BMJ Open

Safety and efficacy of remimazolam in mechanical ventilation in the ICU: a protocol for systematic evaluation and meta-analysis

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To cite: Yang X, Yang Y, Miao G, *et al*. Safety and efficacy of remimazolam in mechanical ventilation in the ICU: a protocol for systematic evaluation and meta-analysis. *BMJ Open* 2024;**14**:e091172. doi:10.1136/bmjopen-2024-091172

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2024-091172).

Received 14 July 2024
Accepted 25 October 2024

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ABSTRACT

Introduction Remimazolam is a novel ultra-short-acting benzodiazepine that allosterically modulates γ-aminobutyric acid type A receptors to induce sedative effects. Remimazolam was approved by China for procedural sedation in 2020. Intensive care unit (ICU) patients frequently exhibit impaired liver and renal function as well as haemodynamic instability; thus, the pharmacokinetic properties of remimazolam may offer advantages for ICU sedation. A comprehensive evaluation of the relevant studies warrants further discussion. This systematic review aims to compare the efficacy and safety of the novel intravenous anaesthetic remimazolam with that of commonly used anaesthetics in the ICU.

Methods and analysis The following databases will be searched: Embase, Cochrane Library, PubMed, MEDLINE, Web of Science, CNKI and WanFang to retrieve relevant randomised controlled trials (RCTs). This protocol was developed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols 2020. RCTs about the use of remimazolam for sedation during ICU mechanical ventilation will be included. Two investigators will independently screen articles and extract data according to predefined inclusion and exclusion criteria. Following a qualitative evaluation of each study, data analysis will be conducted using Review Manager 5.4 software. The planned start and end dates for the study were placed on 1 June 2024 and 31 October 2024, respectively.

Ethics and dissemination This protocol for the systematic evaluation and meta-analysis does not involve individual patient data; thus, ethical approval is not required. This will be the first meta-analysis to assess the sedative efficacy and safety of remimazolam in the ICU and to provide evidence to inform clinical decision-making. The findings will be disseminated through conference presentations and publications in peer-reviewed journals relevant to the field.

PROSPERO registration number CRD42024554425

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This review will adopt a rigorous approach by adhering to Cochrane guidelines and systematic review standards, including the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist.
⇒ The study will encompass both Chinese and English literature and perform a comprehensive review.
⇒ The findings may offer valuable evidence and guidance for clinical practice.
⇒ The study is currently focused on randomised controlled trials, because the available literature may be limited by the scope of research topics (only a few studies are ongoing from the clinical registration), high-quality non-randomised controlled studies are also considered.

INTRODUCTION

Patients in the intensive care unit (ICU) often experience multiple organ dysfunction, require mechanical ventilation to maintain respiration, and necessitate sedatives, analgesics and neuromuscular blockers to mitigate patient-ventilator asynchrony and associated stress. In contrast to procedural sedation used in outpatient gastrointestinal endoscopies or anaesthesia induction, sedation in ICU patients is typically prolonged and requires dose adjustment based on the duration of mechanical ventilation and the patient's stress level.

Remimazolam is a novel ultra-short-acting intravenous benzodiazepine derivative with sedative, hypnotic, anterograde amnesic and anxiolytic effects.[1 2] Compared with traditional sedative agents such as midazolam, propofol and dexmedetomidine, remimazolam is associated with reduced cardiovascular and respiratory depression, minimal injection pain and the availability of reversal agents.[3–7] Several studies on remimazolam have demonstrated that it is characterised by rapid onset, rapid metabolism, short half-life and consistent duration of continuous infusion.[8–10] Remimazolam is rapidly and extensively metabolised by tissue esterases, making it particularly suitable for many ICU patients

with liver and renal impairment.[11 12] It is a new safe and effective option for both the elderly and paediatric patients.[13–16]

A bibliometric article shows that the research on remimazolam has shown an obvious upward trend in recent years, mainly including China and Japan, as well as the European Union and the United States.[17] Most of the initial studies have focused on describing endoscopy and procedural sedation during induction of anaesthesia, and some articles have summarised the advantages of remimazolam.[18 19] Given the increasing demand for remimazolam in the ICU, it is important to evaluate its efficacy and safety in maintaining prolonged sedation for ICU patients. Several studies have assessed the efficacy and safety of remimazolam in ICU patients. These studies found that remimazolam provides effective sedation for ICU patients.[20 21] Some more detailed studies on ICU patients are also in good order.[22–24] Consequently, the advantages of remimazolam as a novel sedative in the ICU warrant further investigation. An updated synthesis and analysis of the existing literature will aid in clinical decision-making. This systematic review will provide a foundation for future research on this novel intravenous anaesthetic.

OBJECTIVES

This systematic review aims to compare the efficacy and safety of the novel intravenous anaesthetic remimazolam with that of commonly used anaesthetics in the ICU. Additionally, it seeks to elucidate the effectiveness of remimazolam and its reduced incidence of adverse effects.

MATERIALS AND METHODS

Registration

The Cochrane Handbook for Systematic Reviews of Interventions was used as guidance for the protocol.[18] This protocol adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) checklist guidelines.[25] In accordance with these guidelines, our systematic evaluation protocol is registered in the International Prospective Register of Systematic Reviews (PROSPERO) under accession number CRD42024554425, as of June 2024. Ethical approval and patient consent are not required because this study is based on published data. We will disseminate our results through submission to peer-reviewed journals. The study is scheduled to commence on 1 June 2024 and conclude on 31 October 2024.

