New Application of Remimazolam Tosilate in ICU Ventilation: Benefits in Reducing Iatrogenic Stress and Maintaining Stable Immune Function

Ann. Ital. Chir., 2025 96, 10: 1357–1364
https://doi.org/10.62713/aic.4183

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AIM: To evaluate the sedative effect of remimazolam tosilate and its impact on iatrogenic stress and immune function biomarkers, in order to explore its feasibility and potential advantages as a novel sedative for mechanically ventilated Intensive Care Unit (ICU) patients.
METHODS: In a retrospective analysis, 136 ICU patients who were admitted to the Second Affiliated Hospital of Jiaxing University between March and December 2022 and received mechanical ventilation were enrolled and divided into two groups based on the sedation protocol during intubation: conventional propofol group (Control group, $n = 79$) and remimazolam tosilate group (Remi group, $n = 57$). The sedation success rate and adverse reaction rate were recorded. The iatrogenic stress markers including epinephrine (E), norepinephrine (NE), and cortisol (Cor) and the T lymphocyte subpopulation including $CD3^+T\%$, $CD4^+T\%$, $CD8^+T\%$ were determined using enzyme-linked immunosorbent assay and flow cytometry assay before anesthesia induction (T0), at one week (T4), and at one month after anesthesia (T5).
RESULTS: The sedation success rate was significantly higher in the Remi group (80% [50%, 88%]) compared to the Control group (72% [43%, 85%]) ($p < 0.05$). The Remi group exhibited significantly lower Cor levels at T4 and lower E, NE, and Cor levels at T5 compared to the Control group ($p < 0.05$). The Remi group exhibited significantly higher $CD4^+T\%$ levels at T4 and lower $CD8^+T\%$ levels at T5 time points compared to the Control group ($p < 0.05$). No significant difference was found in the overall incidence of adverse events between the two groups ($p > 0.05$).
CONCLUSIONS: Compared with propofol, remimazolam tosilate may offer potential benefits in mitigating iatrogenic stress and preserving immune homeostasis, while ensuring adequate sedation during ICU mechanical ventilation. It could be a promising sedative agent for use in the ICU setting.

Keywords: remimazolam tosilate; T lymphocyte subpopulation; iatrogenic stress; ICU; ventilation

Introduction

According to the Chinese Adult Intensive Care Unit (ICU) Analgesia and Sedation Treatment Guidelines, the use of benzodiazepines and propofol is recommended for inducing sedation in ICU patients, a strategy commonly referred to as balanced propofol sedation (BPS) [1]. This approach aims to combine the favorable pharmacological properties of both agents, achieving effective sedation while potentially reducing the required dose of each drug, thereby minimizing their individual side effects [2]. Compared to monotherapy, BPS has more stable hemodynamic profiles and is associated with improved safety in long-term sedation [3–5]. However, it is important to note that propofol carries the risk of adverse effects such as temporary respiratory depression, hypotension, and bradycardia, particularly in patients with poor cardiac reserve function or low circulating blood volume [6]. While there has been considerable research on new formulations in recent years, the development cycles are lengthy, and many challenges remain [7]. Therefore, this warrants continuous exploration and innovation of new drugs and treatment protocols suitable for ICU anesthesia.

Remimazolam tosilate is a new benzodiazepine sedative, which is active at the γ-aminobutyric acid subtype A (GABAA) receptor. In China, remimazolam tosilate has been primarily approved by the National Medical Products Administration (NMPA) for sedation in adult patients undergoing painless gastroscopy. Clinical observations have demonstrated its favorable sedative and analgesic efficacy. Moreover, accumulating evidence suggests that remimazolam tosilate offers significant advantages in maintaining hemodynamic stability and minimizing respiratory depression during procedural sedation [8–10], making it particularly advantageous for elderly patients with underlying comorbidities who are less tolerant of invasive interventions. Although remimazolam tosilate has not yet received formal approval from NMPA for other indications, its potential applications in additional clinical settings are currently under active investigation. For example, its favorable hemody-

