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Effect of remimazolam besylate on elderly patients with mechanical ventilation: a single-center randomized controlled study

Yihui Li[1], Yamin Yuan[1], Jinquan Zhou[1] and Li Ma[1*]

Abstract

Objective To compare the clinical prognosis and offline strategy differences between remimazolam besylate and propofol for sedation in elderly patients undergoing mechanical ventilation.

Methods This single-center prospective randomized controlled study included elderly patients requiring invasive mechanical ventilation in the Emergency Intensive Care Unit (EICU) at The Second Hospital & Clinical Medical School of Lanzhou University from October 2021 to October 2023. Patients were randomly assigned to the remimazolam group (experimental) or propofol group (control) using respective sedation treatments. Clinical treatments remained uninfluenced. After improvement and meeting offline conditions, a cluster offline strategy guided evaluation and treatment. Data on patient demographics, vital signs, clinical outcomes, and adverse events were recorded.

Results There were no significant differences in invasive mechanical ventilation time (107.50 vs. 104.50 h, $P=0.969$), ICU stay (7 days for both groups, $P=0.603$), in-hospital mortality (22.5% vs. 15.0%, $P=0.39$), or 28-day survival rate (69.57% vs. 69.23%, $P=0.98$) between the control and experimental groups. Tracheotomy was performed in 5 control group patients and 2 experimental group patients ($P=0.235$). Sedation-related delirium rates were 7.5% (control) and 5.0% (experimental) ($P=0.613$).

Conclusions Remimazolam besylate and propofol showed no significant differences in safety or effectiveness for elderly patients undergoing mechanical ventilation when using the clustered offline strategy.

Keywords Elderly patients, Critically ill patients, Mechanical ventilation, Sedation, Treatment, Remimazolam

Introduction

Populationaging is a global issue, increasing the proportion of elderly patients in intensive care units (ICUs). Due to physiological decline, elderly patients face weakened organ function, presenting challenges in critical care, especially mechanical ventilation management [1–3]. Multiple chronic diseases and reduced physiological reserve increase the risk of complications and difficult weaning during mechanical ventilation [4].

Mechanical ventilation supports or replaces spontaneous breathing, ensures gas exchange, and reduces respiratory muscle workload [5]. This technique is crucial for elderly patients, who are more susceptible to acute respiratory failure due to physiological decline and multiple comorbidities [6]. While non-invasive mechanical ventilation (NIMV) may be effective for some patients, a significant number of critically ill elderly patients require invasive mechanical ventilation (IMV) to stabilize their condition. IMV provides more precise control over ventilation parameters, ensuring adequate oxygenation and carbon dioxide removal when NIMV

*Correspondence:
Li Ma
ery_mali@lzu.edu.cn
[1] Department of Critical Care Medicine, The Second Hospital & Clinical Medical School, Lanzhou University, Lanzhou City 730030, Gansu Province, China

is insufficient or contraindicated. However, IMV also poses challenges, such as patient-ventilator asynchrony, discomfort, and the risk of ventilator-associated complications, underscoring the need for effective sedation strategies. Proper sedation during IMV not only enhances patient comfort and compliance but also minimizes potential adverse effects, such as ventilator-induced lung injury and prolonged mechanical ventilation. Developing individualized sedation strategies is critical to balancing the benefits of IMV while mitigating its risks in elderly patients. [7].

Opioid receptor antagonists and benzodiazepines are widely used for analgesia and sedation [8]. Elderly patients have decreased organ function and slower drug metabolism, increasing risks of prolonged ventilation and cardiovascular events [4, 9, 10]. Ideal drugs should have rapid onset, fast metabolism, and minimal cardiac impact. Propofol is widely used for sedation in ICU (Intensive Care Unit) patients undergoing mechanical ventilation, including postoperative and trauma cases [11]. Compared to midazolam, propofol achieves similar sedation levels with shorter ventilation and extubation times, indicating quicker recovery and effective sedation across diverse patient groups [12, 13]. Propofol meets some criteria but has cardiovascular limitations [14]. Remimazolam, a new ultra-short-acting benzodiazepine, offers rapid onset and metabolism, potentially addressing limitations associated with propofol and midazolam [15]. Remimazolam has been approved in China, Japan, and South Korea for general anesthesia [16–18]. It is also approved in Belgium for ICU sedation in COVID-19 patients [19].

As a new type of benzodiazepine sedative, remimazolam besylate has been mainly used in anesthesia surgery, especially in endoscopic surgery. In recent years about a small amount of the drug application in intensive care units. Some studies have explored the use of benzodiazepids and propofol in critically ill patients. For example, a randomized controlled study published in Critical Care in 2022 explored the effect of midazolam compared with propofol in the sedation of adult patients with mechanical ventilation: the safety and efficacy of the two drugs were similar [20]. At present, there is no relevant study on the application of remimazolam besylate in elderly patients in the intensive care unit.

Therefore, this study hypothesizes that remimazolam, with its rapid onset, short duration, and favorable safety profile, is a viable alternative to propofol for sedation in elderly ICU patients undergoing mechanical ventilation. This study aims to evaluate and compare the efficacy and safety of propofol and remimazolam in this patient population. The primary outcome of this study is in-hospital mortality, while secondary outcomes include ICU length of stay, invasive mechanical ventilation time, and 28-day survival rate. These outcomes will provide a comprehensive assessment of the clinical effectiveness and safety of these two drugs, contributing to evidence-based sedation strategies for critically ill elderly patients.

