BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-091172
Article Type:	Protocol
Date Submitted by the Author:	14-Jul-2024
Complete List of Authors:	Yang, Xuelian; The Affiliated Hospital of Southwest Medical University, Yang, Yulian; The Affiliated Hospital of Southwest Medical University, Department of Intensive Care Unite Miao, Gelan; The Affiliated Hospital of Southwest Medical University, Department of Intensive Care Unite Yang, Chaobing; The Affiliated Hospital of Southwest Medical University, Department of Intensive Care Unite Liu, Li; Affiliated Hospital of Southwest Medical University, Department of Anesthesiology; Anesthesiology and Critical Care Medicine Key Laboratory of Luzhou Lei, Xianying; The Affiliated Hospital of Southwest Medical University, Department of Intensive Care Unite
Keywords:	Meta-Analysis, INTENSIVE & CRITICAL CARE, Adult intensive & critical care < INTENSIVE & CRITICAL CARE, Medicine, Propofol

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

Xuelian Yang, [1,2†] Yulian Yang,[2] Gelan Miao,[3] Chaobing Yang,[3] Li Liu,[4] Xianying Lei,[5]

[1 2 3 5]Department of Intensive Care Unite, the Affiliated Hospital of Southwest Medical University, Luzhou, China

[4] Department of Anesthesiology, the Affiliated Hospital of Southwest Medical University, Luzhou, China

Corresponding author:

Xianying Lei, Department of Critical Care Medicine, The Affiliated Hospital, Southwest Medical University, Luzhou, Sichuan Province, 646000, China. E-mail address: leixianying310@swmu.edu.cn

Word count: 2513

ABSTRACT

Introduction

Remimazolam is a new ultra-short-acting benzodiazepine drug that allosterically modulates γ -aminobutyric acid type A (GABA A) receptors for sedative effects. Remimazolam has been approved by China for procedural sedation in 2020. ICU patients often have liver and renal function impairment and hemodynamic instability, and the pharmacokinetic properties of remimazolam make it a potential advantage in ICU sedation. The evaluation of the related studies is worthy of further discussion.

Methods and analysis

The following databases will be searched: Embase, Cochrane Library, PubMed, Medline, Web of Science, CNKI, and WanFang database to retrieve the relevant randomized controlled trials. This protocol was prepared based on the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols 2020. Randomized controlled trials related to the use of remimazolam sedation during ICU mechanical ventilation will be included. Two investigators will independently screen articles and extract data based on inclusion and exclusion criteria. After a qualitative evaluation of each study, the analysis will be performed using the Review Manager 5.4 software.

Ethics and dissemination

The protocol for this systematic evaluation and meta-analysis does not involve individual patient data; therefore, ethical approval is not required. This will be the first meta-analysis to evaluate the sedative efficacy of remimazolam used in the ICU as well as safety and provide evidence of decision-making for clinicians. The findings will be disseminated through conference reports and publication in peer-reviewed journals relevant to the field.

PROSPERO registration number

CRD42024554425

Keywords: remimazolam, Intensive Care Units, mechanical ventilation, protocols, meta-analysis

Strengths and limitations of this study

This review will take a rigorous approach, following the Cochrane guidelines and systematic reviews of the preferred reporting items and the Meta-Analysis checklist.

The study will search the Chinese and English literature and will conduct a comprehensive

review.

Our findings may provide evidence and guidance for clinical practice.

Our study is currently randomized, and the relevant literature may also be limited due to the different scope of research topics, as all original randomized controlled trials(RCTs) in English and Chinese that meet the inclusion criteria will be included.

Introduction

Patients in ICU often suffer from multiple organ function damage, need mechanical ventilation to maintain breathing, and need sedative and analgesia and even muscle relaxation-related drugs to reduce human-machine confrontation and related stress states. Unlike procedural sedation in outpatient gastrointestinal endoscopes and induced sedation under anesthesia, sedation in ICU patients is mostly sustained and longer, regulating the dose of sedative drugs according to the duration of mechanical ventilation and the stress status of the patient. There are several studies that have been applied to sedation in ICU patients and are safe and effective. [1,2]

Remimazolam is a novel ultra-short-acting intravenous benzodiazepine derivative with sedative, hypnotic, antegrade forgetting, and anxiolytic effects.[3,4] Compared with the traditional sedative drugs midazolam, propofol, and dexmedetomidine, remimazolam has a smaller cardiovascular and respiratory depression, minimal injection pain, and the availability of reversal agents. [5–9] The results of several remimazolam-related studies showed that remimazolam was characterized by rapid onset, rapid metabolism, short half-life, and constant duration of continuous infusion. [10–12] Remimazolam is rapidly and extensively metabolized by tissue esterase, which is more suitable for many ICU patients with liver and kidney function impairment.[13,14]

Given the gradually increasing demand for the use of remimazolam in the ICU, it is worth thinking about the efficacy and safety of using remimazolam in maintaining sedation for a long time in ICU patients. Several studies have compared the efficacy and safety of remimazolam in ICU patients. Their findings showed that the use of remimazolam provides effective sedation and analgesia to ICU patients. [1,2,15]However, most of the studies involved small sample sizes, and a multicenter study is ongoing and has not yet been published.[16] Therefore, the advantages of remimazolam as a novel sedative in the ICU deserve further discussion. An updated summary and analysis of the existing literature will facilitate clinical decision-making. This systematic

review will lay the foundation for future research on this novel intravenous general anesthetic.

Objectives

This systematic review aims to compare the efficacy and safety of new intravenous remimazolam with the commonly used anesthetic in the ICU. Furthermore, it aims to elucidate effective and fewer adverse effects.

Materials and methods

Registration

Cochrane The systematic evaluation of intervention was used as a guide for the protocol.[17] This protocol is based on the Preferred Reporting Items (PRISMA-P) checklist guidelines for the systematic evaluation and meta-analysis protocol.[18] According to the guidelines, our systematic evaluation protocol was available in the International Prospective Systematic Review registry (accession number: CRD42024554425) in June 2024. Ethical approval and patient consent are not required as this study will be based on the published study. We will submit our results to peer-reviewed journals for publication. The planned start and end dates for the study were placed on 01 June 2024 and 31 October 2024, respectively.

Eligibility criteria

Designs

All published randomized controlled trials (RCTs) comparing the use of remimazolam and other sedative drugs in the ICU will be included. Non-randomized studies including animal studies, observational or descriptive study designs, including cohort studies, case reports, and repeat literature will be excluded.

Participants

We will include studies that recruit mechanically ventilated patients who have had remimazolam sedation in the ICU. There were no restrictions on patient age or sex.

Interventions

Compare remazolam to other sedatives (including benzodiazepines, propofol, dexmedetomidine, or other sedatives). Regarding the interventions used in the study, there was no limit on the interval between applied doses or injection speed.

Comparators

We will include remimazolam as a randomized controlled trial of ICU sedation.

Outcomes

The primary outcome of this study will be the sedation success rate of ICU sedation. Indicators to evaluate the drug safety of the study: drug-related adverse events, such as the incidence of respiratory depression, bradycardia, hypotension, tachycardia, etc. Secondary outcomes will be the duration of mechanical ventilation, length of ICU stay, and tube duration after cessation of sedative medication. Original studies that did not provide relevant data required for this meta-analysis will be excluded.

