamine release, vagal stimulation, or direct activation of airway sensory nerves.

METHODS

Search strategy We conduct a systematic literature search in Medline, Google Scholar, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) from inception through December 2024. The search strategy combined Medical Subject Headings (MeSH) terms and free-text keywords related to ketamine, esketamine, and opioid-induced cough. The complete search string for Medline was: (Ketamine OR Esketamine OR "N-methylaspartate receptor antagonists" OR NMDA OR "dissociative anesthetics") AND (Opioid OR Fentanyl OR Remifentanil OR Sufentanil OR Alfentanil) AND (Cough OR "Respiratory Reflexes" OR "Airway Reflexes"). Similar search strategies were adapted for other databases. We also manually screen the reference lists of included studies and relevant reviews to identify additional eligible trials. No language restrictions were applied.

Participant or population Surgical patients of any age receiving opioids during anesthetic induction.

Intervention Use ketamine or esketamine as a pharmacological strategy to prevent opioid-induced cough.

Comparator Use a placebo or no treatment as a comparator.

Study designs to be included Only randomized controlled trials are included.

Eligibility criteria We included randomized controlled trials (RCTs) that evaluated the efficacy and safety of ketamine or esketamine for preventing opioid-induced cough. Studies were considered eligible if they met the following criteria: (1) included surgical patients of any age receiving opioids during anesthetic induction; (2) compared ketamine or esketamine with either a placebo or no treatment; and (3) reported the incidence of opioid-induced cough as either a primary or secondary outcome.
We excluded observational studies, case reports, reviews, animal studies, and trials that did not report relevant outcomes. Additionally, studies that combined ketamine or esketamine with other agents (e.g., dexmedetomidine or lidocaine) for the prevention of opioid-induced cough were also excluded. For studies with multiple arms comparing ketamine/esketamine alone or in combination with other agents to placebo, only the intervention arm involving ketamine/esketamine alone was included.

Information sources We conducted a systematic literature search in Medline, Google Scholar, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL). We also manually screened the reference lists of included studies and relevant reviews to identify additional eligible trials. We contacted corresponding authors when additional data or clarification was needed. No language or publication status restrictions were applied.

Main outcome(s) The primary outcome was the overall incidence of opioid-induced cough within 3 minutes after opioid administration, regardless of severity.

Additional outcome(s) Secondary outcomes included: (1) severity of cough (mild and moderate-to-severe cough), which was defined based on individual study; (2) hemodynamic changes (i.e., Heart rate and blood pressure) within 3 minutes after opioid administration, with blood pressure measured by mean arterial pressure (MAP) or systolic blood pressure when MAP was unavailable; (3) onset time of cough, defined as the time from opioid administration to the first cough episode; and (4) oxygen saturation (SpO2) changes. For outcomes measured at multiple time points, we collected data closest to opioid administration (preferably 1 minute) to capture the immediate effects during the period when opioid-induced cough is most likely to occur.

Quality assessment / Risk of bias analysis Two reviewers independently assessed the risk of bias in the included studies using the Cochrane Risk of Bias tool 2.0. This tool evaluates five domains: the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting. Each domain was categorized as having a "low risk," "some concerns," or "high risk" of bias. Any discrepancies between the reviewers were resolved through discussion or by involving a third reviewer.

Strategy of data synthesis All statistical analyses were conducted using a random-effects model to account for potential variability among the included studies. The effect sizes for dichotomous outcomes were calculated as risk ratios (RR) with 95% confidence intervals (CIs), while continuous outcomes were expressed as mean differences (MD) with 95% CIs.

Sensitivity analyses were conducted to evaluate the robustness of the findings by systematically excluding each study one at a time. Heterogeneity among studies was quantified with the I^2 statistic. An I^2 value of 25%, 50%, and 75% was interpreted as representing low, moderate, and high heterogeneity, respectively. When significant heterogeneity was detected, potential sources were explored through subgroup analyses and meta-regression. Meta-regression analyses were conducted to investigate the potential impact of ketamine or esketamine dosages on the outcomes. The regression model examined whether variations in dosage could explain differences in the effect sizes across studies. Publication bias was assessed visually using funnel plots for outcomes with at least 10 included studies and statistically using Egger's test. All analyses were performed using Revman, and two-tailed p-values of $p<0.05$ were considered statistically significant.

Subgroup analysis Subgroup analysis is performed based on dosage of ketamine/esketamine or patient age (e.g., adult or child).

Sensitivity analysis Sensitivity analyses were conducted to evaluate the robustness of the findings by systematically excluding each study one at a time.

Language restriction No language restrictions were applied.

Country(ies) involved Taiwan.

Keywords opioid, cough, ketamine, esketamine.

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