Methods

Study subjects

This was a single-center prospective randomized controlled study. Elderly patients requiring invasive mechanical ventilation admitted to the Emergency intensive care unit (EICU) of Lanzhou University Second Hospital from October 2021 to October 2023 were enrolled. Figure 1 shows the flowchart of this study.

The inclusion criteria were followed: (1) Age $\geq$ 60 years old; (2) Invasive mechanical ventilation for $\geq$ 20 h; (3) Sedative and analgesic drugs should be used.

The exclusion criteria were followed: (1) patients with brain diseases involving the respiratory center and unable to maintain spontaneous breathing rhythm; Patients with respiratory muscle weakness caused by neuromuscular diseases; And those with severe damage to lung structures that cannot sustain life and require organ transplantation; (2) patients with end-stage malignant tumors; Other patients who are critically ill and have reached the end stage. (3) previous diagnosis of depression or schizophrenia; Patients who were allergic to peanut or soybean, or to remimazolam besylate and other components of propofol emulsion injection.

This research is based on the declaration of Helsinki and national and institutional standards, has passed the hospital ethics committee review (Approval number: 2020A-276), before the patients' informed consent and immediate family members.

Sample size

The primary indicator of this research is hospital mortality rates. The significance level is set at 0.025 for a one-sided test, with a power of 80%. Based on prior research comparing benzodiazepines and propofol in adult patients with severe overall prognosis, this study hypothesizes a difference in in-hospital mortality rates between patients treated with remimazolam besylate and those treated with propofol. The estimated mortality rates for the two independent groups are 23.3% for the experimental group and 16.7% for the control group. Both groups were designed with a 1:1 ratio, and the dropout rate was estimated at 10%. Using these parameters, the required sample size for each group was calculated, resulting in a total sample size of 80 patients.

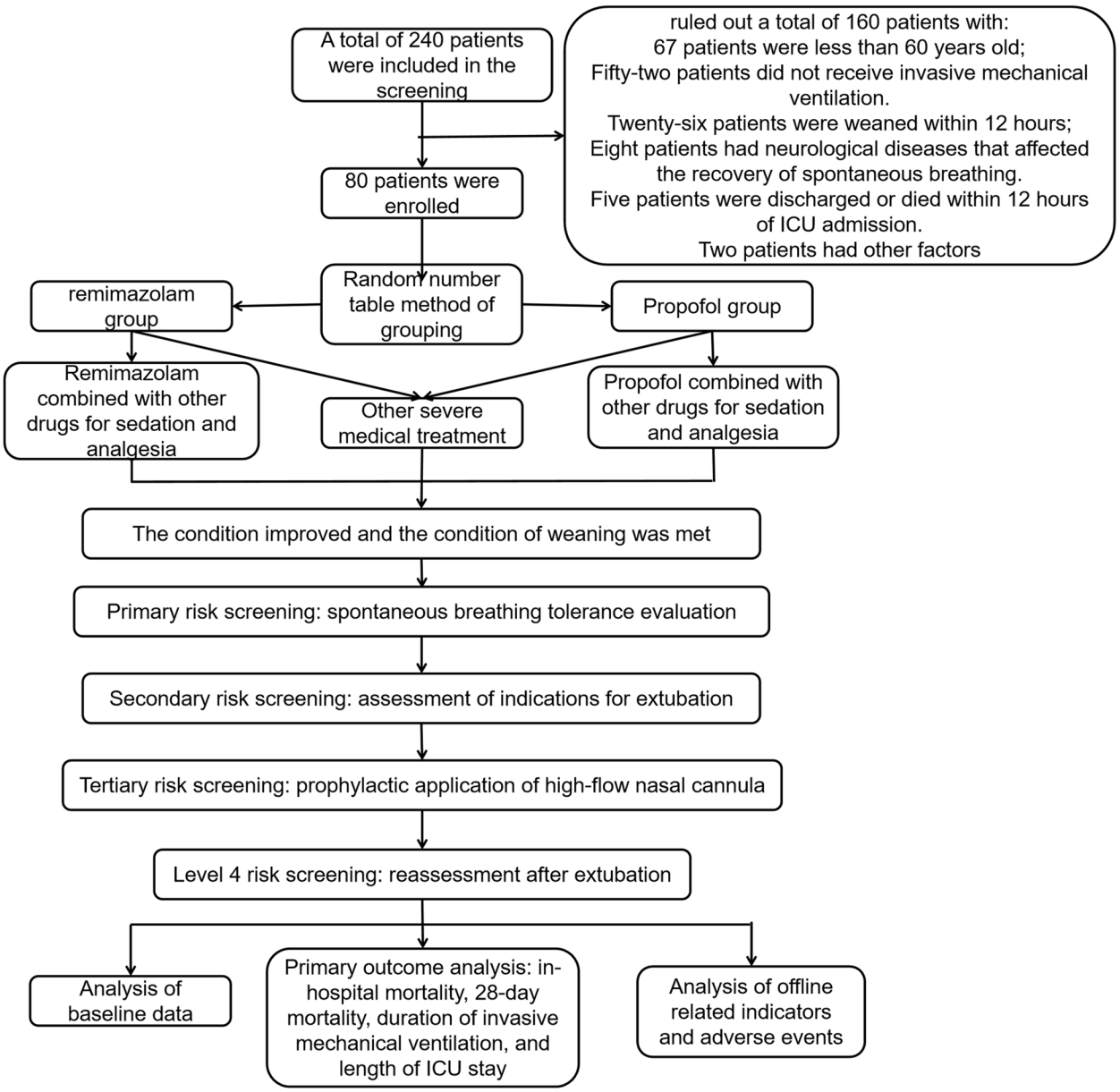

Fig. 1 CONSORT diagram of the study

Patients were randomly assigned to either the remimazolam group (experimental group) or the propofol group (control group) in a 1:1 ratio using the random number table method (Fig. 1).