Information sources

To determine all relevant studies, regardless of their publication status, we systematically searched the following seven electronic databases: Embase, Cochrane Library, PubMed, MEDLINE, Web of Science, CNKI, and WanFang database, and the searched literature was a randomized controlled trial. To ensure the completeness of the literature search, we will scan the list of identified references for inclusion in the study or related review. The literature search will be limited to articles published in both English and Chinese.

Search strategy

All database searches will be based on a combination of subject words and free words and will be adjusted for the specific database, with the main keywords including mechanical ventilation, ICU, remimazolam, and more. Specific retrieval strategies will be developed by health science librarians with expertise in systematic review retrieval. Before the systematic evaluation and meta-analysis, the database will be searched periodically and a final search will be performed to update the results before the full text is completed. The specific search strategy applied to the PubMed database is found in Supplementary File 1.

Study records

Study selection

We followed the PRISMA guidelines in our study selection. Different databases were searched by two researchers and included and screened according to predetermined conditions. The

literature retrieved will be managed using the literature management software Zotera and duplicates removed. After reading the title and abstract of the literature. Full text of studies that passed the first eligibility screen will be obtained to make a final decision on whether they are eligible for inclusion. All disagreements were resolved by the study team by consensus or by a third researcher. In addition, we will record the specific reasons for excluding each study. The screening flow chart for the selected studies is shown in the Supplementary file, fig 1.

Data extraction

After identifying the literature eligible for inclusion, data are extracted according to the requirements of the initial design, disagreement regarding data extraction will be checked by the original text, and final consensus on any inconsistency through discussion with a third researcher.

The following data will be extracted:

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

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

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

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

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

Outcomes and prioritization

The primary outcome was the percentage of time in the target sedation range without rescue sedation, and safety endpoints which include respiratory depression, bradycardia, hypotension, tachycardia, etc.

The secondary outcomes include length of ICU stay, duration of mechanical ventilation, extubation,etc.

Risk of bias assessment

We will evaluate each study using the risk of bias tool (RoB 2), independently by two different investigators. The RoB for each included trial will be assessed in areas: offset during randomization; offset in the timing of identifying or recruiting subjects; deviation from established interventions; true offset in outcome data; offset from outcome measures; and offset in selectively reported results. Each domain name is rated "low," "high" or "some questions". If there is a gap in the results of the two researchers, it will be discussed further with the third researcher and the results.

Data synthesis

We will perform a meta-analysis using RevMan (V.5.4). Calculated standard deviation (SMD) was used for the measurement data and its 95% confidence interval (95%CI); count data using odds ratio (OR) and hazard ratio (RR) as the combined statistics, each statistic is expressed as 95%CI. Statistical heterogeneity of the included literature was assessed by the Q test and I^2 test. If P> 0.1 and I^2 50% indicates no statistical heterogeneity among documents, Meta-analysis was performed by fixed-effects model; P 0.1 or I^2> 50% indicates statistical heterogeneity among each literature, Meta-analysis was performed by random effects model.[19,20] Furthermore, sensitivity analysis will be conducted to detect the sources of heterogeneity and evaluate the robustness of the findings. Draw a funnel plot for the outcome indicators of 10 included articles to determine whether there was publication bias in the literature. A $p<0.05$ will be considered statistically significant.

Patient and public involvement

There will be no direct patient or public involvement in this study.

Ethics and dissemination

Ethical approval is not required for this systematic evaluation as this is a systematic evaluation protocol using only published data. The analysis results of relevant studies will be published or shared after evaluation by peer experts.

Supplementary Material

supplemental instrument.docx

Footnotes

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 manuscript.All authors approved the final manuscript.

Funding: This study was supported by 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.

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

Reference

1. Tang Y, Yang X, Yu Y, et al. Remimazolam besylate versus propofol for long-term sedation during invasive mechanical ventilation: a pilot study. *Crit Care*. 2022;26:279. doi:10.1186/s13054-022-04168-w

2. S L, L S, B Z, et al. The Availability and Safety Study of Remimazolam Besylate for Injection on Sedation of ERAS Patients Under Mechanical Ventilation in ICU: Protocol for a Randomized, Open-Label, Controlled Trial. *Frontiers in medicine*. 2021;8. doi:10.3389/fmed.2021.735473

3. Remimazolam: an ultrashort-acting intravenous anesthetic suitable for general anesthesia - Minerva Anestesiologica 2021 October;87(10):1059-63 - Minerva Medica - Journals. Accessed June 26, 2024. https://www.minervamedica.it/en/journals/minerva-anestesiologica/article.php?cod=R02Y2021N10A1059

4. Li X, Tian M, Deng Y, She T, Li K. Advantages of Sedation With Remimazolam Compared to Midazolam for the Removal of Impacted Tooth in Patients With Dental Anxiety. *J Oral*

Maxillofac Surg. 2023;81(5):536-545. doi:10.1016/j.joms.2023.02.001

5. Choi JY, Lee HS, Kim JY, et al. Comparison of remimazolam-based and propofol-based total intravenous anesthesia on postoperative quality of recovery: A randomized non-inferiority trial. *J Clin Anesth*. 2022;82:110955. doi:10.1016/j.jclinane.2022.110955

6. Dong SA, Guo Y, Liu SS, et al. A randomized, controlled clinical trial comparing remimazolam to propofol when combined with alfentanil for sedation during ERCP procedures. *J Clin Anesth*. 2023;86:111077. doi:10.1016/j.jclinane.2023.111077

7. Kim H, Park SS, Shim J. Differences in midazolam premedication effects on recovery after short-duration ambulatory anesthesia with propofol or sevoflurane for gynecologic surgery in young patients. *Medicine (Baltimore)*. 2020;99(47):e23194. doi:10.1097/MD.0000000000023194

8. Worthington MT, Antonik LJ, Goldwater DR, et al. A phase Ib, dose-finding study of multiple doses of remimazolam (CNS 7056) in volunteers undergoing colonoscopy. *Anesth Analg*. 2013;117(5):1093-1100. doi:10.1213/ANE.0b013e3182a705ae

9. Chen X, Sang N, Song K, et al. Psychomotor Recovery Following Remimazolam-induced Sedation and the Effectiveness of Flumazenil as an Antidote. *Clin Ther*. 2020;42(4):614-624. doi:10.1016/j.clinthera.2020.02.006

10. Pastis NJ, Yarmus LB, Schippers F, et al. Safety and Efficacy of Remimazolam Compared With Placebo and Midazolam for Moderate Sedation During Bronchoscopy. *Chest*. 2019;155(1):137-146. doi:10.1016/j.chest.2018.09.015

11. Wiltshire HR, Kilpatrick GJ, Tilbrook GS, Borkett KM. A placebo- and midazolam-controlled phase I single ascending-dose study evaluating the safety, pharmacokinetics, and pharmacodynamics of remimazolam (CNS 7056): Part II. Population pharmacokinetic and pharmacodynamic modeling and simulation. *Anesth Analg*. 2012;115(2):284-296. doi:10.1213/ANE.0b013e318241f68a