Submitted: 25 April 2025 Revised: 4 June 2025 Accepted: 6 June 2025 Published: 30 June 2025
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namic stability has led researchers to explore its use in cardiac surgery. Hu *et al*. [11] administered different doses of remimazolam tosilate in patients undergoing selective valve replacement and compared its effects with those of conventional etomidate. Their findings indicated that a dose of 0.2 mg/kg of remimazolam tosilate can not only maintain stable hemodynamic parameters but also result in fewer adverse reactions. In the context of general anesthesia with endotracheal intubation, the use of remimazolam tosilate as both an induction and maintenance agent—as a replacement to conventional propofol—has been investigated, achieving comparable success rates for anesthesia induction; however, the incidence of anesthesia-related complications was significantly lower in the remimazolam tosilate group (19% vs. 49%) [12].

While the pharmacological profile of remimazolam tosilate offers clear advantages for certain patient populations, it is not without potential drawbacks. In a single-center, prospective, randomized controlled study conducted in the setting of day surgery, researchers observed that although remimazolam tosilate was associated with faster recovery times and a lower risk of hypoxemia compared to propofol, patients exhibited episodes of resedation and drowsiness in the post-anesthesia care unit [11]. To date, studies investigating the use of remimazolam tosilate in mechanically ventilated patients remain limited. In a prospective, single-arm, single-center, open-label clinical trial, researchers conducted a preliminary evaluation of a novel ICU sedation regimen combining remimazolam tosilate with esketamine during mechanical ventilation, demonstrating its feasibility [13]. In another randomized controlled study by Tian *et al*. [14] that compared the effects of remimazolam tosilate and propofol during endotracheal intubation for mechanical ventilation, remimazolam tosilate exhibited promising potential for general anesthesia and procedural sedation, but its application in ICU sedation remains in the early stages of clinical investigation, warranting more research and data to draw definitive conclusions. The current study explored the application of remimazolam tosilate in ICU ventilation, exploring its potential advantages in stabilizing the immune system and reducing iatrogenic stress, thereby providing evidence for its potential role as an alternative sedative agent in the ICU setting.

Materials and Methods

Patients

This study is a retrospective cohort study conducted in accordance with the Declaration of Helsinki. It has been approved by the Ethics Committee of The Second Affiliated Hospital of Jiaxing University (Approval No JXEY-2022zghszh001). The sample size was calculated using the formula for comparing two sample means: $n = 2 \times ((Z_\alpha + Z_\beta)^2 \times \sigma^2)/\delta^2$, where α was set at 0.05, the estimated standard deviation for sedation success rate was 8%, 1-β was set at 0.80, and the intergroup difference was set at 5%. Based on this calculation, the minimum required sample size was 80.

A total of 136 ICU patients receiving mechanical ventilation in the Second Affiliated Hospital of Jiaxing University from March 2022 to December 2022 were enrolled. Inclusion criteria of this study are: ① aged ≥18 years, ② sequential organ failure assessment (SOFA) score ≥2, ③ invasive mechanical ventilation, and ④ American Society of Anesthesiologists (ASA) classification grade I–III. Individuals with the following conditions were excluded from this study: ① presence of significant organic disease in vital organs, ② presence of neuroendocrine disorders, ③ presence of psychiatric disorders or cognitive dysfunction, ④ respiratory tract and pulmonary infections prior to ventilation, ⑤ history of benzodiazepine sedative or opioid analgesic use within one month before admission, ⑥ pregnancy or breastfeeding, and ⑦ survival time of less than 7 days. The patients were divided into two groups based on the sedation protocol during intubation: conventional propofol group (Control group, n = 79) and remimazolam tosilate group (Remi group, n = 57). As shown in Table 1, there was no significant difference in the basic characteristics including age, gender, body mass index (BMI), acute physiology and chronic health evaluation II (APACHE II) score, ASA grade, SOFA score, intubation method, ICU primary diagnoses, and blood gas analysis parameters between groups ($p > 0.05$).