ELIGIBILITY CRITERIA

Designs

All published randomised controlled trials (RCTs) that compare remimazolam with other sedative agents in the ICU will be included. Non-randomised studies, including animal research, observational or descriptive study designs (such as cohort studies and case reports), as well as duplicate literature, will be excluded.

Participants

We will include studies involving mechanically ventilated ICU patients who have received remimazolam sedation. There will be no restrictions on patient age or sex.

Interventions

Interventions using remimazolam alone or in combination with other sedative agents (including benzodiazepines, propofol, opioids and other sedatives) to achieve sedative effects are of interest. There were no restrictions on the interval between doses or the rate of administration for the interventions used in the study.

Comparators

We will include RCTs on other sedative agents (including benzodiazepines, propofol, opioids and other sedatives) sedation as the control for ICU sedation.

Outcomes

The primary outcome of this study will be the success rate of sedation in the ICU (as maintaining RASS(Richmond Agitation-Sedation Scale) scores between −2 and 0 with the appropriate and safe dosage of remimazolam). Drug safety will be evaluated based on indicators such as drug-related adverse events, including the incidence of respiratory depression, bradycardia, hypotension and tachycardia. Secondary outcomes will include the duration of mechanical ventilation, length of ICU stay and duration of endotracheal tube use after the cessation of sedative medication. Studies that do not provide the relevant data required for this meta-analysis will be excluded.

Information sources

To identify all relevant studies, irrespective of publication status, we systematically searched seven electronic databases: Embase, Cochrane Library, PubMed, MEDLINE, Web of Science, CNKI and WanFang. Only RCTs were included in the search. To ensure a comprehensive literature search, we will also review the reference lists of included studies and relevant reviews. The literature search will be restricted to articles published in English and Chinese.

Search strategy

All database searches will use a combination of subject headings and free-text terms, tailored to each specific database. Key terms will include “mechanical ventilation,” “ICU,” and “remimazolam,” among others. Retrieval strategies will be developed by health science librarians with expertise in systematic reviews. Before the systematic evaluation and meta-analysis, databases will be searched periodically, with a final search conducted to update results before finalising the full text. The detailed search strategy used for the PubMed database is provided in online supplemental file 1.

Study records

Study selection

Our study selection adhered to PRISMA guidelines. Two researchers independently searched various databases and screened studies according to predetermined criteria. Retrieved literature will be managed using Zotero, and duplicates will be removed. After reviewing titles and abstracts, full texts of studies that pass the initial eligibility screening will be obtained to make a final inclusion decision. Any disagreements will be resolved by consensus among the study team or, if necessary, by a third researcher. Additionally, we will document the specific reasons for excluding each study. The screening flowchart for the selected studies is provided in online supplemental file 1, figure 1.

Data extraction

After identifying eligible literature, data will be extracted according to the initial design requirements by two researchers independently. Discrepancies in data extraction will be resolved by consulting the original text, and any inconsistencies will be finalised through discussion with a third researcher. The following data will be extracted.

Basic information: article title, year of publication, author information, centre (single-centre, multi-centre), registration logo and funding.

Participants: sample size, country/region, mean age, gender, range of sedation and duration of sedation.

Interventions: loading dose, maintenance infusion dose and duration of treatment.

Comparison: placebo or other sedative agent, loading dose, maintenance infusion dose and duration of treatment.

Outcome: length of ICU stay, duration of mechanical ventilation, extubation time and safe outcomes, such as hypotension and bradycardia hypoxemia.

Outcomes and prioritisation

The primary outcome was the percentage of time spent within the target sedation range without the need for rescue sedation. Safety endpoints included respiratory depression, bradycardia, hypotension and tachycardia.

Secondary outcomes included length of ICU stay, duration of mechanical ventilation and time to extubation.

Risk of bias assessment

Each study will be evaluated independently by two investigators using the Risk of Bias tool (RoB 2).[26] The RoB for each included trial will be assessed in the following areas: randomisation process, timing of subject identification or recruitment, deviations from intended interventions, completeness of outcome data, measurement of outcomes and selective reporting of results. Each domain will be rated as 'low', 'high', or 'some concerns'. Any discrepancies between the two researchers will be resolved through discussion with a third researcher, and the final results will be documented.

Data synthesis

We will conduct a meta-analysis using RevMan, V.5.4. The standardised mean difference with its 95% CI will be used for continuous data, whereas OR and HR with their 95% CI will be used for categorical data. Statistical heterogeneity among the included studies will be assessed using the Q test and I^2 statistic. If $p>0.1$ and $I^2<50\%$ indicate no significant statistical heterogeneity, a fixed-effects model will be used for the meta-analysis. Conversely, if $p\leq0.1$ or $I^2\geq50\%$ indicates significant heterogeneity, a random-effects model will be applied.[27 28] Additionally, sensitivity analysis will be performed to identify sources of heterogeneity and assess the robustness of the findings. A funnel plot will be created for the outcome indicators of at least 10 included studies to assess potential publication bias. A p value of <0.05 will be considered statistically significant.

Patient and public involvement

There will be no direct involvement of patients or the public in this study.

Ethics and dissemination

Ethical approval is not required for this systematic review, as it relies solely on published data. The results of the analysis will be published or disseminated following evaluation by peer experts.

Contributors XY contributed substantially to the design and conception of the study, registered in the PROSPERO database, writing and editing of the study protocol. XY and YY contributed to the design of the statistical methods. GM and CY planned the data extraction. XL and LL revised several versions of the article. All authors approved the final article. XL is the guarantor.

Funding This study was supported by the Sichuan Science and Technology Program,2022YFS0632.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer-reviewed.

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