12. Rex DK, Bhandari R, Desta T, et al. A phase III study evaluating the efficacy and safety of remimazolam (CNS 7056) compared with placebo and midazolam in patients undergoing colonoscopy. *Gastrointest Endosc*. 2018;88(3):427-437.e6. doi:10.1016/j.gie.2018.04.2351

13. Freyer N, Knöspel F, Damm G, et al. Metabolism of remimazolam in primary human hepatocytes during continuous long-term infusion in a 3-D bioreactor system. *Drug Des Devel Ther*. 2019;13:1033-1047. doi:10.2147/DDDT.S186759

14. Kilpatrick GJ, McIntyre MS, Cox RF, et al. CNS 7056: a novel ultra-short-acting Benzodiazepine. *Anesthesiology*. 2007;107(1):60-66. doi:10.1097/01.anes.0000267503.85085.c0

15. Yao Z, Liao Z, Li G, Wang L, Zhan L, Xia W. Remimazolam tosylate's long-term sedative properties in ICU patients on mechanical ventilation: effectiveness and safety. *European Journal of Medical Research*. 2023;28. doi:10.1186/s40001-023-01440-9

16. Liu N, Jiang Z, Nie Y, et al. Study Protocol of a Multicenter, Randomized, Single-Blind Trial: Efficacy and Safety of Remimazolam Tosylate for Sedation in ICU Patients. *Adv Ther*. 2023;40(5):2524-2533. doi:10.1007/s12325-023-02456-7

17. Cochrane Handbook for Systematic Reviews of Interventions. Accessed June 27, 2024. https://training.cochrane.org/handbook

18. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi:10.1136/bmj.n71

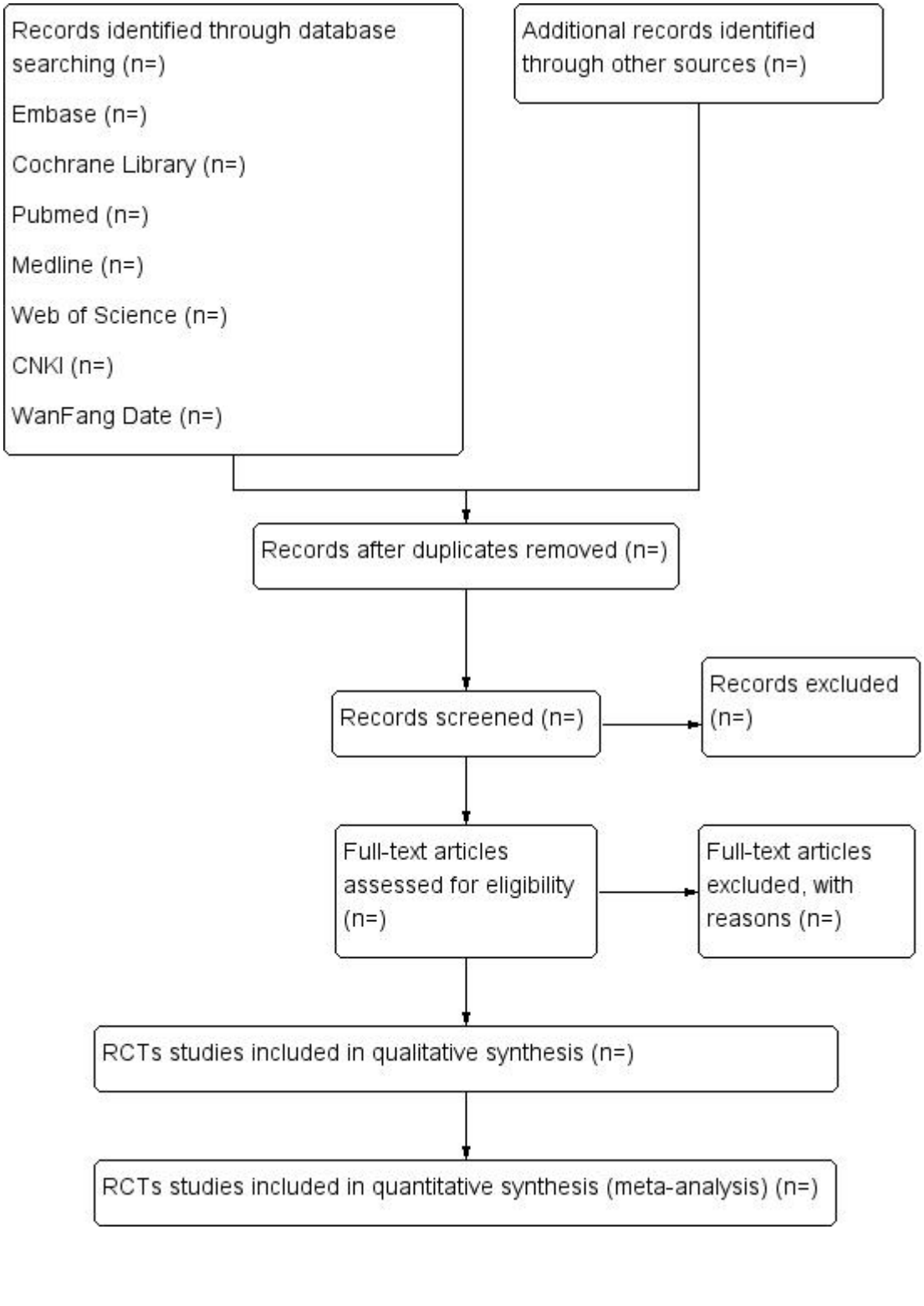
19. Barili F, Parolari A, Kappetein PA, Freemantle N. Statistical Primer: heterogeneity, random- or fixed-effects model analyses? *Interact Cardiovasc Thorac Surg*. 2018;27(3):317-321. doi:10.1093/icvts/ivy163

20. Riley RD, Higgins JPT, Deeks JJ. Interpretation of random effects meta-analyses. *BMJ*. 2011;342:d549. doi:10.1136/bmj.d549

1.Search strategies：

Search Number	Query	Filters	Results	Time
#1	(((Remimazolam[Supplementary Concept]) OR (CNS 7056[Title/Abstract])) OR (methyl 3-(8-bromo-1-methyl-6-(2-pyridinyl)-4H-imidazo(1,2-a)(1,4)benzodiazepin-4-yl)propanoate[Title/Abstract])) OR (ONO 2745[Title/Abstract])	None	374	2024/06/12
#2	((((Respiration, Artificial[MeSH Terms]) OR (Artificial Respiration[Title/Abstract])) OR (Artificial Respirations[Title/Abstract])) OR (Mechanical Ventilations[Title/Abstract])) OR (Mechanical Ventilation[Title/Abstract])	None	12736	2024/06/12
#3	((Intensive Care Units[MeSH Terms]) OR (Intensive Care Unit[Title/Abstract])) OR (Unit, Intensive Care[Title/Abstract])	None	198333	2024/06/12
#4	#1 AND (#2 OR #3)	None	16	2024/06/12
#5	#1 AND (#2 OR #3)	RCT	6	2024/06/12