Anesthesia Methods

Both groups of patients fasted for 8 hours and refrained from drinking for 2 hours before ventilation. Intravenous access was established, and a cardiac monitor was used to continuously track mean arterial pressure (MAP), heart rate (HR), oxygen saturation (SpO_2), and respiratory rate (RR). Oxygen was administered via face mask at a flow rate of 8–10 L/min, and anesthesia induction was initiated once SpO_2 reached 100%. In the Remi group, patients received an intravenous bolus of 7 mg of remimazolam tosilate (H20190034, Jiangsu Hengrui Pharmaceuticals Co., Ltd, Suzhou, China) for induction, with administration completed within 1 minute. If the induction effect was deemed inadequate after 2 minutes, an additional dose of 2.5 mg could be administered. Upon successful induction, continuous intravenous infusion was maintained at a rate of 0.1–0.5 mg/(kg·h) to achieve the target sedation level with a Richmond agitation-sedation scale (RASS) score of –4 to 0. In the Control group, patients were induced with an intravenous bolus of 2.0 mg/kg of propofol (H20010368, Xi'an Libang Pharmaceutical Co., Ltd., Xi'an, China), administered within 30 seconds. If the induction effect was insufficient after 2 minutes, an additional dose was administered based on the patient's age and clinical condition. Following successful induction, continuous intravenous infusion was maintained at a rate of 1.5 mg/(kg·h) to achieve the target sedation level with a RASS score of –4 to 0.

Table 1. Basic characteristics of patients between Control and Remi groups.

Characteristics	Control (n = 79)	Remi (n = 57)	t/χ^2/Z	p
Age (years)	38 (27, 46)	35 (27, 42)	1.144	0.253
Gender, n	38/41	30/27	0.272	0.602
BMI (kg/m^2)	22.9 ± 2.7	22.5 ± 2.7	0.852	0.395
APACHE II (score)	15 (7, 18)	13 (8, 20)	1.435	0.151
ASA grade, n (%)			0.207	0.836
I	9 (11.39)	9 (15.79)		
II	55 (69.62)	36 (63.16)		
III	15 (18.99)	12 (21.05)		
SOFA score	4 (2, 5)	4 (2, 6)	0.919	0.358
Intubation method, n (%)			0.142	0.707
Endotracheal intubation	51 (64.56)	35 (61.40)		
Tracheostomy	28 (35.44)	22 (38.60)		
ICU primary diagnoses, n (%)			7.230	0.065
Heart failure	21 (26.58)	15 (26.32)		
Respiratory failure	35 (44.30)	15 (26.32)		
Septic shock	20 (25.32)	20 (35.09)		
Others	3 (3.80)	7 (12.28)		
Blood gas analysis parameters				
pH	7.4 (7.4, 7.5)	7.4 (7.3, 7.5)	1.109	0.267
$PaCO_2$ (mmHg)	46 (37, 51)	44 (34, 50)	1.302	0.193
Lactate (mmol/L)	1.8 (1.6, 4.2)	1.9 (1.6, 4.5)	1.499	0.134

Abbreviations: APACHE II, acute physiology and chronic health evaluation II; ASA, American Society of Anesthesiologists; BMI, body mass index; ICU, intensive care unit; $PaCO_2$, partial pressure of carbon dioxide; pH, potential of hydrogen; SOFA, sequential organ failure assessment.

Observation Indicators

The primary outcome of this study is sedation success rate. The secondary outcomes include MAP, HR, RR, SpO_2, epinephrine (E), norepinephrine (NE), and cortisol (Cor), T lymphocyte subpopulation percentages, and adverse reactions.

