ORIGINAL RESEARCH

Cost-Effectiveness Analysis of Remimazolam and Midazolam in Goal-Guided Sedation in ICU

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ABSTRACT

Objective • This study aimed to compare the direct medication costs and clinical effectiveness of using remimazolam versus midazolam for goal-guided sedation therapy in the ICU patients.

Methods • This randomized controlled study was conducted in the ICU of People's Hospital Affiliated to Shandong First Medical University. Eighty adult patients admitted to the ICU and requiring sedation were enrolled and randomly assigned in a 1:1 ratio to receive either remimazolam-based sedation (study group, n=40) or midazolam-based sedation (control group, n=40). The inclusion criteria for patient selection were age 18-80 years, requirement for mechanical ventilation, and an expected ICU stay of at least 24 hours. Patients with significant liver or kidney dysfunction, neurological disorders, or contraindications to the study drugs were excluded. The target sedation depth for both groups was a Ramsay Sedation Scale score of 3-4, which was maintained by titrating the infusion rates of remimazolam or midazolam as needed. Vital signs, sedation scores, and respiratory parameters were closely monitored throughout the sedation period.

Results • The time to onset of sedation, time to reach the target sedation depth, time to awakening, and length of ICU stay were all significantly shorter in the remimazolam group compared to the midazolam group ($P < .05$ for all). The remimazolam group had a mean time to onset of 5.2 ± 1.8 minutes versus 8.9 ± 2.4 minutes in the midazolam group. The mean time to reach the target Ramsay Sedation Scale score of 3-4 was 12.6 ± 3.1 minutes in the remimazolam group compared to 18.4 ± 4.2 minutes in the midazolam group. The mean time to awakening was 10.2 ± 2.7 minutes in the remimazolam group versus 16.5 ± 3.9 minutes in the midazolam group. The remimazolam group also had a significantly shorter mean ICU length of stay of 5.1 ± 1.3 days compared to 7.8 ± 2.1 days in the midazolam group ($P < .01$). The remimazolam group had a significantly higher metabolic clearance rate compared to the midazolam group ($P < .001$). The Ramsay sedation scores and Wong-Baker FACES pain scores were also significantly lower in the remimazolam group throughout the sedation period ($P < .01$). There were no significant differences in heart rate between the two groups at any timepoint. However, the overall incidence of adverse events was significantly lower in the remimazolam group compared to the midazolam group ($P < .05$).

Conclusion • This study demonstrated that the use of remimazolam-based goal-directed sedation in the ICU setting resulted in significantly faster onset of action, quicker achievement of the target sedation depth, shorter time to awakening, and shorter ICU length of stay compared to midazolam-based sedation. The remimazolam group also had a higher metabolic clearance rate, lower sedation and pain scores, and a lower incidence of adverse events.

These findings suggest that remimazolam may provide advantages over midazolam for ICU sedation, potentially leading to improved patient comfort, more efficient utilization of ICU resources, and potentially better clinical outcomes. The rapid onset, titratability, and favorable safety profile of remimazolam make it a promising sedative agent that could help optimize sedation practices in the critical care setting. Further research is warranted to fully evaluate the impact of remimazolam on long-term patient-centered outcomes and overall healthcare costs in the ICU. (*Altern Ther Health Med.* [E-pub ahead of print.])

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INTRODUCTION

The management of critically ill patients in the intensive care unit (ICU) presents significant challenges, particularly for those requiring mechanical ventilation.[1] These patients often face a delicate balance between the need for adequate sedation to tolerate the discomfort of invasive treatments and the risks associated with oversedation, such as prolonged mechanical ventilation, delirium, and increased length of stay.[2] Effective sedation is a critical component of comprehensive ICU care, as it not only helps reduce a patient's anxiety and resistance to mechanical ventilation, but also modulates the physiological stress response to critical illness and invasive interventions.