2.**Study flow diagram**



BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-091172.R1
Article Type:	Protocol
Date Submitted by the Author:	26-Sep-2024
Complete List of Authors:	Yang, Xuelian; The Affiliated Hospital of Southwest Medical University, Yang, Yulian; The Affiliated Hospital of Southwest Medical University, Department of Intensive Care Unite Miao, Gelan; The Affiliated Hospital of Southwest Medical University, Department of Intensive Care Unite Yang, Chaobing; The Affiliated Hospital of Southwest Medical University, Department of Intensive Care Unite Liu, Li; The Affiliated Hospital of Southwest Medical University, Department of Anesthesiology; The Affiliated Hospital of Southwest Medical University Lei, Xianying; The Affiliated Hospital of Southwest Medical University, Department of Intensive Care Unite
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Intensive care
Keywords:	Meta-Analysis, INTENSIVE & CRITICAL CARE, Adult intensive & critical care < INTENSIVE & CRITICAL CARE, Medicine, Propofol

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

Xuelian Yang, [1,2†] Yulian Yang,[2] Gelan Miao,[3] Chaobing Yang,[3] Li Liu,[4] Xianying Lei,[5]

[1 2 3 5]Department of Intensive Care Unite, the Affiliated Hospital of Southwest Medical University, Luzhou, China

[4] Department of Anesthesiology, the Affiliated Hospital of Southwest Medical University, Luzhou, China

Corresponding author:

Xianying Lei, Department of Critical Care Medicine, The Affiliated Hospital, Southwest Medical University, Luzhou, Sichuan Province, 646000, China. E-mail address: leixianying310@swmu.edu.cn

Word count: 2513

Commented [1]: Thank you so much for your professional comments. The manuscript has been revised and re-polished by a native English speakers.

ABSTRACT

Introduction

Remimazolam is a new ultra-short-acting benzodiazepine drug that allosterically modulates γ -aminobutyric acid type A (GABA A) receptors for sedative effects. Remimazolam has been approved by China for procedural sedation in 2020. ICU patients often have liver and renal function impairment and hemodynamic instability, and the pharmacokinetic properties of remimazolam make it a potential advantage in ICU sedation. The evaluation of the related studies is worthy of further discussion.

Methods and analysis

The following databases will be searched: Embase, Cochrane Library, PubMed, Medline, Web of Science, CNKI, and WanFang database to retrieve the relevant randomized controlled trials. This protocol was prepared based on the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols 2020. Randomized controlled trials related to the use of remimazolam sedation during ICU mechanical ventilation will be included. Two investigators will independently screen articles and extract data based on inclusion and exclusion criteria. After a qualitative evaluation of each study, the analysis will be performed using the Review Manager 5.4 software.

Ethics and dissemination

The protocol for this systematic evaluation and meta-analysis does not involve individual patient data; therefore, ethical approval is not required. This will be the first meta-analysis to evaluate the sedative efficacy of remimazolam used in the ICU as well as safety and provide evidence of decision-making for clinicians. The findings will be disseminated through conference reports and publication in peer-reviewed journals relevant to the field.

PROSPERO registration number

CRD42024554425

Keywords: remimazolam, Intensive Care Units, mechanical ventilation, protocols, meta-analysis

Strengths and limitations of this study

This review will take a rigorous approach, following the Cochrane guidelines and systematic reviews of the preferred reporting items and the Meta-Analysis checklist.

The study will search the Chinese and English literature and will conduct a comprehensive

Commented [2]: Add the aim of the study" This systematic review aims to compare the efficacy and safety of the novel intravenous anesthetic remimazolam with that of commonly used anesthetics in the ICU."

Commented [3]: Inserted the dates of the search " The planned start and end dates for the study were placed on 01 June 2024 and 31 October 2024, respectively."

review.

Our findings may provide evidence and guidance for clinical practice.

Our study is currently randomized, and the relevant literature may also be limited due to the different scope of research topics, as all original randomized controlled trials(RCTs) in English and Chinese that meet the inclusion criteria will be included.

Introduction

Patients in ICU often suffer from multiple organ function damage, need mechanical ventilation to maintain breathing, and need sedative and analgesia and even muscle relaxation-related drugs to reduce human-machine confrontation and related stress states. Unlike procedural sedation in outpatient gastrointestinal endoscopes and induced sedation under anesthesia, sedation in ICU patients is mostly sustained and longer, regulating the dose of sedative drugs according to the duration of mechanical ventilation and the stress status of the patient. There are several studies that have been applied to sedation in ICU patients and are safe and effective. [1,2]

Remimazolam is a novel ultra-short-acting intravenous benzodiazepine derivative with sedative, hypnotic, antegrade forgetting, and anxiolytic effects.[3,4] Compared with the traditional sedative drugs midazolam, propofol, and dexmedetomidine, remimazolam has a smaller cardiovascular and respiratory depression, minimal injection pain, and the availability of reversal agents. [5–9] The results of several remimazolam-related studies showed that remimazolam was characterized by rapid onset, rapid metabolism, short half-life, and constant duration of continuous infusion. [10–12] Remimazolam is rapidly and extensively metabolized by tissue esterase, which is more suitable for many ICU patients with liver and kidney function impairment.[13,14]

Given the gradually increasing demand for the use of remimazolam in the ICU, it is worth thinking about the efficacy and safety of using remimazolam in maintaining sedation for a long time in ICU patients. Several studies have compared the efficacy and safety of remimazolam in ICU patients. Their findings showed that the use of remimazolam provides effective sedation and analgesia to ICU patients. [1,2,15]However, most of the studies involved small sample sizes, and a multicenter study is ongoing and has not yet been published.[16] Therefore, the advantages of remimazolam as a novel sedative in the ICU deserve further discussion. An updated summary and analysis of the existing literature will facilitate clinical decision-making. This systematic

Commented [4]: We change it to" The study is currently focused on randomized controlled trials"

Commented [5]: We incorporated relevant literature as references in response to the reviewers' feedback and acknowledged that the limited market for remimazolam may lead to study failure. Consequently, we will consider several high-quality non-randomized controlled studies.

Commented [6]: change for "neuromuscular blockers"

Commented [7]: Change for "mitigate patient-ventilator asynchrony"

Commented [8]: This sentence is deleted

Commented [9]: Change for "maintaining sedation"

Commented [10]: Delete ANALGESIA with remimazolam

review will lay the foundation for future research on this novel intravenous general anesthetic.

Objectives

This systematic review aims to compare the efficacy and safety of new intravenous remimazolam with the commonly used anesthetic in the ICU. Furthermore, it aims to elucidate effective and fewer adverse effects.

Materials and methods

Registration

Cochrane The systematic evaluation of intervention was used as a guide for the protocol.[17] This protocol is based on the Preferred Reporting Items (PRISMA-P) checklist guidelines for the systematic evaluation and meta-analysis protocol.[18] According to the guidelines, our systematic evaluation protocol was available in the International Prospective Systematic Review registry (accession number: CRD42024554425) in June 2024. Ethical approval and patient consent are not required as this study will be based on the published study. We will submit our results to peer-reviewed journals for publication. The planned start and end dates for the study were placed on 01 June 2024 and 31 October 2024, respectively.

Eligibility criteria

Designs

All published randomized controlled trials (RCTs) comparing the use of remimazolam and other sedative drugs in the ICU will be included. Non-randomized studies including animal studies, observational or descriptive study designs, including cohort studies, case reports, and repeat literature will be excluded.