Experimental and clinical intervention

Study groups

Patients were randomly divided into two groups: the experimental group (remimazolam group) and the control group (propofol group), with each group receiving corresponding sedation treatment. Sedation depth was assessed using the Richmond Agitation and Sedation Scale (RASS), with a target range of 0 to 1 points. Pain levels were evaluated using the Critical-Care Pain Observation Tool (CPOT), with a target value of < 3.

Interventions

Patients in the experimental group received remimazolam (Yichang F Pharmaceutical Co., Ltd., China) for sedation. The drug solution was prepared by diluting 100 mg of remimazolam in 50 ml of physiological saline.

For agitation, an initial bolus dose of 0.02–0.05 mg/kg was administered intravenously, either as a single dose or in multiple doses. Once adequate sedation was achieved, a continuous infusion was started at 0.1 mg/kg/h using a micro-infusion pump, with a maximum infusion rate of 0.5 mg/kg/h. Patients in the control group received propofol emulsion (Corden Pharma S.P.A, Switzerland). For agitation, an initial bolus dose of 0.5–1 mg/kg was administered intravenously, followed by a continuous infusion at 0.3–0.5 mg/kg/h using a micro-infusion pump, with a maximum infusion rate of 4 mg/kg/h.

If sedation requirements were not met in either group after dose adjustments, adjunctive sedation with dexmedetomidine (Jiangsu Hengrui Medicine Co., Ltd., China) was administered at an infusion rate of 0.1–0.5 μg/kg/h. In the propofol group, some patients also received midazolam during the early treatment phase, with an infusion rate of 0.02–0.1 mg/kg/h. All sedative medications were discontinued at least 24 h before weaning evaluation.

For analgesia, both groups received fentanyl at an infusion rate of 0.05–1 μg/kg/min. If further pain relief was needed, morphine (3–10 μg/kg/h) or butorphanol (0.2–0.5 mg/h) was added. All analgesic drugs were discontinued at least 2 h before the evaluation for spontaneous breathing trials.

Mechanical ventilation modes and parameters were determined by the attending physician and treatment team based on the patient's age, disease severity, and lung function. Adjustments were made dynamically according to vital signs, blood gas analyses, and respiratory mechanics indices.

Cluster offline strategy

The cluster offline strategy is a systematic approach designed to safely transition patients from mechanical ventilation to spontaneous breathing while minimizing risks associated with extubation. This method incorporates multiple levels of risk assessment and preventive interventions, ensuring a structured and individualized process for weaning patients from mechanical support. The strategy was chosen for this study because elderly patients undergoing mechanical ventilation often face significant challenges during weaning, including high risks of extubation failure, respiratory muscle fatigue, and complications such as re-intubation. By implementing a cluster offline strategy, the study aims to improve patient outcomes and ensure a safer and more efficient weaning process.

1) Weaning and extubation condition assessment: Following cessation of sedative and analgesic medications, the patient must meet the following criteria: a) resolution of underlying disease causing respiratory failure without any new potentially serious lesions; b) improvement in oxygenation with FiO2 ≤ 40%, PeeP ≤ 5 cm H_2O, $PaO_2/FiO_2 \geq 150–200$; c) stable hemodynamics with heart rate < 120 times/min, mean arterial pressure maintained at satisfactory levels (according to patient's condition and basic situation), minimal use or no use of vasoactive drugs, dopamine dosage < 5 ug/kg/min; d) return of spontaneous breathing and clear consciousness with cooperation; e) presence of cough response; f) stable acid–base balance.
2) Level 1 risk assessment: Spontaneous breathing tolerance evaluation involves weaning screening followed by treatment with PS mode (FiO_2 35%, PeeP 5 cm H_2O, PS:10–12 cm H2O), CPAP (FiO_2 35%, PeeP 5 cm H_2O), or T-tube weaning for a duration of thirty minutes. Failure to pass this test is indicated by any one or more of the following conditions: respiratory rate > 35 beats /min over five minutes; rapid shallow breathing index (RSBI) > 100/min; oxygen saturation < 88% lasting for more than five minutes; a rise in baseline levels greater than twenty percent or respiratory rate > 120 times/min during testing; systolic blood pressure < 90 mmHg or > 180 mmHg for more than five minutes; new onset acute chest pain or changes in electrocardiogram readings; dyspnea,anxiety, or sweating.

If successful completion occurs during spontaneous breathing tolerance evaluation, then patients may proceed to level two risk assessment while those who fail will continue mechanical ventilation until reassessment on the next day.