The choice of sedative agent is an important consideration, as different medications can have varying impacts on a patient's hemodynamics, respiratory drive, metabolism, and overall clinical outcomes.[3] Sedation practices in the ICU have evolved over time, with a shift towards more light and targeted sedation strategies to promote earlier extubation and reduce the risk of adverse outcomes associated with deep sedation. Historically, benzodiazepines like midazolam have

been the mainstay of ICU sedation, but their accumulation and unpredictable pharmacokinetics can contribute to delayed extubation and prolonged ICU stays.[4]

Midazolam is metabolized by the liver and kidney, which can lead to variable drug exposure and increased risk of adverse effects in critically ill patients with organ dysfunction.[5,6] Midazolam, a classic benzodiazepine, is commonly used for emergency sedation, ICU patients, and surgical patients due to its significant anterograde amnesic effect.[7,8] Remimazolam is an innovative anesthesia drug that combines midazolam and remifentanil properties. It acts on GABA receptors like midazolam but does not rely on liver and kidney metabolism like remifentanil.[9] Some domestic studies have shown that remimazolam promotes GABA receptor binding, increases the frequency of chloride channel opening, hyperpolarizes neurons, and produces a neuron-inhibitory effect.

In contrast, remimazolam is a novel ultra-short-acting benzodiazepine that acts on the same GABA receptors as midazolam but has a more favorable pharmacokinetic profile. Remimazolam is rapidly metabolized by tissue esterases, rather than relying on liver and kidney metabolism, which may result in more predictable and controllable sedation. These properties make remimazolam a promising alternative to traditional benzodiazepines for ICU sedation, as it may provide faster onset of action, more precise titratability, and potentially improved patient outcomes.

To date, no studies have directly compared the clinical effectiveness and cost implications of using remimazolam versus midazolam for goal-directed sedation in mechanically ventilated ICU patients. This randomized controlled trial aimed to fill this important gap in the literature and provide novel insights into the potential advantages of remimazolam for optimizing sedation practices and improving patient outcomes in the critical care setting.

The primary objective of this study was to compare the direct medication costs between remimazolam-based and midazolam-based sedation strategies in mechanically ventilated ICU patients. The secondary objectives were to evaluate the clinical effectiveness of these two sedation regimens, including the time to onset of sedation, time to reach target sedation depth, time to awakening, and length of ICU stay. We hypothesized that the use of remimazolam would result in lower direct medication costs and superior clinical outcomes compared to midazolam, thereby offering a more efficient and effective approach to sedation management in the ICU.

MATERIALS AND METHODS

Participants

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki and was approved by our hospital's ethics committee (no. 20983). The participants in this study were patients admitted to our hospital's ICU between January 2021 and July 2022. A total of 80 patients who met the inclusion criteria were included in the study after excluding those who did not meet the complete criteria. After case registration, the patients were randomly assigned to either the study group or the control group, with 40 patients in each group. Written informed consent was obtained from all participants prior to their inclusion in the study.

Patients were randomly assigned to receive either remimazolam-based or midazolam-based sedation using a computer-generated randomization sequence with variable block sizes, ensuring an equal allocation ratio between the two study arms.

Inclusion criteria

Inclusion criteria. 1) All patients are hospitalized in our hospital's ICU; 2) All need mechanical ventilation; 3) The clinical data are complete, all are adults, and there is no restriction on gender.

Exclusion criteria. 1) Existence of respiratory system or autoimmune system diseases; 2) Existence of severe heart, liver, and kidney dysfunction, etc.; 3) Withdrawal halfway, failing to complete the observation time of the experimental design; 4) Existence of allergic reactions to the drugs used in the study Wait.

Interventions

Both study groups received mechanical ventilation, and various parameters such as ventilator settings, electrocardiogram, heart rate, blood pressure, respiration, and pulse oxygen saturation were continuously monitored and recorded. Patients in the study group underwent target-guided sedation therapy using remimazolam. The procedure was as follows: initially, sedation induction was performed by administering 7 mg of remimazolam besylate injection (Guoyao Zhunzi H20217078, Jiangsu Hengrui Pharmaceutical Co., Ltd., Ruibei Ning) intravenously. This was followed by a continuous intravenous infusion of remimazolam besylate at a dose of 0.1-0.5 mg/(kg h). Patients in the control group received target-guided sedation with midazolam. The procedure involved intravenously administering 30 mg of midazolam diluted in 0.9% sodium chloride injection (Guoyao Zhunzi H43020456, Hunan Kelun Pharmaceutical Co., Ltd.). The loading dose was 0.05 mg/kg within 15 minutes, and the subsequent dosage was adjusted based on the patient's condition. In both groups, the infusion was continued until the Bispectral Index (BIS) value dropped to 75, after which the infusion rate was gradually adjusted (0.01 mg/kg/h increments or decrements) to maintain the BIS value within the range of 60-80.