Participants

We will include studies that recruit mechanically ventilated patients who have had remimazolam sedation in the ICU. There were no restrictions on patient age or sex.

Interventions

Compare remimazolam to other sedatives (including benzodiazepines, propofol, dexmedetomidine, or other sedatives). Regarding the interventions used in the study, there was no limit on the interval between applied doses or injection speed.

Comparators

Commented [11]: Change for "The Cochrane Handbook for Systematic Reviews of Interventions was used as guidance for the protocol"

Commented [12]: Change for "the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) checklist guidelines"

Commented [13]: Change for "International Prospective REGISTER of Systematic Reviews (PROSPERO)"

Commented [14]: Change for "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. "

We will include remimazolam as a randomized controlled trial of ICU sedation.

Outcomes

The primary outcome of this study will be the sedation success rate of ICU sedation. Indicators to evaluate the drug safety of the study: drug-related adverse events, such as the incidence of respiratory depression, bradycardia, hypotension, tachycardia, etc. Secondary outcomes will be the duration of mechanical ventilation, length of ICU stay, and tube duration after cessation of sedative medication. Original studies that did not provide relevant data required for this meta-analysis will be excluded.

Information sources

To determine all relevant studies, regardless of their publication status, we systematically searched the following seven electronic databases: Embase, Cochrane Library, PubMed, MEDLINE, Web of Science, CNKI, and WanFang database, and the searched literature was a randomized controlled trial. To ensure the completeness of the literature search, we will scan the list of identified references for inclusion in the study or related review. The literature search will be limited to articles published in both English and Chinese.

Search strategy

All database searches will be based on a combination of subject words and free words and will be adjusted for the specific database, with the main keywords including mechanical ventilation, ICU, remimazolam, and more. Specific retrieval strategies will be developed by health science librarians with expertise in systematic review retrieval. Before the systematic evaluation and meta-analysis, the database will be searched periodically and a final search will be performed to update the results before the full text is completed. The specific search strategy applied to the PubMed database is found in Supplementary File 1.

Study records

Study selection

We followed the PRISMA guidelines in our study selection. Different databases were searched by two researchers and included and screened according to predetermined conditions. The

Commented [15]: Change for "We will include RCTs on other sedative agents (including benzodiazepines, propofol, opioids, and other sedatives) sedation as the control for ICU sedation."

Commented [16]: We add the definition"The RASS scores were maintained at -2-0, with the appropriate safe remimazolam dose"

Commented [17]: Change for "duration of endotracheal tube" This refers to the duration of the endotracheal tube placement, which differs from the timing of mechanical ventilation, as the clinician assesses whether the patient is ready for tracheal extubation. The patient's ventilator is typically paused; during this period, the patient exhibits some respiratory function, relying solely on a transtracheal nasal catheter for oxygen delivery.

literature retrieved will be managed using the literature management software Zotera and duplicates removed. After reading the title and abstract of the literature. Full text of studies that passed the first eligibility screen will be obtained to make a final decision on whether they are eligible for inclusion. All disagreements were resolved by the study team by consensus or by a third researcher. In addition, we will record the specific reasons for excluding each study. The screening flow chart for the selected studies is shown in the Supplementary file, fig 1.

Data extraction

After identifying the literature eligible for inclusion, data are extracted according to the requirements of the initial design, disagreement regarding data extraction will be checked by the original text, and final consensus on any inconsistency through discussion with a third researcher.

The following data will be extracted:

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

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

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

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

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

Commented [18]: Deleted this word

Outcomes and prioritization

The primary outcome was the percentage of time in the target sedation range without rescue sedation, and safety endpoints which include respiratory depression, bradycardia, hypotension, tachycardia, etc.

The secondary outcomes include length of ICU stay, duration of mechanical ventilation, extubation,etc.

Risk of bias assessment

We will evaluate each study using the risk of bias tool (RoB 2), independently by two different investigators. The RoB for each included trial will be assessed in areas: offset during randomization; offset in the timing of identifying or recruiting subjects; deviation from established interventions; true offset in outcome data; offset from outcome measures; and offset in selectively reported results. Each domain name is rated "low," "high" or "some questions". If there is a gap in the results of the two researchers, it will be discussed further with the third researcher and the results.

Commented [19]: Change for some concerns

Data synthesis

We will perform a meta-analysis using RevMan (V.5.4). Calculated standard deviation (SMD) was used for the measurement data and its 95% confidence interval (95%CI); count data using odds ratio (OR) and hazard ratio (RR) as the combined statistics, each statistic is expressed as 95%CI. Statistical heterogeneity of the included literature was assessed by the Q test and I^2 test. If P> 0.1 and I^2 50% indicates no statistical heterogeneity among documents, Meta-analysis was performed by fixed-effects model; P 0.1 or I^2> 50% indicates statistical heterogeneity among each literature, Meta-analysis was performed by random effects model.[19,20] Furthermore, sensitivity analysis will be conducted to detect the sources of heterogeneity and evaluate the robustness of the findings. Draw a funnel plot for the outcome indicators of 10 included articles to determine whether there was publication bias in the literature. A p<0.05 will be considered statistically significant.

Patient and public involvement

There will be no direct patient or public involvement in this study.

Ethics and dissemination

Ethical approval is not required for this systematic evaluation as this is a systematic evaluation protocol using only published data. The analysis results of relevant studies will be published or shared after evaluation by peer experts.

Supplementary Material

supplemental instrument.docx

Footnotes

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 manuscript.All authors approved the final manuscript. XL is the guarantor.

Funding: This study was supported by 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.

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

Reference

1. Tang Y, Yang X, Yu Y, et al. Remimazolam besylate versus propofol for long-term sedation during invasive mechanical ventilation: a pilot study. *Crit Care*. 2022;26:279. doi:10.1186/s13054-022-04168-w

2. S L, L S, B Z, et al. The Availability and Safety Study of Remimazolam Besylate for Injection on Sedation of ERAS Patients Under Mechanical Ventilation in ICU: Protocol for a Randomized, Open-Label, Controlled Trial. *Frontiers in medicine*. 2021;8. doi:10.3389/fmed.2021.735473

3. Remimazolam: an ultrashort-acting intravenous anesthetic suitable for general anesthesia - Minerva Anestesiologica 2021 October;87(10):1059-63 - Minerva Medica - Journals. Accessed June 26, 2024. https://www.minervamedica.it/en/journals/minerva-anestesiologica/article.php?cod=R02Y2021N10A1059

4. Li X, Tian M, Deng Y, She T, Li K. Advantages of Sedation With Remimazolam Compared to Midazolam for the Removal of Impacted Tooth in Patients With Dental Anxiety. *J Oral*

Maxillofac Surg. 2023;81(5):536-545. doi:10.1016/j.joms.2023.02.001

5. Choi JY, Lee HS, Kim JY, et al. Comparison of remimazolam-based and propofol-based total intravenous anesthesia on postoperative quality of recovery: A randomized non-inferiority trial. *J Clin Anesth*. 2022;82:110955. doi:10.1016/j.jclinane.2022.110955

6. Dong SA, Guo Y, Liu SS, et al. A randomized, controlled clinical trial comparing remimazolam to propofol when combined with alfentanil for sedation during ERCP procedures. *J Clin Anesth*. 2023;86:111077. doi:10.1016/j.jclinane.2023.111077