Secondary risk assessment: decannulation indications evaluation: patients with spontaneous breathing trial, after the following any one thing that does not meet, as extubation failure assessment: a) no serious disturbance of consciousness; b). cough reflex; c). gag reflex; d). cycle stability (such as HR < 120 times/min, dopamine dosage < 5 ug/kg/min; No ECG of myocardial ischemia, without severe arrhythmia); e). R R < 35 times/min; f). fast shallow breathing index (RSBI) < 100 times/min; g). the air leakage test positive.

After the extubation assessment passed, the ventilator could be removed and entered the tertiary risk assessment. If the failure occurred, mechanical ventilation could be continued until reassessment the next day.

4) Three levels of risk assessment: the preventive use of nasal high flow oxygen therapy indications evaluation: meet the following any one, after the withdraw machine preventive use of nasal high flow oxygen

therapy: a). heart failure is the reason of endotracheal intubation; b). the illness severity (APACHE II score > 12 points).

5) Level 4 risk assessment: after extubation judgment within 48 h after extubation given oxygen cure whether can meet the demand of patients with ventilation, evaluate whether need intubation again: a). R R > 35 times/min for more than 5 min; b).saao < 88% for more than 5 min; c). R > 120 times/min, or a testing baseline levels increased by more than 20%; d). systolic blood pressure < 90 MMHG or a lower limit above 30 MMHG lasts for 5 min or abnormal ECG; e). onset of chest pain; f). dyspnea, anxiety or sweating.

Any a ventilation adjuvant therapy, such as patients have used the traditional oxygen therapy is first determining the nasal high flow oxygen therapy indications and contraindications, there are indications immediate applications, such as nasal high flow line treatment failure immediately endotracheal intubation and has a breathing machine auxiliary support treatment.

Data measurement

1) Baseline data analysis: patients' gender, age, basic disease, the group of heart rate, breathing, systolic blood pressure, body temperature, APACHE—II, sequential organ failure assessment (SOFA), glasgow coma scale (GCS); blood and biochemical indicators: white blood cell count (WBC), hemoglobin (HB), red blood cell count (RBC), platelet count (PLT), total bilirubin (TB), indirect bilirubin (IB), albumin, creatinine (CRE), international normalized ratio (INR), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), and coagulation indices [prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen (FIB)], and lactic acid (Lac).
2) Main clinical indicators analysis: invasive mechanical ventilation time and ICU length of hospital stay, 28 days in hospital mortality, mortality.
3) Sequential offline treatment effect evaluation: number of level of risk assessment, the secondary risk assessment, the application of preventive nasal high flow, reintubation rates.
4) Adverse events analysis: tracheostomy events; Delirium events, delirium by clinicians based on confusion assessment method-intensive care unit (CAM—ICU) standard definition.

Statistical analyses

For normally distributed data, use mean ± standard deviation, and apply the t-test to compare differences between the two groups. For non-normally distributed data, use the median and interquartile range, and apply the rank-sum test for group comparisons. Categorical data are described using frequency and percentage, and the chi-square test (χ^2 test) is used to compare differences between groups. SPSS 27.00 was used for statistical analysis. Statistical significance was set at $P < 0.05$.

Results

Baseline characteristics

From the baseline characteristics (Table 1), the average age was around 74 years in both groups (74.63 ± 8.10 vs. 74.80 ± 9.02; $P = 0.928$), with slightly more men (57.5% vs. 67.5%; $P = 0.356$). No significant differences were found in age, sex, heart rate, blood pressure, APACHE II, body temperature, SOFA, GCS scores, and the case of underlying diseases ($P > 0.05$), indicating initial comparability. However, the experimental group's respiratory rate median (IQR) was lower (18.00 [18.00–25.00]) compared to the control group (19.50 [17.00–21.00]; $P = 0.037$). In addition, comparing the blood and biochemical indices of the two groups at the time of enrollment, the results were not statistically different ($P > 0.05$; Table 2), indicating that the two groups had similar early disease conditions.

Comparison of clinical data between offline and non-offline patients

This study included 80 patients, with 31 failing to wean off mechanical ventilation, resulting in 49 successful weaning. Analysis (Table 3.) showed no significant differences in age, sex, heart rate, blood pressure, APACHE II, body temperature, SOFA score, GCS score, or blood test indices upon admission ($P > 0.05$).

Comparison of clinical outcome between the two groups

Ten control and eight experimental patients were discharged without extubation, affecting ICU stay and 28-day follow-up inclusion. Hospital mortality was 22.50% in the control group and 15.00% in the experimental group ($P = 0.39$). The 28-day survival rates were nearly equal (69.57% control, 69.23% experimental; $P = 0.98$), showing no significant difference between the sedation strategies (Table 4). Data also showed no significant differences in invasive mechanical ventilation time (control: 107.50 days, experimental: 104.50 days; $P = 0.969$) and ICU stay (7 days in both groups; $P = 0.603$). This indicates similar clinical effects of propofol and remimazolam (Table 4).