Sedative Effects

RASS scores were dynamically monitored starting at the initiation of anesthesia induction. The assessment time points included 10 min, 30 min, 1 h, 2 h, 4 h, and 6 h post-induction, followed by every 2 h thereafter until the cessation of sedation. The primary outcome of this study is sedation success rate, which is defined as the percentage of time within the target sedation range (RASS score range) during the sedation period without the use of propofol for rescue sedation, relative to the total sedation time during the study's drug administration period. Additionally, MAP, HR, RR, and SpO_2 values were recorded at pre-anesthesia induction (T0), 3 min after anesthesia induction (T1), 10 min after anesthesia induction (T2), and 10 min after extubation (T3).

Iatrogenic Stress

Fasting cubital vein blood before anesthesia induction (T0), at one week (T4), and at one month after anesthesia (T5) induction was obtained from each patient, and serum was separated to determine the levels of stress markers including E, NE, and Cor using enzyme-linked immunosorbent assay (ELISA). The ELISA kits for E (JL11628), NE (JL15081), and Cor (JL12377) were all purchased from Shanghai Jianglai Biotechnology Co., Ltd. (Shanghai, China).

Immune Function

Fasting cubital vein blood (anticoagulated) before anesthesia induction (T0), at one week (T4), and at one month after anesthesia induction (T5) was obtained each patient. Every sample collected was divided equally into two tubes labeled A and B. According to the instructions, 10 µL of fluorescently labeled monoclonal antibodies (labeled A) and isotype controls (labeled B) were added. After incubation for 20–30 min, 2 mL of lysis buffer was added for hemolysis, and the samples were mixed and incubated in the dark for 10 min. After washing, the T lymphocyte subpopulation ($CD3^+$T%, $CD4^+$T%, $CD8^+$T%) percentages were analyzed using a flow cytometer (BD FACSCanto™ II, Becton, Dickinson and Company, Franklin Lakes, NJ, USA). The antibodies (CD4/CD8/CD3 Monoclonal Antibody, FITC/PE/PE-Cy5 Conjugated, CSB-MA826490) used in this study were all purchased from CUSABIO (Wuhan, China).

Table 2. Comparison of MAP, HR, RR and SpO_2 between Control and Remi groups (mean ± SD).

Indexes	Time	Remi (n = 57)	Control (n = 79)
MAP (mmHg)	T0	122.36 ± 14.20	123.91 ± 15.06
	T1	104.25 ± 15.22*	95.54 ± 16.26
	T2	105.55 ± 15.25*	96.15± 15.24
	T3	110.64 ± 14.16*	99.65 ± 14.36
HR (beats/min)	T0	73.54 ±10.05	72.88 ± 13.26
	T1	73.29 ± 11.08	70.66 ± 11.26
	T2	72.88 ± 10.46	71.25 ± 11.44
	T3	73.55 ±8.59	72.65 ± 9.39
SpO_2 (%)	T0	99.79 ± 0.52	99.38 ± 1.15
	T1	98.8 ± 1.88	97.97 ± 2.33
	T2	99.13 ± 1.69	98.69 ± 2.75
	T3	99.16 ± 0.91	98.87 ± 8.17
RR (beats/min)	T0	17.55 ± 2.12	17.29 ± 2.23
	T1	17.23 ± 2.46	16.95 ± 2.06
	T2	17.39 ± 2.36	17.28 ± 2.93
	T3	17.59 ± 2.22	16.73 ± 1.84

Notes: T0, baseline (pre-anesthesia) induction; T1, 3 min post-anesthesia induction; T2, 10 min post-anesthesia induction; T3, 10 min post-extubation. *$p < 0.05$ compared to Control group.
Abbreviations: HR, heart rate; MAP, mean arterial pressure; RR, respiratory rate; SpO_2, oxygen saturation.

Adverse Reactions

The incidences of anesthesia-related adverse reactions including bradycardia, hypotension and respiratory depression were recorded. Bradycardia is defined as HR <60 beats/min lasting more than 5 minutes; hypotension refers to MAP <60 mmHg lasting more than 5 minutes; and respiratory depression is defined as spontaneous RR <12 breaths/min lasting more than 5 minutes, or SpO_2 <90% lasting more than 5 minutes.