7. Kim H, Park SS, Shim J. Differences in midazolam premedication effects on recovery after short-duration ambulatory anesthesia with propofol or sevoflurane for gynecologic surgery in young patients. *Medicine (Baltimore)*. 2020;99(47):e23194. doi:10.1097/MD.0000000000023194

8. Worthington MT, Antonik LJ, Goldwater DR, et al. A phase Ib, dose-finding study of multiple doses of remimazolam (CNS 7056) in volunteers undergoing colonoscopy. *Anesth Analg*. 2013;117(5):1093-1100. doi:10.1213/ANE.0b013e3182a705ae

9. Chen X, Sang N, Song K, et al. Psychomotor Recovery Following Remimazolam-induced Sedation and the Effectiveness of Flumazenil as an Antidote. *Clin Ther*. 2020;42(4):614-624. doi:10.1016/j.clinthera.2020.02.006

10. Pastis NJ, Yarmus LB, Schippers F, et al. Safety and Efficacy of Remimazolam Compared With Placebo and Midazolam for Moderate Sedation During Bronchoscopy. *Chest*. 2019;155(1):137-146. doi:10.1016/j.chest.2018.09.015

11. Wiltshire HR, Kilpatrick GJ, Tilbrook GS, Borkett KM. A placebo- and midazolam-controlled phase I single ascending-dose study evaluating the safety, pharmacokinetics, and pharmacodynamics of remimazolam (CNS 7056): Part II. Population pharmacokinetic and pharmacodynamic modeling and simulation. *Anesth Analg*. 2012;115(2):284-296. doi:10.1213/ANE.0b013e318241f68a

12. Rex DK, Bhandari R, Desta T, et al. A phase III study evaluating the efficacy and safety of remimazolam (CNS 7056) compared with placebo and midazolam in patients undergoing colonoscopy. *Gastrointest Endosc*. 2018;88(3):427-437.e6. doi:10.1016/j.gie.2018.04.2351

13. Freyer N, Knöspel F, Damm G, et al. Metabolism of remimazolam in primary human hepatocytes during continuous long-term infusion in a 3-D bioreactor system. *Drug Des Devel Ther*. 2019;13:1033-1047. doi:10.2147/DDDT.S186759

14. Kilpatrick GJ, McIntyre MS, Cox RF, et al. CNS 7056: a novel ultra-short-acting Benzodiazepine. *Anesthesiology*. 2007;107(1):60-66. doi:10.1097/01.anes.0000267503.85085.c0

15. Yao Z, Liao Z, Li G, Wang L, Zhan L, Xia W. Remimazolam tosylate's long-term sedative properties in ICU patients on mechanical ventilation: effectiveness and safety. *European Journal of Medical Research*. 2023;28. doi:10.1186/s40001-023-01440-9

16. Liu N, Jiang Z, Nie Y, et al. Study Protocol of a Multicenter, Randomized, Single-Blind Trial: Efficacy and Safety of Remimazolam Tosylate for Sedation in ICU Patients. *Adv Ther*. 2023;40(5):2524-2533. doi:10.1007/s12325-023-02456-7

17. Cochrane Handbook for Systematic Reviews of Interventions. Accessed June 27, 2024. https://training.cochrane.org/handbook

18. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi:10.1136/bmj.n71

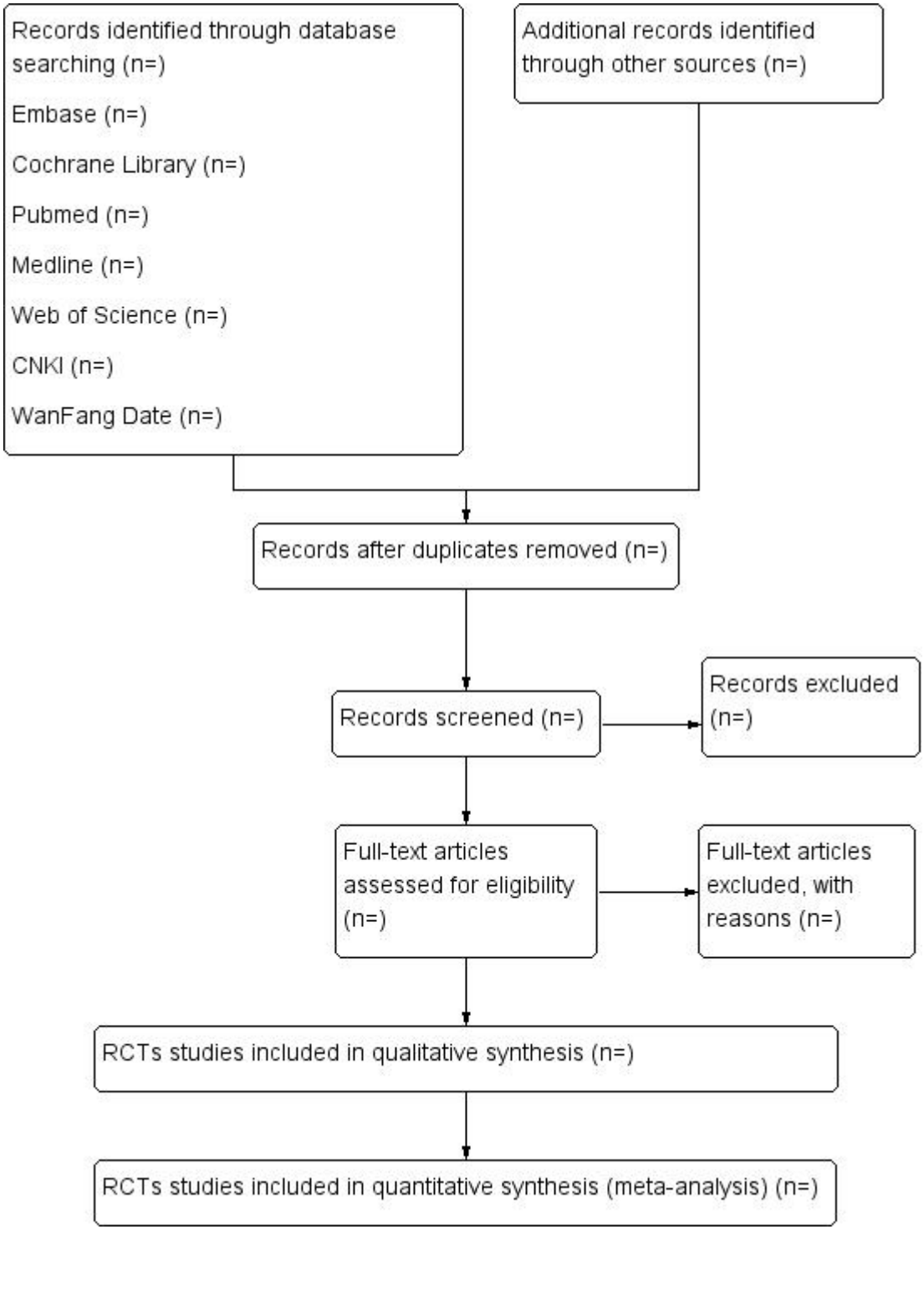
19. Barili F, Parolari A, Kappetein PA, Freemantle N. Statistical Primer: heterogeneity, random- or fixed-effects model analyses? *Interact Cardiovasc Thorac Surg*. 2018;27(3):317-321. doi:10.1093/icvts/ivy163