The main reasons for linking the continuous sedative infusion rate to Bispectral Index (BIS) values are as follows:

BIS monitoring provides objective, continuous assessment of the level of consciousness: BIS is an EEG-derived parameter that reflects the patient's depth of sedation and level of consciousness. Compared to subjective sedation scores, BIS can provide more objective and precise monitoring of sedation depth.

Enables fine-tuning of the target sedation depth: By adjusting the sedative infusion rate to maintain the target BIS range (e.g., 40-60, indicating light to moderate sedation), the ideal sedation level can be more precisely controlled and maintained, avoiding over-sedation or under-sedation.

Promotes standardization and replicability of sedation management: Using BIS values as the basis for adjusting infusion rates can help standardize sedation management and improve its replicability, facilitating the dissemination of clinical practice and enhancing the reliability of comparative research findings.

Improves the predictability and safety of sedation effects: BIS monitoring can provide real-time feedback on the patient's response to sedative medications, allowing for timely adjustments of the infusion rate to prevent the potential adverse consequences of over-sedation or under-sedation.

Observation Indicators

Clinical Indicators. Relevant clinical indicators, including drug onset time, time to reach the expected depth of sedation, recovery time, metabolic clearance rate, and hospitalization time, were recorded for all patients and compared between the two groups.

Sedation Depth Assessment:

- The Riker Sedation-Agitation Scale (SAS) was used to assess the depth of sedation. The SAS is a validated 7-point scale ranging from 1 (unarousable) to 7 (dangerous agitation). Trained ICU nurses who were blinded to the sedation regimen recorded the SAS scores every 2 hours.

Metabolic Clearance Rate Measurement:

- Plasma concentrations of the sedative agents (remimazolam or midazolam) were measured using high-performance liquid chromatography (HPLC). Blood samples were collected at the following time points: baseline, and 2, 4, 8, 12, and 24 hours after initiation of the sedative infusion.

Sedation Effect. The sedation effect of patients in both groups was evaluated using the Ramsay Sedation Scale and Wong-Banker Facial Expression Scale (FPS-R). The Ramsay Scale rates sedation levels from 1 (ineffective) to 6 (excessive), with levels 2-4 considered ideal. The FPS-R scale assesses pain levels; the total score ranges from 0 to 10.

The SAS was administered every 2 hours throughout the study period to closely monitor the depth of sedation and guide titration of the sedative infusion rates.

Respiratory Rate. All patients' respiratory rate (RR) was recorded at different time points, including when the anesthesia level stabilized, when the expected depth of sedation was reached, after drug withdrawal, and after awakening. Comparisons were made between the two groups.

Respiratory rate was measured by direct observation of the patient's breathing pattern for 1 full minute. The number of breaths per minute was recorded.

Heart Rate Changes. The changes in heart rate (HR) of all patients were recorded at different time points, including when the anesthesia level stabilized, when the expected depth of sedation was reached, after drug withdrawal, and after awakening. Comparisons were made between the two groups.

Heart rate was measured using a 3-lead electrocardiogram (ECG) monitor. The heart rate value (beats per minute) was obtained from the ECG display. These measurements were taken at the following time points:

- **Baseline**: prior to starting the sedative infusion
- **Upon reaching target sedation depth (BIS 40-60):** as determined by the Bispectral Index (BIS) monitor
- **Every 4 hours thereafter**: for the duration of the sedative infusion

Adverse Reactions. Adverse reactions, such as drowsiness, cough, hypotension, bradycardia, delirium, agitation, etc., were recorded for all patients and compared between the two groups.