Table 1 The vital signs and basic situation when patients into groups

Project	The control group (mean ± SD) *N* = 40	Experimental group (mean ± SD) *N* = 40	t/Z	*P*
age	74.63 ± 8.10	74.80 ± 9.02	0.091	0.928
Gender (male)	23 (57.50%)	27 (67.50%)	0.853	0.356
Heart rate (b/min)	93.95 ± 18.73	99.93 ± 20.18	1.372	0.174
SBP (mmHg)	119.25 ± 33.40	115.45 ± 23.58	0.588	0.558
DBP (mmHg)	73.80 ± 20.80	71.10 ± 16.38	0.645	0.521
Breathing (breaths/min)	18.50 (17.00, 21.00)	19.50 (18.00, 25.00)	2.091	**0.037**
Temperature (℃)	37.05 (36.70,37.70)	37.10 (36.68, 38.10)	0.554	0.580
APACHE-II	21.75 ± 3.69	22.10 ± 3.87	0.414	0.680
SOFA	13.00 (11.00, 14.75)	13.00 (11.00, 17.00)	0.73	0.465
GCS	11.00 (8.00, 12.00)	11.00 (8.00, 13.00)	0.222	0.824
Past history, n (%)				
COPD	3 (7.50)	5 (12.50)	0.556	0.456
Heart failure	3 (7.50)	5 (12.50)	0.556	0.456
Gastrointestinal illness	4 (10.00)	4 (10.00)	0.000	1.000
Chronic kidney disease	3 (7.50)	3(7.50)	0.000	1.000
Chronic liver disease	0 (0.00)	3 (7.50)	3.117	0.077
Cerebrovascular accident	9 (22.50)	5 (12.50)	1.385	0.239
diabetes	23 (57.50)	22 (55.00)	0.051	0.822
Coronary heart disease	20 (50.00)	15 (37.50)	1.270	0.260
hypertension	22 (55.00)	15 (37.50)	2.464	0.116

APACHE II for acute physiology and chronic health evaluation system II score, *SOFA* Sequential organ failure assessment, *GCS* Glasgow coma scale, statistical significance was set at $P < 0.05$

Performance of patients in remimazolam group and propofol group during weaning

Further comparison of the effects of sedative drugs on the deconditioning process. The effects of sedatives on offline processes, including spontaneous breathing tolerance, tube removal, nasal high flow, and reintubation, showed no significant differences between the experimental and control groups ($P > 0.05$) (Tables 5, 6 and 7). These results suggested that isoproterenol and remazolam have similar clinical outcomes..

Under the guidance of a clustering strategy, the spontaneous breathing tolerance evaluation was initially conducted offline. During this process, 9 cases (33%) in the experimental group passed the assessment on the first attempt, while 6 cases (27%) in the control group passed directly through the evaluation. Among patients who underwent repeated assessments two, three, and five times, the experimental group showed slightly higher percentages compared to the control group. Overall, both groups exhibited similar levels of risk assessment during this process (Table 5 and Fig. 2).

After 30 spontaneous breathing tests, 17 patients (62.9%) in the experimental group and 15 (75%) in the control group passed extubation assessment on the first attempt. Both groups required up to three evaluations, with similar secondary risk assessment results (Table 6, Fig. 2). Twenty-seven experimental and 22 control group patients were successfully weaned off mechanical ventilation. Both groups underwent primary and secondary evaluations. Patients who were extubated for the first attempt were grouped separately. A rank sum test showed no significant difference in the total number of weaning procedures ($P = 0.449$) (Table 6).

Patients who weaned off mechanical ventilation and met preventive nasal high flow therapy criteria were included in the study. Three patients from each group did not receive this treatment due to various factors (Table 7). Post-weaning, patients were observed, and three from each group required re-intubation due to increased respiratory rate or poor oxygenation ($PaO_2 < 60$ mmHg). One experimental group patient needed re-intubation after inadequate oxygen support. Both groups received similar analgesia and sedation post-weaning, without further use of the experimental or control drugs.