20. Riley RD, Higgins JPT, Deeks JJ. Interpretation of random effects meta-analyses. *BMJ*. 2011;342:d549. doi:10.1136/bmj.d549

1.Search strategies：

Search Number	Query	Filters	Results	Time
#1	(((Remimazolam[Supplementary Concept]) OR (CNS 7056[Title/Abstract])) OR (methyl 3-(8-bromo-1-methyl-6-(2-pyridinyl)-4H-imidazo(1,2-a)(1,4)benzodiazepin-4-yl)propanoate[Title/Abstract])) OR (ONO 2745[Title/Abstract])	None	374	2024/06/12
#2	((((Respiration, Artificial[MeSH Terms]) OR (Artificial Respiration[Title/Abstract])) OR (Artificial Respirations[Title/Abstract])) OR (Mechanical Ventilations[Title/Abstract])) OR (Mechanical Ventilation[Title/Abstract])	None	12736	2024/06/12
#3	((Intensive Care Units[MeSH Terms]) OR (Intensive Care Unit[Title/Abstract])) OR (Unit, Intensive Care[Title/Abstract])	None	198333	2024/06/12
#4	#1 AND (#2 OR #3)	None	16	2024/06/12
#5	#1 AND (#2 OR #3)	RCT	6	2024/06/12

2.**Study flow diagram**



BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-091172.R2
Article Type:	Protocol
Date Submitted by the Author:	19-Oct-2024
Complete List of Authors:	Yang, Xuelian; The Affiliated Hospital of Southwest Medical University, Yang, Yulian; The Affiliated Hospital of Southwest Medical University, Department of Intensive Care Unite Miao, Gelan; The Affiliated Hospital of Southwest Medical University, Department of Intensive Care Unite Yang, Chaobing; The Affiliated Hospital of Southwest Medical University, Department of Intensive Care Unite Liu, Li; The Affiliated Hospital of Southwest Medical University, Department of Anesthesiology; The Affiliated Hospital of Southwest Medical University Lei, Xianying; The Affiliated Hospital of Southwest Medical University, Department of Intensive Care Unite
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Intensive care
Keywords:	Meta-Analysis, INTENSIVE & CRITICAL CARE, Adult intensive & critical care < INTENSIVE & CRITICAL CARE, Medicine, Propofol

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

Xuelian Yang, [1,2†] Yulian Yang,[2] Gelan Miao,[3] Chaobing Yang,[3] Li Liu,[4] Xianying Lei,[5]

[1 2 3 5]Department of Intensive Care Unite, the Affiliated Hospital of Southwest Medical University, Luzhou, China

[4] Department of Anesthesiology, the Affiliated Hospital of Southwest Medical University, Luzhou, China

Corresponding author:

Xianying Lei, Department of Critical Care Medicine, The Affiliated Hospital, Southwest Medical University, Luzhou, Sichuan Province, 646000, China. E-mail address: leixianying310@swmu.edu.cn

Word count: 2872

ABSTRACT

Introduction

Remimazolam is a novel ultra-short-acting benzodiazepine that allosterically modulates γ-aminobutyric acid type A (GABA A) receptors to induce sedative effects. Remimazolam was approved by China for procedural sedation in 2020. ICU patients frequently exhibit impaired liver and renal function as well as hemodynamic 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 anesthetic remimazolam with that of commonly used anesthetics 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 randomized controlled trials. This protocol was developed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols 2020. Randomized controlled trials 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 01 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

Keywords: remimazolam, Intensive Care Units, mechanical ventilation, protocols, meta-analysis

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 (PRISMA) 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 randomized 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-randomized controlled studies are also considered.

Introduction

Patients in the 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 anesthesia 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 characterized by rapid onset, rapid metabolism, short half-life, and consistent duration of continuous infusion. [8–10] Remimazolam is rapidly and extensively metabolized 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 pediatric 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 anesthesia, and some articles have summarized 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 anesthetic.

Objectives

This systematic review aims to compare the efficacy and safety of the novel intravenous anesthetic remimazolam with that of commonly used anesthetics 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.[26] 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 June 1, 2024, and conclude on October 31, 2024.

Eligibility criteria

Designs

All published randomized controlled trials (RCTs) that compare remimazolam with other sedative agents in the ICU will be included. Non-randomized 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 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 following 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 randomized controlled trials 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 utilize 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 finalizing the full text. The detailed search strategy used for the PubMed database is provided in Supplementary 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 flow chart for the selected studies is provided in Supplementary 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 finalized through discussion with a third researcher.

The following data will be extracted:

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

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

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

Comparison: placebo or other sedative agent, loading dose, maintenance infusion dose, duration

of treatment.

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

Outcomes and prioritization

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).[25] The RoB for each included trial will be assessed in the following areas: randomization 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 version 5.4. The standardized mean difference (SMD) with its 95% confidence interval (95% CI) will be used for continuous data, while odds ratios (OR) and hazard ratios (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 $p \leqslant 0.1$ or $I^2 \geqslant 50\%$ 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 < 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.

Supplementary Material

supplemental instrument.docx

Footnotes

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 manuscript. All authors approved the final manuscript. 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, conduct, reporting, or dissemination plans of this research.

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

Reference

1. Remimazolam: an ultrashort-acting intravenous anesthetic suitable for general anesthesia - Minerva Anestesiologica 2021 October;87(10):1059-63 - Minerva Medica - Journals. Accessed June 26, 2024. https://www.minervamedica.it/en/journals/minerva-anestesiologica/article.php?cod=R02Y2

021N10A1059

2. Li X, Tian M, Deng Y, She T, Li K. Advantages of Sedation With Remimazolam Compared to Midazolam for the Removal of Impacted Tooth in Patients With Dental Anxiety. *J Oral Maxillofac Surg*. 2023;81(5):536-545. doi:10.1016/j.joms.2023.02.001

3. Choi JY, Lee HS, Kim JY, et al. Comparison of remimazolam-based and propofol-based total intravenous anesthesia on postoperative quality of recovery: A randomized non-inferiority trial. *J Clin Anesth*. 2022;82:110955. doi:10.1016/j.jclinane.2022.110955

4. Dong SA, Guo Y, Liu SS, et al. A randomized, controlled clinical trial comparing remimazolam to propofol when combined with alfentanil for sedation during ERCP procedures. *J Clin Anesth*. 2023;86:111077. doi:10.1016/j.jclinane.2023.111077

5. Kim H, Park SS, Shim J. Differences in midazolam premedication effects on recovery after short-duration ambulatory anesthesia with propofol or sevoflurane for gynecologic surgery in young patients. *Medicine (Baltimore)*. 2020;99(47):e23194. doi:10.1097/MD.0000000000023194

6. Worthington MT, Antonik LJ, Goldwater DR, et al. A phase Ib, dose-finding study of multiple doses of remimazolam (CNS 7056) in volunteers undergoing colonoscopy. *Anesth Analg*. 2013;117(5):1093-1100. doi:10.1213/ANE.0b013e3182a705ae