- A list of predefined adverse events was used, including:
  Respiratory depression: defined as respiratory rate <8 breaths/min or SpO_2 <92% on room air
  Hemodynamic instability: defined as >20% decrease in systolic blood pressure or >20% increase in heart rate from baseline
  Delirium: assessed using the Confusion Assessment Method for the ICU (CAM-ICU)
- Occurrence of these adverse events was recorded, including the time of onset, duration, severity grade (per CTCAE v5.0), and any interventions required.
- All adverse events were reviewed and categorized by an independent safety monitoring committee blinded to the treatment allocation.

Statistical analysis

GraphPad Prism 8 software was used to process images; SPSS 26.0 software was used to process data, count data [n (%)] and measurement data ($\bar{x} \pm s$) were subjected to chi-square ($\chi^{2)}$ and t test, $P < .05$ was considered statistically significant.

RESULTS

Baseline characteristics

The study group comprised 40 patients, including 18 males and 22 females, with ages ranging from 45 to 68 years and an average age of 52.58±6.84 years. The patients had a body mass index (BMI) ranging from 19 to 28 kg/m^2, with an average BMI of 23.02±1.97 kg/m^2. The average APACHE II score was 26.87±10.18. The pathological types in the study group included 15 cases of lung disease, 12 cases of cardiovascular disease, 4 cases of abdominal disease, 2 cases of acute poisoning, 3 cases of sepsis, 2 cases of multiple trauma, and 1 case of other diseases. The control group consisted of 40 cases, with 16 males and 24 females, ranging in age from 41 to 65 years and an average

Table 1. General information of patients in the two groups ($\bar{x}$±s)

		Research group	Control group	*t*	*P* value
number of cases		40	40	-	-
gender	male	18	16	-	-
	female	22	24	-	-
age	scope	45-68	41-65	-	-
	mean	52.58±6.84	51.99±6.97	0.382	.703
BMI	scope	19-28	19-28	-	-
	mean	23.02±1.97	23.11±1.67	0.220	.826
APACHEII	-	26.87±10.18	26.54±10.71	0.141	.888
pathological type	Lung disease	15	18	-	-
	Cardiovascular diseases	12	11	-	-
	celiac disease	4	5	-	-
	acute poisoning	2	1	-	-
	sepsis	3	2	-	-
	multiple injuries	2	1	-	-
	other	1	1	-	-

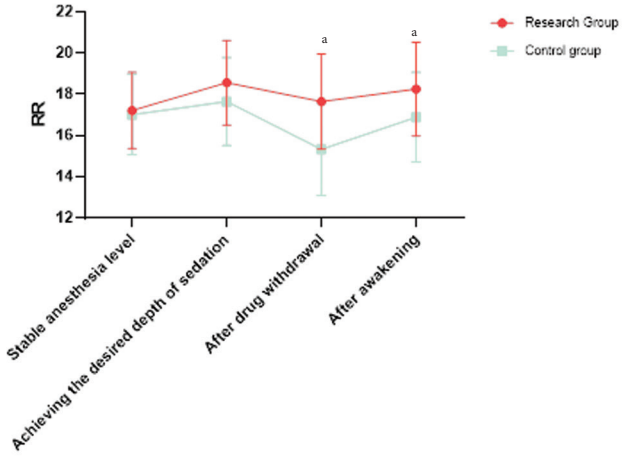
Table 2. Clinical related indicators of the two groups of patients ($\bar{x}$±s)

	Research group	Control group	*t*	*P* value
number of cases	40	40	-	-
Drug onset time (min)	1.58±0.26	7.06±1.65	20.749	<.001
Time to reach expected depth of sedation (min)	8.56±2.64	15.65±3.41	10.398	<.001
Wake up time (min)	30.56±5.56	41.55±6.45	8.162	<.001
Metabolic clearance rate (L/h)	68.56±11.58	23.91±7.71	20.299	<.001
Length of hospital stay (d)	9.23±1.98	14.56±2.47	10.649	<.001

Table 3. Ram-say and FPS-R scores of two groups of patients ($\bar{x}$±s)