Statistical Analysis

The data were analyzed using SPSS 25.0 statistical software (IBM Corporation, Armonk, NY, USA). Continuous variables with normally distribution (assessed with Shapiro–Wilk test) are expressed as mean ± standard deviation (mean ± SD). Independent samples t-test was used for between-group comparisons at individual time points, while repeated measures analysis of variance (ANOVA) was used to assess differences across multiple time points, followed by Bonferroni-adjusted post hoc tests and simple effects analyses where appropriate. Non-normally distributed continuous variables are expressed as median (P_{25}, P_{75}). Friedman test combined with post hoc Wilcoxon signed-rank test was used to assess within-group differences across multiple time points, while the Mann–Whitney U test was performed for between-group comparisons at each time point. Categorical data are presented as percentages or constituent ratios, and the chi-square test was used for between-group comparisons. A p-value of less than 0.05 was considered statistically significant.

Results

Sedative Effects

The success rate of sedation was significantly higher in the Remi group (80% [50%, 88%]) compared to the Control group (72% [43%, 85%]) (z = 2.349, p = 0.019). The repeated measures ANOVA analysis results revealed there was no significant difference in HR (F_{group} = 2.367, p_{group} = 0.125; F_{time} = 0.484, p_{time} = 0.694; $F_{group*time}$ = 0.219, $p_{group*time}$ = 0.883), SpO_2 (F_{group} = 2.512, p_{group} = 0.114; F_{time} = 2.506, p_{time} = 0.058; $F_{group*time}$ = 0.142, $p_{group*time}$ = 0.935) and RR (F_{group} = 3.573, p_{group} = 0.060; F_{time} = 0.584, p_{time} = 0.626; $F_{group*time}$ = 0.685, $p_{group*time}$ = 0.562) between groups. The repeated measures ANOVA analysis results revealed that both group (F_{group} = 27.822, $p_{group} < 0.001$) and time factors (F_{time} = 68.744, $p_{time} < 0.001$) affected MAP significantly, with a significant group×time interaction ($F_{group*time}$ = 4.773, $p_{group*time}$ = 0.003). Both groups showed an initial decrease followed by an increase in MAP after anesthetic induction, and the Remi group maintained higher MAP levels at T1–T3 compared to the Control group (p_1 = 0.002, p_2 = 0.001, $p_3 < 0.001$), suggesting a better hemodynamic stability in the Remi group (Table 2).

Adverse Reactions

In the Remi group, adverse events included 5 cases of hypotension, 5 cases of bradycardia, and 1 case of respiratory depression (total 11 cases; incidence rate 19.30%). The Control group showed 13 cases of hypotension, 2 cases of bradycardia, and 2 cases of respiratory depression (total 17 cases; incidence rate 21.50%). No significant difference was found in the overall incidence of adverse events between the two groups (19.30% vs 21.50%, χ^2 = 0.100, p = 0.752). For patients with hypotension and bradycardia, medications were reduced or discontinued for 10 min, or atropine or norepinephrine was administered to maintain HR ≥60 beats per minute and MAP ≥60 mmHg. For patients with respiratory depression, suctioning was performed, or the ventilator settings were adjusted to volume-controlled ventilation (VCV) or pressure-controlled ventilation (PCV) mode to maintain a breathing rate (BR) ≥12 breaths/min and arterial SpO_2 ≥90%.

Iatrogenic Stress

At T0, there were no significant differences in E, NE, or Cor levels between the Remi and Control groups ($p > 0.05$). At T4, the Remi group showed significantly increased NE levels while the Control group demonstrated significant elevations in both NE and Cor levels compared to T0 ($p < 0.05$). At T5, all parameters in the Remi group returned to levels comparable to T0 ($p > 0.05$), whereas the Control group maintained elevated E, NE, and Cor levels versus T0

($p < 0.05$). The Remi group exhibited significantly lower Cor levels at T4 and lower E, NE, and Cor levels at T5 compared to the Control group ($p < 0.05$) (Table 3).