7. Chen X, Sang N, Song K, et al. Psychomotor Recovery Following Remimazolam-induced Sedation and the Effectiveness of Flumazenil as an Antidote. *Clin Ther*. 2020;42(4):614-624. doi:10.1016/j.clinthera.2020.02.006

8. Pastis NJ, Yarmus LB, Schippers F, et al. Safety and Efficacy of Remimazolam Compared With Placebo and Midazolam for Moderate Sedation During Bronchoscopy. *Chest*. 2019;155(1):137-146. doi:10.1016/j.chest.2018.09.015

9. Wiltshire HR, Kilpatrick GJ, Tilbrook GS, Borkett KM. A placebo- and midazolam-controlled phase I single ascending-dose study evaluating the safety, pharmacokinetics, and pharmacodynamics of remimazolam (CNS 7056): Part II. Population pharmacokinetic and pharmacodynamic modeling and simulation. *Anesth Analg*. 2012;115(2):284-296. doi:10.1213/ANE.0b013e318241f68a

10. Rex DK, Bhandari R, Desta T, et al. A phase III study evaluating the efficacy and safety of remimazolam (CNS 7056) compared with placebo and midazolam in patients undergoing colonoscopy. *Gastrointest Endosc*. 2018;88(3):427-437.e6. doi:10.1016/j.gie.2018.04.2351

11. Freyer N, Knöspel F, Damm G, et al. Metabolism of remimazolam in primary human hepatocytes during continuous long-term infusion in a 3-D bioreactor system. *Drug Des Devel Ther*. 2019;13:1033-1047. doi:10.2147/DDDT.S186759

12. Kilpatrick GJ, McIntyre MS, Cox RF, et al. CNS 7056: a novel ultra-short-acting Benzodiazepine. *Anesthesiology*. 2007;107(1):60-66. doi:10.1097/01.anes.0000267503.85085.c0

13. J G, C Y, Q J, J L. Effect of remimazolam versus propofol for the induction of general anesthesia on cerebral blood flow and oxygen saturation in elderly patients undergoing carotid endarterectomy. *BMC anesthesiology*. 2023;23(1). doi:10.1186/s12871-023-02095-z

14. J D, X J, X W, N L, S X, S W. Effects of Remimazolam and Propofol on Emergence Agitation in Elderly Patients Undergoing Hip Replacement: A Clinical, Randomized, Controlled Study. *Drug design, development and therapy*. 2023;17. doi:10.2147/DDDT.S419146

15. Lee S, Oh C, Jung J, et al. Retrospective comparison of the effects of remimazolam and dexmedetomidine on postoperative delirium in elderly patients undergoing orthopedic surgery of the lower extremities under spinal anesthesia. *J Anesth*. Published online August 25, 2024. doi:10.1007/s00540-024-03386-6

16. Pieri M, D'Andria Ursoleo J, Di Prima AL, et al. Remimazolam for anesthesia and sedation in pediatric patients: a scoping review. *J Anesth*. Published online June 7, 2024. doi:10.1007/s00540-024-03358-w

17. Hu X, Wang B, Hu L, Han D, Wu J. Bibliometric Analysis of Global Trends in Remimazolam-Related Research Over the Past 15 Years: Compared with Propofol. *Drug Des Devel Ther*. 2023;17:2119-2135. doi:10.2147/DDDT.S411829

18. D'Andria Ursoleo J, Licheri M, Barucco G, et al. Remimazolam for anesthesia and sedation in cardiac surgery and for cardiac patients undergoing non-cardiac surgery: a systematic-narrative hybrid review. *Minerva Anestesiol*. 2024;90(7-8):682-693. doi:10.23736/S0375-9393.24.17943-6

19. Ho CH, Chang CY, Lu CW. A Comparison of Hypotension, Bradycardia, and Hypoxia Incidence between the Use of Remimazolam and Other Sedative Agents during Colonoscopy Procedures: A Systematic Review and Meta-Analysis. *J Clin Med*. 2024;13(15):4352. doi:10.3390/jcm13154352

20. Tang Y, Yang X, Yu Y, et al. Remimazolam besylate versus propofol for long-term sedation during invasive mechanical ventilation: a pilot study. *Crit Care*. 2022;26:279. doi:10.1186/s13054-022-04168-w

21. Tang Y, Gao X, Xu J, et al. Remimazolam besylate versus propofol for deep sedation in critically ill patients: a randomized pilot study. *Crit Care*. 2023;27:474. doi:10.1186/s13054-023-04760-8

22. S L, L S, B Z, et al. The Availability and Safety Study of Remimazolam Besylate for Injection on Sedation of ERAS Patients Under Mechanical Ventilation in ICU: Protocol for a Randomized, Open-Label, Controlled Trial. *Frontiers in medicine*. 2021;8. doi:10.3389/fmed.2021.735473

23. Yang X, Tang Y, Du R, et al. Long-term sedation with remimazolam besylate versus propofol in critically ill patients during invasive mechanical ventilation: a study protocol for a multicenter randomized non-inferior trial. *Front Pharmacol*. 2023;14:1139872. doi:10.3389/fphar.2023.1139872

24. Liu N, Jiang Z, Nie Y, et al. Study Protocol of a Multicenter, Randomized, Single-Blind Trial: Efficacy and Safety of Remimazolam Tosylate for Sedation in ICU Patients. *Adv Ther*. 2023;40(5):2524-2533. doi:10.1007/s12325-023-02456-7

25. Cochrane Handbook for Systematic Reviews of Interventions. Accessed June 27, 2024. https://training.cochrane.org/handbook

26. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi:10.1136/bmj.n71

27. Barili F, Parolari A, Kappetein PA, Freemantle N. Statistical Primer: heterogeneity, random- or fixed-effects model analyses? *Interact Cardiovasc Thorac Surg*. 2018;27(3):317-321. doi:10.1093/icvts/ivy163

28. Riley RD, Higgins JPT, Deeks JJ. Interpretation of random effects meta-analyses. *BMJ*. 2011;342:d549. doi:10.1136/bmj.d549

1.Search strategies：

Search Number	Query	Filters	Results	Time
#1	(((Remimazolam[Supplementary Concept]) OR (CNS 7056[Title/Abstract])) OR (methyl 3-(8-bromo-1-methyl-6-(2-pyridinyl)-4H-imidazo(1,2-a)(1,4)benzodiazepin-4-yl)propanoate[Title/Abstract])) OR (ONO 2745[Title/Abstract])	None	374	2024/06/12
#2	((((Respiration, Artificial[MeSH Terms]) OR (Artificial Respiration[Title/Abstract])) OR (Artificial Respirations[Title/Abstract])) OR (Mechanical Ventilations[Title/Abstract])) OR (Mechanical Ventilation[Title/Abstract])	None	12736	2024/06/12
#3	((Intensive Care Units[MeSH Terms]) OR (Intensive Care Unit[Title/Abstract])) OR (Unit, Intensive Care[Title/Abstract])	None	198333	2024/06/12
#4	#1 AND (#2 OR #3)	None	16	2024/06/12
#5	#1 AND (#2 OR #3)	RCT	6	2024/06/12

2.**Study flow diagram**