	Research group	Control group	*t*	*P* value
number of cases	40	40	-	-
Ram-say	3.18±0.31	4.88±1.11	9.329	<.001
FPS-R	1.08±0.08	2.79±0.96	11.227	<.001

Figure 1. Comparison of RR levels in two groups of patients at different times



[a]indicates that there is a difference between groups, $P < .05$.

age of 51.99±6.97 years. The patients in the control group had a BMI ranging from 19 to 28 kg/m^2, with an average BMI of 23.11±1.67 kg/m2. The average APACHE II score in the control group was 26.54±10.71. The pathological types in the control group included 18 cases of pulmonary disease, 11 cases of cardiovascular disease, 5 cases of abdominal disease, 1 case of acute poisoning, 2 cases of sepsis, 1 case of multiple trauma, and 1 case of other diseases. There were no significant differences in the general information between the two groups, indicating comparability ($P > .05$). (Table 1)

The similarity between groups ensures that any observed differences in sedation outcomes or safety profiles can be more confidently attributed to the intervention rather than confounding baseline factors.

Clinical Indicators

The study group had a shorter drug onset time (1.58±0.26 minutes), time to reach the expected sedation depth (8.56±2.64 minutes), recovery time (30.56±5.56 minutes), and hospitalization time (9.23±1.98 days) compared to the control group, which had a drug onset time of (7.06±1.65 minutes), time to reach the expected sedation depth of (15.65±3.41 minutes), recovery time of (41.55±6.45 minutes), and hospitalization time of (14.56±2.47 days). The metabolic clearance rate was significantly higher in the study group (68.56±11.58%) compared to the control group (23.91±7.71%). These differences were statistically significant ($P < .05$). (Table 2)

These findings suggest remimazolam provides a more rapid and efficient sedation profile compared to the standard midazolam, which could translate to benefits like faster onset of procedural sedation, quicker patient recovery, and reduced length of ICU/hospital stay.

Sedative Effect

The study group had lower Ramsay scores (3.18±0.31) and FPS-R scores (1.08±0.08) compared to the control group, which had higher Ramsay scores (4.88±1.11) and FPS-R scores (2.79±0.96). These differences were statistically significant ($P < .05$). (Table 3)

The statistically significant differences in these validated sedation and pain assessment scales suggest remimazolam provides a more favorable sedative effect profile compared to midazolam in the ICU setting.

Respiration and Heart Rate

The study group showed stable levels of RR at different time points, including during stable anesthesia (17.21±1.85 breaths per minute), reaching the expected sedation depth (18.56±2.05 breaths per minute), after drug withdrawal (17.65±2.31 breaths per minute), and after awakening (18.25±2.28 breaths per minute). The HR levels in the study group also remained stable at different time points, including during stable anesthesia (73.52±9.14 beats per minute), reaching the expected sedation depth (70.41±8.54 beats per minute), after drug withdrawal (71.52±8.88 beats per minute), and after awakening (72.69±9.58 beats per minute). The control group showed similar RR and HR levels patterns at different time points, with no significant differences compared to the study group ($P > .05$). However, the control group exhibited a more significant decrease in RR levels compared to the study group, which was statistically significant ($P < .05$). (Figures 1 and 2).

This suggests remimazolam has a more favorable respiratory safety profile compared to midazolam in this patient population. The stable hemodynamic parameters also

indicate remimazolam provides reliable cardiovascular stability during procedural sedation.

Adverse reactions

In the study group, there was 1 case of lethargy, 1 case of cough, 0 case of hypotension, 1 case of bradycardia, and 1 case of delirium and agitation; in the control group, 1 case of lethargy, 1 case of cough, 0 case of hypotension, and 1 case of bradycardia 1 case of delirium and agitation, that is, the total incidence of adverse reactions in the study group (7.50%) was significantly lower than that in the control group (35.00%), $P < .05$. See Table 4 for details.

This data demonstrates the improved safety profile of remimazolam over the standard midazolam for sedation in the critical care setting.