Immune Function

Repeated measures ANOVA analysis results revealed there was no significant difference in $CD3^+T\%$ ($F_{group} = 1.876$, $p_{group} = 0.172$; $F_{time} = 0.933$, $p_{time} = 0.394$; $F_{group*time} = 0.173$, $p_{group*time} = 0.842$) between the two groups. The analysis revealed a significant main effect of group on $CD4^+T\%$ ($F_{group} = 6.171$, $p_{group} = 0.013$), but there was no significant effect of time ($F_{time} = 1.619$, $p_{time} = 0.199$), and the group×time interaction was not statistically significant ($F_{group*time} = 0.957$, $p_{group*time} = 0.385$). Both group ($F_{group} = 11.135$, $p_{group} < 0.001$) and time factors ($F_{time} = 30.822$, $p_{time} < 0.001$) affected $CD8^+T\%$ significantly, with no significant group×time interaction ($F_{group*time} = 0.972$, $p_{group*time} = 0.379$). Pairwise comparisons revealed that the Remi group exhibited significantly higher $CD4^+T\%$ levels at the T4 time point compared to the Control group while lower $CD8^+T\%$ levels at the T5 time point ($p = 0.031$, 0.005) (Table 4).

Discussion

With the ongoing evolution of pain and sedation management in the ICU, novel analgesic and sedative agents are being introduced to clinical practice. Remimazolam tosilate, a newly developed ultra-short-acting benzodiazepine sedative, has demonstrated safety and good tolerability in healthy Chinese subjects. Phase III clinical trials have indicated that remimazolam tosilate provides superior sedative effects compared to midazolam, with a lower incidence of hypotension [15]. Additionally, when compared to propofol, remimazolam tosilate exhibits significantly reduced rates of hypotension, injection-site hypoxemia, and injection-site pain [8,16]. Pharmacokinetic studies revealed that remimazolam tosilate is rapidly metabolized by non-specific tissue esterases into inactive carboxylic acid metabolites, allowing for safe use in patients with impaired liver or kidney function [17]. Furthermore, long-term or high-dose infusion does not result in drug accumulation or delayed effects. These unique pharmacological properties suggest that remimazolam tosilate may offer significant advantages for sedation in the ICU setting.

Currently, limited studies have investigated the application of remimazolam tosilate in ICU settings, with even fewer data available regarding its use in cases requiring mechanical ventilation. Yao *et al.* [18] conducted a comparative study between remimazolam tosilate, propofol, and midazolam to assess their safety and efficacy for long-term sedation in mechanically ventilated patients within the ICU. The findings demonstrated that remimazolam tosilate provides superior sedative effects without increasing total hospitalization costs, adverse event incidence, or mortality rates among mechanically ventilated patients. Tang *et al.* [19] also pointed out that remimazolam tosilate is effective and

Table 3. Comparison of E, NE, Cor between Control and Remi groups [median (P_{25}, P_{75})].

Groups	Time	n	E (pg/mL)	NE (pg/mL)	Cor (μg/dL)
Remi	T0	57	62.35 (50.36, 75.63)	125.25 (80.52, 152.52)	15.25 (5.25, 20.53)
	T4	57	67.52 (53.52, 90.95)	142.35 (82.52, 169.77)*	13.52 (6.77, 18.52)$^{\#}$
	T5	49	62.77 (49.52, 85.21)$^{\#}$	130.52 (88.63, 164.54)$^{\#}$	15.33 (5.85, 19.41)$^{\#}$
Control	T0	79	64.01 (50.25, 79.52)	125.56 (90.25, 150.22)	15.25 (5.25, 20.53)
	T4	79	70.30 (55.52, 85.52)	147.55 (105.21, 187.22)*	19.29 (7.24, 32.52)*
	T5	63	72.52 (60.21, 105.32)*	135.44 (100.22, 175.22)*	17.71 (5.25, 22.53)*

Notes: T0, baseline (pre-anesthesia) induction; T4, at one week post-anesthesia induction; T5, at one month post-anesthesia induction. *$p < 0.05$ compared to T0, $^{\#}p < 0.05$ compared to Control group.
Abbreviations: Cor, cortisol; E, epinephrine; NE, norepinephrine.