Table 2 Comparison of blood and biochemical indicators at enrollment

project	The control group (*N* = 40), median (IQR)	The experimental group (*N* = 40), median (IQR)	t/Z	*P*
WBC($\times 10^9$/L)	12.34 (5.57, 19.1)	13.28 (6.13, 20.43)	0.606	0.546
N%	70.50 (54.50, 81.25)	77.00 (63.25, 83.25)	1.348	0.178
LY ($\times 10^9$/L)	29.50 (11.00, 40.00)	15.50 (8.75, 32.25)	1.059	0.289
RBC($\times 10^{12}$/L)	4.30 (3.22, 5.69)	4.35 (3.30, 6.12)	0.645	0.519
HB (g/L)	129.05 (99.18, 158.92)	129.40 (100.89, 157.91)	0.054	0.957
HCT (%)	36.10 (28.48, 43.72)	37.37 (29.02, 45.72)	0.711	0.479
PLT ($\times 10^9$/L)	221.70 (114.10, 329.30)	208.68 (114.59, 302.77)	0.576	0.566
PCT (ng/mL)	3.60 (0.87, 8.80)	5.50 (1.48, 11.30)	1.270	0.204
CRP (mg/L)	14.55 (4.90, 58.50)	31.50 (6.15, 64.50)	0.903	0.366
ALT (IU/L)	35.50 (23.50, 73.00)	30.50 (18.00, 49.25)	0.847	0.397
AST (IU/L)	38.50 (25.25, 57.00)	33.50 (23.75, 63.50)	0.361	0.718
TB (IU/L)	11.85 (6.05.21.13)	9.05 (7.28, 15.93)	0.140	0.889
The IB (IU/L)	5.70(2.50,11.48)	5.20 (3.78, 10.60)	0.250	0.802
Propagated(g/L)	35.89 (29.13, 42.65)	35.48 (28.50, 42.46)	0.268	0.789
BUN(mmol/L)	17.81 (6.33, 35.62)	22.25 (6.79, 37.71)	1.460	0.148
CRE (μmol/L)	59.00 (38.75, 113.25)	54.00 (34.75, 96.00)	0.558	0.577
PT (s)	14.90(12.58,16.90)	13.50 (12.00, 19.50)	0.750	0.453
INR	1.10(1.01,1.54)	1.23 (1.08, 1.42)	0.966	0.334
FIB (g/L)	2.61 (1.3,3.92)	2.99 (1.5, 4.48)	1.220	0.226
APTT (s)	36.44 (25.87, 47.01)	32.69 (24.53, 40.85)	1.765	0.082
PH	7.43 (7.39, 7.48)	7.44 (7.40, 7.49)	1.255	0.209
PCO2(mmHg)	38.55 (33.25, 41.93)	38.00 (32.95, 41.00)	0.494	0.621
PO2 (g/L)	78.70 (70.43, 94.33)	75.50 (62.85, 86.15)	1.472	0.141
BE	1.52 (4.59, 7.63)	2.32 (3.79, 8.43)	0.555	0.581
SO2%	96.00 (92.00, 97.90)	94.00 (91.25, 96.65)	1.510	0.131
Lac (mmol/L)	1.05 (0.80, 1.40)	1.60 (0.85, 2.20)	1.680	0.093
HCO3(mmol/L)	25.43 (20.21, 30.65)	26.48 (21.06, 31.90)	0.790	0.433

Statistical significance was set at $P < 0.05$

Data analysis showed no significant drug accumulation effects or differences in safety between remimazolam and propofol.

Comparison of adverse events between the two groups

In adverse events analysis, tracheostomy occurred in 5 control (12.5%) and 2 experimental (5.0%) patients, with no significant difference. Tracheostomy was included in the analysis as it is often performed in response to severe respiratory complications or clinical deterioration, which may reflect the safety and tolerability of the treatment protocols. Similarly, delirium, excluding general agitation, was noted in 3 control (7.5%) and 2 experimental (5.0%) patients, also with no significant difference (Table 8).

Discussion

Regarding in-hospital mortality, the results showed that it was 15.0% in the remimazolam group and 22.5% in the propofol group, with no statistically significant difference between the two groups ($P = 0.39$). Similarly, there were no significant differences observed in outcomes such as invasive mechanical ventilation time, ICU length of stay, and 28-day survival rates. These findings suggest that remimazolam besylate is comparable to propofol in terms of safety and efficacy for elderly patients undergoing mechanical ventilation, particularly when using a clustered offline strategy. This indicates that remimazolam besylate could serve as a viable alternative to propofol in this patient population.

This study compared remimazolam besylate and propofol in elderly critically ill patients undergoing

Table 3 Comparison of indexes between patients who were weaned and those who were not weaned at enrollment

Items	weaning patients (*N* = 49) (mean ± SD)	not weaning patients (*N* = 31) (mean ± SD)	t/Z	*P*
Age	73.34 ± 8.74	76.87 ± 7.80	1.82	0.071
Gender (male)	33 (67.3%)	17 (54.8%)	0.79	0.374
Heart rate (b/min)	94.55 ± 22.64	100.70 ± 12.84	1.55	0.125
SBP (mmHg)	20.38 ± 5.44	20.35 ± 4.32	0.028	0.977
DBP (mmHg)	119.04 ± 31.22	114.67 ± 24.70	0.658	0.512
Breathing (/min)	71.65 ± 19.88	73.70 ± 16.74	0.478	0.634
Body temperature(°C)	37.19 ± 0.80	37.23 ± 0.80	0.218	0.828
APACHEII	21.77 ± 3.89	22.16 ± 3.60	0.445	0.658
SOFA	12.81 ± 3.61	14.56 ± 3.42	1.561	0.126
GCS	10.45 ± 3.23	10.09 ± 3.13	0.491	0.625
WBC ($\times 10^9$/L)	12.47 ± 6.33	13.33 ± 7.40	0.538	0.592
N%	68.75 ± 18.42	72.29 ± 13.08	0.929	0.356
LY ($\times 10^9$/L)	30.26 ± 20.77	20.74 ± 15.57	2.191	**0.031**
RBC ($\times 10^{12}$/L)	5.32 ± 2.43	4.21 ± 1.53	2.502	**0.014**
HB (g/L)	130.10 ± 30.93	127.83 ± 26.10	0.338	0.736
HCT (%)	37.64 ± 8.71	35.29 ± 6.48	1.296	0.199
PLT ($\times 10^9$/L)	217.53 ± 13.70	211.48 ± 19.61	0.26	0.795
PCT (ng/mL)	8.72 ± 1.74	6.67 ± 1.38	0.847	0.4
CRP (mg/L)	40.68 ± 6.32	40.22 ± 9.08	0.043	0.966
ALT (IU/L)	52.48 ± 9.03	52.93 ± 11.04	0.031	0.975
AST (IU/L)	53.61 ± 8.33	55.32 ± 10.68	0.127	0.899
TB (IU/L)	16.17 ± 2.31	15.70 ± 2.54	0.133	0.894
IB (IU/L)	10.35 ± 1.95	9.55 ± 1.88	0.279	0.781
Propagated (g/L)	35.45 ± 0.96	36.04 ± 1.27	0.378	0.707
BUN (mmol/L)	20.11 ± 2.12	19.9 ± 2.14	0.067	0.947
CRE (umol/L)	118.55 ± 31.83	143.29 ± 34.08	0.512	0.61
PT (s)	16.7 ± 0.96	15.28 ± 0.77	1.146	0.255
INR	1.27 ± 0.06	1.36 ± 0.09	0.933	0.354
FIB (g/L)	2.72 ± 0.20	2.92 ± 0.25	0.612	0.543
APTT (s)	33.78 ± 1.40	35.92 ± 1.69	0.964	0.338
PH	7.41 ± 0.11	7.43 ± 0.07	0.694	0.49
PCO2 (mmHg)	39.34 ± 12.26	38.77 ± 8.41	0.224	0.823
PO2 (g/L)	78.91 ± 27.35	81.34 ± 23.54	0.401	0.689
BE	2.07 ± 6.54	1.68 ± 5.25	0.257	0.798
SO2%	91.11 ± 12.36	92.95 ± 7.57	0.73	0.468
Lac (mmol/L)	1.67 ± 1.29	1.4 ± 0.84	1.023	0.31
HCO3 (mmol/L)	25.77 ± 5.68	26.19 ± 4.75	0.308	0.759