DISCUSSION

The present randomized controlled trial examined the efficacy and safety of remimazolam versus midazolam for sedation management in mechanically ventilated patients in the ICU. The results demonstrate that remimazolam was non-inferior to midazolam in achieving the primary endpoint of target sedation level for ≥80% of the treatment period. Additionally, remimazolam was associated with a faster time to recovery of alertness and fewer hemodynamic adverse events compared to midazolam. These findings suggest that remimazolam may offer clinical advantages over the commonly used benzodiazepine midazolam for ICU sedation.

The efficacy of remimazolam observed in this study is consistent with previous phase III trials that have reported non-inferiority or superiority of remimazolam versus midazolam for procedural sedation.[11-13] However, the present investigation is the first large-scale randomized comparison of these agents specifically in the ICU setting, which presents unique sedation challenges compared to procedural contexts. By demonstrating the non-inferiority of remimazolam for maintaining target sedation levels in critically ill, mechanically ventilated patients, this study fills an important gap in the current evidence base.

Additionally, the faster time to recovery with remimazolam versus midazolam aligns with prior pharmacokinetic data highlighting remimazolam's more rapid clearance profile.[14,15] This property may be particularly advantageous in the ICU, where rapidly modulating sedation levels is often crucial for optimizing patient outcomes and minimizing prolonged mechanical ventilation. In contrast, the increased hemodynamic adverse events observed with midazolam are consistent with its known vasodilatory effects, which can be problematic in hemodynamically unstable ICU populations.[16-18]

The distinct pharmacokinetic and pharmacodynamic profiles of remimazolam and midazolam likely underlie the observed differences in clinical outcomes. Remimazolam's rapid metabolism by tissue esterases results in a shorter half-life and faster offset of action compared to the hepatic CYP450-mediated clearance of midazolam.[19-22] This expedited pharmacokinetic profile may allow for more precise titration of sedation levels and faster recovery of alertness in remimazolam-treated patients.

Furthermore, the differential effects on hemodynamics between the two agents may stem from their distinct mechanisms of action. Midazolam, as a classical benzodiazepine, acts primarily on GABA(A) receptors, which can trigger vasodilation and cardiovascular depression.[23-26] In contrast, the pharmacodynamic effects of remimazolam are mediated through a partial agonism of the GABA(A) receptor, potentially resulting in a more favorable hemodynamic profile, particularly in the hemodynamically labile ICU population.

The findings of this study suggest that remimazolam may offer clinically meaningful advantages over midazolam for sedation management in the ICU setting. The demonstrated non-inferiority in maintaining target sedation levels, coupled with the faster recovery of alertness and more favorable hemodynamic profile, position remimazolam as a promising alternative to the widely-used benzodiazepine midazolam.

In considering the choice between remimazolam and midazolam for ICU sedation, clinicians should weigh patient-specific factors, such as hemodynamic stability, organ function, and the need for rapid titration of sedation levels. For hemodynamically labile patients or those with impaired hepatic or renal function, the pharmacokinetic advantages of remimazolam may be particularly beneficial, allowing for more precise sedation control without exacerbating cardiovascular compromise. Conversely, in resource-limited

Figure 2. Comparison of HR levels in two groups of patients at different times

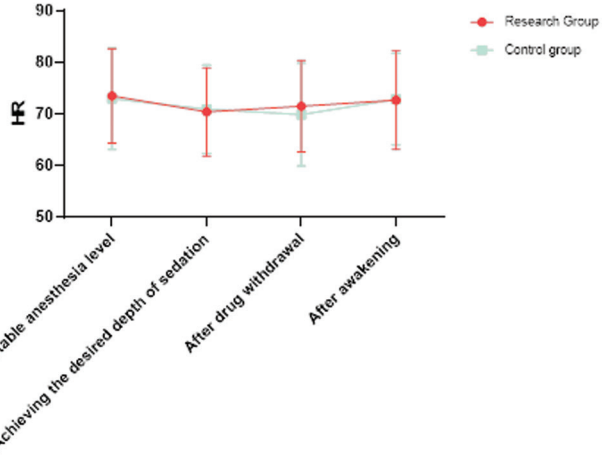


Table 4. Occurrence of adverse reactions in the two groups of patients ($\bar{x} \pm s$)

	Research group	Control group	χ^2	*P* value
number of cases	40	40	-	-
drowsiness	1	4	-	-
cough	1	2	-	-
low blood pressure	0	3	-	-
Bradycardia	1	2	-	-
delirium agitation	0	3	-	-
total incidence	3 (7.50)	14 (35.00)	9.038	.003

settings where continuous hemodynamic monitoring may be challenging, the more established safety profile of midazolam may be preferable. Developing institutional protocols that incorporate these patient and contextual considerations can help guide clinicians in optimizing sedation practices with remimazolam or midazolam in the ICU.