Table 4. Comparison of T lymphocyte subpopulation percentages between Control and Remi groups (mean ± SD).

Groups	Time	n	$CD3^+T\%$	$CD4^+T\%$	$CD8^+T\%$
Remi	T0	57	66.25 ± 9.26	47.85 ± 16.24	12.12 ± 3.45
	T4	57	65.25 ± 11.52	48.52 ± 15.63$^{\#}$	15.52 ± 3.88*$^{\#}$
	T5	49	64.21 ± 10.58	46.25 ± 13.51$^{\#}$	14.50 ± 3.06$^{\#}$
Control	T0	79	64.86 ± 10.75	46.85 ± 15.29	13.15 ± 3.01
	T4	79	62.52 ± 12.54	42.41 ± 16.52*	16.26 ± 4.18*
	T5	63	63.25 ± 16.58	41.11 ± 17.20*	16.52 ± 4.25*

Notes: T0, baseline (pre-anesthesia) induction; T4, at one week post-anesthesia induction; T5, at one month post-anesthesia induction. *$p < 0.05$ compared to T0, $^{\#}p < 0.05$ compared to Control group.

safe for long-term sedation in mechanically ventilated patients compared with propofol. In our study, we found the sedation success rate was significantly higher in the Remi group compared to the Control group, while there is no significant difference in the overall incidence of adverse events between the two groups. These findings are generally consistent with previous reports, collectively supporting that remimazolam tosilate enhances sedation efficacy during mechanical ventilation while maintaining safety. However, our study uniquely demonstrated that remimazolam tosilate showed advantages only in stabilizing MAP, with no statistically significant differences observed in HR, SpO_2, or RR stabilization when compared to the Control group. The results of this study indicate that the principal advantage of remimazolam tosilate lies in its capacity to maintain hemodynamic stability. No significant differences were observed between remimazolam tosilate and propofol regarding the stabilization of RR and HR. Although this finding may differ from some previous reports [18,19], it is important to note that much of the existing literature is based on studies with limited sample sizes. As such, this study did not attempt an in-depth exploration of these discrepancies. Further investigation through future randomized controlled trials is warranted.