Statistical significance was set at $P < 0.05$

mechanical ventilation and found no statistically significant differences in key outcomes such as in-hospital mortality, 28-day survival rates, total mechanical ventilation time, or ICU length of stay. These findings align with prior studies suggesting that remimazolam provides comparable safety and efficacy to propofol in critical care settings. Most existing studies on remimazolam have focused on its use in surgical anesthesia, with limited data on its impact on in-hospital mortality. For instance, previous studies reported that remimazolam was associated with a lower incidence of hypotension and bradycardia during general anesthesia in elderly patients undergoing endotracheal intubation, highlighting its potential advantage in reducing adverse events [21]. Although adverse events such as tracheotomy and delirium did not significantly differ between the two groups in this study, these outcomes are influenced by multiple factors. For example, patients who underwent tracheotomy were on mechanical ventilation for more than 10 days and did not meet weaning criteria. Tracheotomy, in these cases, was performed to improve comfort, facilitate secretion management, and reduce sedative dosage, adhering to clinical guidelines [20]. Similarly, delirium episodes observed in both groups were likely related to comorbid conditions, such as septic encephalopathy or organ dysfunction, rather than the sedative drugs themselves. Previous studies have shown that midazolam, a benzodiazepine sedative, is an independent risk factor for delirium due to its slower metabolism and cumulative effects [20]. In contrast, remimazolam's pharmacokinetics may contribute to its safer profile, although this warrants further investigation.

The lack of significant differences in ICU and hospital stays is consistent with prior research. For example, a study comparing remimazolam with midazolam in ICU patients found significant differences in ICU length of stay (7.27 ± 0.31 vs. 8.49 ± 0.34, $P < 0.001$) [22]. However, other studies reported no significant differences in ICU or hospital stay durations when remimazolam was compared with propofol or other sedatives [23].

In this study, the use of fentanyl as the primary analgesic ensured minimal drug accumulation and reduced potential interference with sedation or extubation outcomes. This aligns with ICU guidelines recommending opioids as the first-line treatment for non-neuropathic pain [24]. Despite these precautions, elderly patients with high APACHE-II scores (median 21.75 and 22) were inherently at risk for poor outcomes due to age-related physiological decline and severe disease burden.

Several limitations must be addressed. First, the single-center design limits the generalizability of the results, and the inability to implement blinding due to differences in drug appearance and injection pain may introduce bias. Second, while treatment protocols were standardized, individual clinical judgment variations among physicians could influence patient outcomes. Finally, focusing on

Table 4 Comparison of clinical outcome

	Control group median (IQR)	Experimental group median (IQR)	χ^2		*P*
Hospital mortality (rates)			0.738		0.39
yes	9 (22.50)	6 (15.00)			
no	31 (77.50)	34 (85.00)			
Live in 28 days (rates)			0.001		0.98
yes	16 (69.57)	18 (69.23)			
no	7 (30.43)	8 (30.77)			
Invasive mechanical ventilation time (h)	107.50 (63.75, 142.75)	104.50(70.00,138.00)	0.038	0.069	
ICU length of stay	7.00 (5.00,8.00)	7.00 (5.00, 8.50)	0.52	0.603	

Table 5 Comparison of the secondary risk assessment between the two groups

	Number of times	Control group (*N* = 22) median (IQR)	Experimental group (*N* = 27) median (IQR)	Z	*P*
Spontaneous breathing tolerance evaluation (primary risk assessment)	1	6 (27.30)	9 (33.33)	0.519	0.604
	2	7 (31.80)	7 (25.93)		
	3	3 (13.60)	7 (25.93)		
	4	4 (18.20)	2 (7.41)		
	5	1 (4.50)	2 (7.41)		
Assessment of indications for extubation (Level 2 risk assessment)	1	16 (72.70)	17 (62.96)	0.631	0.528
	2	3 (13.60)	6 (22.22)		
	3	3 (13.60)	4 (14.81)		