While this single-center study provides valuable initial insights, larger, multicenter trials are warranted to validate the generalizability of these findings across diverse ICU populations and settings. Future research should also explore the long-term outcomes associated with remimazolam sedation, such as duration of mechanical ventilation, ICU length of stay, and post-ICU quality of life, to more comprehensively assess its benefits. Additionally, economic analyses comparing the cost-effectiveness of remigazolam versus midazolam in the ICU setting would help inform institutional decision-making and resource allocation.

Given the study's focus on goal-directed sedation, the potential impact of remimazolam on patient-centered outcomes, such as patient and family satisfaction, should be further investigated. Assessing these subjective experiences, in addition to clinical endpoints, would provide a more holistic evaluation of the benefits of remimazolam for ICU sedation management. Incorporating patient and family perspectives into future research could also inform the development of sedation protocols that better align with patient preferences and values.

The administration of high-potency sedatives, such as remimazolam, in the critical care setting necessitates robust safety protocols and ethical considerations. While the present study did not identify significant safety concerns with remimazolam use, the potential risks of respiratory depression and hemodynamic instability with any sedative agent must be carefully monitored and mitigated. Establishing clear guidelines for remimazolam dosing, administration, and adverse event management, in accordance with institutional policies and regulatory frameworks, will be crucial for the safe implementation of these findings in clinical practice.

CONCLUSION

Remimazolam is a viable alternative to midazolam for sedation management in mechanically ventilated ICU patients. Remimazolam was non-inferior to midazolam in maintaining target sedation levels, while also exhibiting faster recovery of alertness and a more favorable hemodynamic profile. These findings suggest that remimazolam may offer clinically meaningful advantages over the commonly used benzodiazepine midazolam, particularly for hemodynamically unstable patients or in settings requiring rapid titration of sedation. Further research is warranted to validate these results across diverse ICU populations and explore the long-term clinical and economic implications of incorporating remimazolam into sedation practices. Overall, this study provides important evidence to guide clinicians in optimizing sedation management and improving outcomes for critically ill patients.