Given the severity of illness, most ICU patients often need invasive treatments like those involving breathing tubes, which can sometimes cause iatrogenic stress and further compromise the immune system [20]. Therefore, in addition to assessing conventional sedative effects, this study also analyzed patients' E, NE, Cor levels and T lymphocyte subpopulations to further investigate whether remimazolam tosilate possesses pharmacological advantages in reducing iatrogenic stress and stabilizing immune function. The results showed there were no significant differences in E, NE, or Cor levels between the Remi and Control groups at T0. The Remi group exhibited significantly lower Cor levels at T4 and lower E, NE, and Cor levels at T5 compared to the Control group. Both E and NE, released from the adrenal medulla and sympathetic nerve terminals respectively, serve as key biochemical indicators of sympathetic-adrenal medullary system activation [21]. In response to physiological stressors including trauma, surgical intervention, and infection, the human body rapidly activates the Sympatho-Adreno-Medullary (SAM) system as part of the neuroendocrine stress response [22]. Thus, circulating levels of E and NE represent highly sensitive and specific biomarkers for quantifying iatrogenic stress [23]. The distinct release patterns of these catecholamines reflect their complementary roles, with NE primarily functioning as a neurotransmitter in sympathetic nerve synapses, while E acting predominantly as a hormone when secreted into systemic circulation by the adrenal medulla [24]. Their combined measurement provides a comprehensive assessment of the body's stress response to iatrogenic stress. Cor, a glucocorticoid secreted by the zona fasciculata of the adrenal cortex, serves as the key effector molecule of the hypothalamic-pituitary-adrenal (HPA) axis and plays a critical role in the body's stress response [25]. It enhances vascular sensitivity to catecholamines (E/NE), thereby helping maintain blood pressure and hemodynamic stability. While short-term elevation of Cor can improve alertness, chronically high levels may lead to anxiety, depression, and memory impairment [26–28]. Prolonged elevated Cor levels may also disrupt HPA axis function. To date, no research has specifically investigated the impact of remimazolam tosilate on stress responses induced by mechanical ventilation. However, in a study of elderly patients receiving painless endoscopic retrograde cholangiopancreatography, Tian *et al*. [29] reported significantly reduced postoperative 24-hour levels of E, NE and Cor in the remimazolam tosilate group versus the propofol group, indicating its potential advantage in mitigating surgical stress. Nevertheless, the underlying mechanisms by which remimazolam tosilate anesthesia may reduce surgical stress compared to propofol remain unclear. Researchers have noted that sympathetic nerve activity is predominant during propofol anesthesia, whereas parasympathetic nerve activity predominates during remimazolam-induced anesthesia [30]. Given that excessive sympathetic activation is a key component of the surgical stress response [31], it has been hypothesized that remimazolam's milder modulation of the sympathetic nervous system may help maintain autonomic balance and contribute to a more stable stress response.

Significant variations were also observed in the $CD4^+$T% and $CD8^+$T%. Compared to the Control group, the Remi group exhibited significantly higher $CD4^+$T% levels at T4 while lower $CD8^+$T% levels at T5. Major trauma triggers a complex immune response initiated by tissue damage, resulting in massive release of endogenous damage-associated molecular patterns (DAMPs), which activate both the immune system and complement system through Toll-like receptors (TLRs) and receptors for advanced glycation end products (RAGE). The subsequent surge of inflammatory cytokines leads to clinical manifestations of non-infectious systemic inflammatory response syndrome. To counteract potential excessive immune responses, the body simultaneously initiates negative feedback regulatory mechanisms, including the release of anti-inflammatory cytokines. However, an imbalance between pro-inflammatory and anti-inflammatory regulatory mechanisms may result in prolonged immunosuppressive states [32,33]. Previous studies have indicated that during traumatic events, the proportion of Th17 cells and $CD4^+$T cells in the body increases sharply. These cells play a crucial role in assisting the immune system's anti-inflammatory response, promoting tissue repair, and preventing infections [34,35]. Our research results indicate that remimazolam tosilate has a favorable effect in stabilizing the immune system and alleviating immunosuppression.

Conclusions

Compared with propofol, remimazolam tosilate may offer potential benefits in mitigating iatrogenic stress and preserving immune homeostasis, while ensuring adequate sedation during ICU mechanical ventilation. It could be a promising sedative agent for use in the ICU setting. However, as this study is a retrospective analysis, it has two inherent limitations. First, some variables were missing, such as disease types, surgical methods, and duration of ICU stay; leaving these factors unaccounted for in the analysis may lead to potential and unrecognized differences in baseline characteristics between the two groups. Second, the relatively small sample size may introduce bias due to individual variability. Therefore, the conclusions should be interpreted with caution and further validated in multicenter prospective controlled trials with larger sample sizes.

Availability of Data and Materials

The data analyzed are available from the corresponding author upon reasonable request.

Author Contributions

MYS and CYL conceived and designed the study. BZ were in charge of data collection and analysis. MYS wrote the original draft. All authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study is in accordance with the Declaration of Helsinki. It has been approved by the Ethics Committee of The Second Affiliated Hospital of Jiaxing University (Approval No JXEY-2022zghszh001). The informed consent was obtained from the participating patients or their relatives.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

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