Statistical significance was set at $P < 0.05$

Table 6 Comparison of experience offline process between the two groups

Number of times	Control group (*N* = 22) median (IQR)	Experimental group (*N* = 27) median (IQR)	Z	*P*
1	6 (27.30)	9 (33.33)	0.134	0.449
2	7 (31.80)	5 (18.50)		
3	2 (9.10)	4 (14.81)		
4	2 (9.10)	4 (14.81)		
5	2 (9.10)	3 (11.11)		
6	1 (4.50)	0 (0.00)		
7	2 (9.10)	2 (7.41)		

Statistical significance was set at $P < 0.05$

critically ill elderly patients inherently limits the potential for favorable outcomes, requiring careful contextualization of the findings. Future studies should adopt multi-center designs to validate these findings and improve generalizability. Additionally, exploring the long-term impact of sedation strategies on recovery and combining sedatives to optimize safety and efficacy could provide valuable insights into managing elderly critically ill patients.

Conclusions

In conclusion, remimazolam besylate is a safe and effective alternative for sedation in elderly critically ill patients undergoing mechanical ventilation. While both agents demonstrate similar efficacy and safety, remimazolam's

Table 7 Comparison of three level risk assessment

	Whether to Apply	Control group (*N* = 20) median (IQR)	Experimental group (*N* = 27) median (IQR)	χ^2	P
Preventive nasal high flow applications (level 3 risk assessment)	no	3 (15.00)	3 (11.11)	0.156	0.693
	yes	17 (85.00)	24 (88.89)		
Re-evaluation after extubation after intubation (level 4 risk assessment)	yes	3 (15.00)	3 (11.11)	0.156	0.693

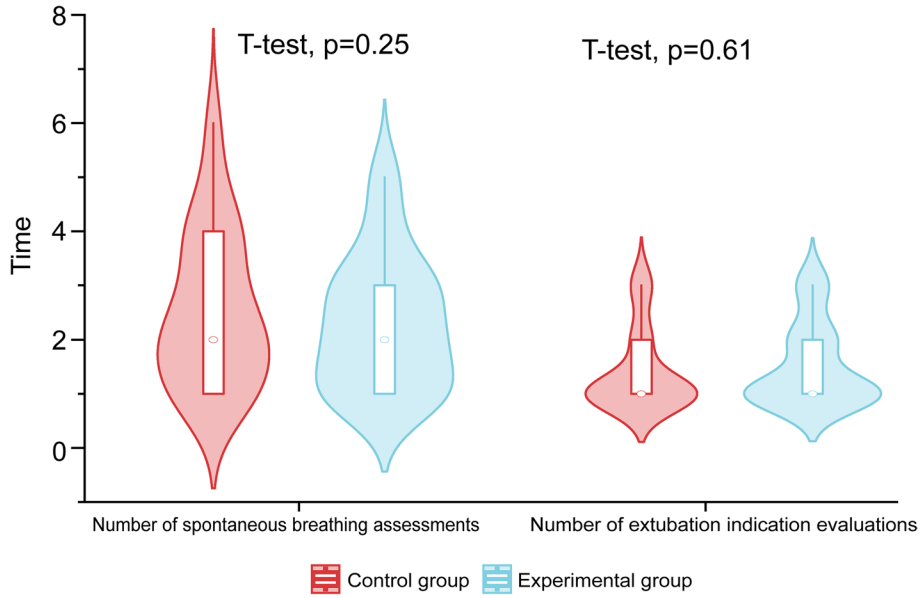

Fig. 2 Secondary risk assessment between the two groups

Table 8 Comparison of adverse events between the two groups

	Control group (*N* = 40) median (IQR)	Experimental group (*N* = 40) median (IQR)	χ^2	*P*
Tracheotoy	5 (12.50)	2 (5.00)	1.409	0.235
Delirium	3 (7.50)	2 (5.00)	0.215	0.613

lower risk of drug accumulation and better hemodynamic stability make it particularly suitable for this population. Further multi-center studies are needed to validate these findings and assess their generalizability.

Abbreviations

ICUs Intensive care units
NIMV Non-invasive mechanical ventilation
EICU Emergency intensive care unit
RASS Richmond Agitation and sedation scale
CPOT Critical-care Pain Observation Tool

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Not applicable.

Authors' contributions
Conceptualization, Li Ma. and Yihui Li.; methodology, Li Ma. and Yihui Li; software, Yihui Li; validation, Yihui Li, Yamin Yuan and Jinquan Zhou; formal analysis, Yihui Li; investigation, Yihui Li; resources, Yihui Li, Yamin Yuan; data curation, Yamin Yuan and Jinquan Zhou; writing—original draft preparation, Yihui Li and Yamin Yuan Jinquan Zhou; writing—review and editing, Yihui Li, Yamin Yuan and Jinquan Zhou; visualization, Yihui Li, Yamin Yuan and Jinquan Zhou; supervision, Li Ma; project administration, Li Ma; funding acquisition, none. All authors have read and agreed to the published version of the manuscript.

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Data availability
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Medical Ethics Committee of the First People's Hospital of Fuyang District, Hangzhou (2020A-276). Clinical registry number: ChiCTR2100046702 (https://trialsearch.who.int/).

Competing interests
The authors declare no competing interests.

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