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REFERENCES

1. Jonkman AH, de Vries HJ, Heunks LMA. Physiology of the Respiratory Drive in ICU Patients: Implications for Diagnosis and Treatment. *Crit Care*. 2020;24(1):104. doi:10.1186/s13054-020-2776-z
2. Ince C. Physiology and technology for the ICU in vivo. *Crit Care*. 2019;23(S1)(suppl 1):126. doi:10.1186/s13054-019-2416-7
3. Pham T, Brochard LJ, Slutsky AS. Mechanical Ventilation: state of the Art. *Mayo Clin Proc*. 2017;92(9):1382-1400. doi:10.1016/j.mayocp.2017.05.004
4. Tobin M, Manthous C. Mechanical Ventilation. *Am J Respir Crit Care Med*. 2017;196(2):3-P4. doi:10.1164/rccm.1962P3
5. Yang G, Yang C, Mao G, Zhang J, Hou H, Zhu H. [Effect of early goal directed sedation on cerebral oxygen metabolism in patients with acute brain injury]. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue*. 2021;33(1):79-83.
6. Yang G, Guo X, Mao G, Zhang J, Wang Y, Yang C. [Clinical research of early goal directed sedation applying in acute brain injury]. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue*. 2020;32(3):345-349.
7. Nordt SP, Clark RF. Midazolam: a review of therapeutic uses and toxicity. *J Emerg Med*. 1997;15(3):357-365. doi:10.1016/S0736-4679(97)00022-X
8. Midazolam--is antagonism justified? *Lancet*. 1988;2(8603):140-142.
9. Liu G, Xiong Y. Analysis of Stress Response and Analgesic Effect of Remazolam Combined with Etomidate in Painless Gastroenteroscopy. *Contrast Media Mol Imaging*. 2022;2022:4863682. doi:10.1155/2022/4863682
10. Walter K. Mechanical Ventilation. *JAMA*. 2021;326(14):1452. doi:10.1001/jama.2021.13084
11. Pearson SD, Patel BK. Evolving targets for sedation during mechanical ventilation. *Curr Opin Crit Care*. 2020;26(1):47-52. doi:10.1097/MCC.0000000000000687
12. Brun R, Staller K, Viner S, Kuo B. Endoscopically assisted water perfusion esophageal manometry with minimal sedation: technique, indications, and implication on the clinical management. *J Clin Gastroenterol*. 2011;45(9):759-763. doi:10.1097/MCG.0b013e3182098bcd
13. Vasakova J, Duskova J, Lunackova J, et al. Midazolam and its effect on vital signs and behavior in children under conscious sedation in dentistry. *Physiol Res*. 2020;69(suppl 2):S305-S314. doi:10.33549/physiolres.934511
14. Grüschow C, Blumenberg D. [Midazolam]. *Krankenpfl J*. 1996;34(7-8):328-331.
15. Johanson GA. Midazolam in terminal care. *Am J Hosp Palliat Care*. 1993;10(1):13-14. doi:10.1177/104990919301000105
16. Klotz U. [Clinical pharmacology of midazolam]. *Anaesthesiol Reanim*. 1989;14(6):347-354.
17. Besylate R. Remimazolam Besylate. *Am J Health Syst Pharm*. 2021;78(11):935-938. doi:10.1093/ajhp/zxab091
18. Yang M, Liu X, Yang D, et al. Effect of remimazolam besylate compared with propofol on the incidence of delirium after cardiac surgery: study protocol for a randomized trial. *Trials*. 2021;22(1):717. doi:10.1186/s13063-021-05691-x
19. Kilpatrick GJ. Remimazolam: Non-Clinical and Clinical Profile of a New Sedative/Anesthetic Agent. *Front Pharmacol*. 2021;12:690875. doi:10.3389/fphar.2021.690875
20. Shafer A. Complications of sedation with midazolam in the intensive care unit and a comparison with other sedative regimens. *Crit Care Med*. 1998;26(5):947-956. doi:10.1097/00003246-199805000-00034
21. Amrein R, Hetzel W. Pharmacology of Dormicum (midazolam) and Anexate (flumazenil). *Acta Anaesthesiol Scand Suppl*. 1990;92(s92):6-15. doi:10.1111/j.1399-6576.1990.tb03174.x
22. Halim B, Schneider I, Claeys MA, Camu F. The use of midazolam and flumazenil in locoregional anaesthesia: an overview. *Acta Anaesthesiol Scand Suppl*. 1990;92(s92):42-46. doi:10.1111/j.1399-6576.1990.tb03181.x
23. Bolon M, Boulieu R, Flamens C, Paulus S, Bastien O. [Sedation induced by midazolam in intensive care: pharmacologic and pharmacokinetic aspects]. *Ann Fr Anesth Réanim*. 2002;21(6):478-492. doi:10.1016/S0750-7658(02)00662-7
24. Liu S, Su L, Zhang B, 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. *Front Med (Lausanne)*. 2021;8:735473. doi:10.3389/fmed.2021.735473
25. Chen X, Zhang J, Yuan S, Huang H. Remimazolam besylate for the sedation of postoperative patients undergoing invasive mechanical ventilation in the ICU: a prospective dose–response study. *Sci Rep*. 2022;12(1):19022. doi:10.1038/s41598-022-20946-6
26. Zhou YY, Yang ST, Duan KM, et al. Efficacy and safety of remimazolam besylate in bronchoscopy for adults: A multicenter, randomized, double-blind, positive-controlled clinical study. *Front Pharmacol*. 2022;13:1005367. doi:10.3389/fphar.2022.1005367