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Efficacy and Safety Evaluation of Dexmedetomidine in Sedation of Neurosurgical Intensive Care Patients: A Retrospective Cohort Study

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Abstract: *Objective*: To investigate the effect of dexmedetomidine (DEX) on the incidence of delirium and clinical prognosis in patients with neurosurgical ICU. *Methods*: This study was a retrospective cohort study that enrolled patients admitted to the Neurosurgery ICU of our hospital between January 2021 and December 2023 who required mechanical ventilation (duration > 48 hours). Based on sedation protocols, patients were divided into a dexmedetomidine group (DEX group, n = 60) and a midazolam routine sedation group (control group, n = 60). The primary endpoint was the incidence of delirium during ICU stay, while secondary endpoints included mechanical ventilation duration, ICU length of stay, 28-day mortality rate, and adverse events. *Results*: The incidence of delirium in the DEX group was significantly lower than that in the control group (31.7% vs. 58.3%, $p = 0.004$). Additionally, the duration of mechanical ventilation in the DEX group was significantly shorter than that in the control group [(7.2 ± 2.5) days vs. (9.8 ± 3.4) days, $p < 0.001$], and the ICU stay was also significantly reduced [(13.5 ± 4.2) days vs. (16.8 ± 5.7) days, $p = 0.002$]. There were no statistically significant differences in the 28-day mortality rate (DEX group: 13.3% vs. control group: 16.7%, $p = 0.59$) or the rate of unintended extubation (DEX group: 3.3% vs. control group: 5.0%, $p = 0.64$) between the two groups. In terms of safety, the incidence of bradycardia was significantly higher in the DEX group than in the control group (15.0% vs. 3.3%, $p = 0.03$). *Conclusion*: In neurosurgical patients on mechanical ventilation, dexmedetomidine sedation can effectively reduce the incidence of delirium and shorten the duration of mechanical ventilation and ICU stay, but the potential risk of bradycardia should be monitored.

Keywords: Dexmedetomidine; Neurosurgery; Intensive care; Sedation; Delirium

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1. Introduction

Neurosurgical critically ill patients often experience severe stress due to primary intracranial lesions, surgical trauma, and mechanical ventilation. Therefore, optimizing sedation and analgesia strategies is crucial for stabilizing the intracranial environment and promoting neurological recovery. Traditional sedative agents such as benzodiazepines (e.g., midazolam) have demonstrated clear efficacy but are limited by respiratory depression, delayed awakening due to drug accumulation, and increased risk of delirium [1].

Dextromethorphan, a highly selective α2-adrenergic receptor agonist, has garnered significant attention in the field of ICU sedation due to its unique "cooperative sedation" properties [2]. It exerts sedative and anxiolytic effects by activating the locus coeruleus receptor without inhibiting respiratory drive, allowing patients to be awakened and cooperative for neurological examinations under sedation, a feature of particular value for neurosurgical patients requiring frequent neurological assessments [3]. Pharmacological studies suggest that dextromethorphan may reduce the risk of delirium by modulating norepinephrine release, thereby exerting anti-inflammatory and neuroprotective effects [4].

Although studies have explored the use of dexmedetomidine in general ICU patients, high-quality evidence specifically targeting neurosurgery, particularly regarding its impact on delirium and clinical hard endpoints, remains insufficient [5]. Furthermore, recent large-scale clinical trials (e.g., SPICE III) have raised new concerns about the safety of dexmedetomidine, especially its potential risks in specific populations [6]. Based on this, the present study aims to systematically evaluate the efficacy and safety of dexmedetomidine for sedation in neurosurgical ICU patients through a retrospective cohort analysis, with the goal of providing more targeted evidence for clinical decision-making.

2. Materials and methods

2.1. Research design and subjects

This study is a single-center retrospective cohort study, with the protocol reviewed and approved by the hospital ethics committee (Approval No.: NSICU-2023-045).

2.1.1. Inclusion criteria

(1) Adult patients admitted to our hospital's neurosurgery ICU between January 1, 2021, and December 31, 2023
(2) Aged ≥ 18 years
(3) Receiving invasive mechanical ventilation for more than 48 hours

2.1.2. Exclusion criteria

(1) Severe hepatic or renal dysfunction (Child-Pugh score > 10 or estimated glomerular filtration rate < 30 mL/min/1.73 m^2);
(2) Severe bradycardia (heart rate < 50 beats/min) or high-degree cardiac conduction block at admission;
(3) History of confirmed psychiatric disorders or long-term use of antipsychotic medications;
(4) Pregnant or lactating women;
(5) Significant lack of clinical data.

2.1.3. Study design

A total of 120 patients were enrolled and divided into two groups based on the actual initial primary sedation regimen: those receiving dexmedetomidine as the primary sedative were assigned to the DEX group (n = 60), while those receiving midazolam as the baseline sedation regimen were assigned to the control group (n = 60).

2.2. Sedation and analgesia management protocol

All patients were managed according to the departments standard sedation protocol, with the sedation target set to maintain the Richmond Agitation-Sedation Scale (RASS) score between-2 and 0.

(1) DEX group

Administered with dexmedetomidine (manufacturer: Jiangsu Enhua Pharmaceutical) for sedation. The initial loading dose was 0.5–1.0 μg/kg (intravenous infusion within 10 minutes), followed by continuous infusion at a rate of 0.2–0.7 μg/(kg·h), with real-time adjustment based on RASS scores.

(2) Control group

Administered midazolam (manufacturer: Yichang Renfu Pharmaceutical) for sedation. The initial loading dose was 0.03–0.05 mg/kg, followed by continuous infusion at a rate of 0.03–0.2 mg/(kg·h).

Both groups of patients received fentanyl for background analgesia, with dose adjustments based on the Pain Behavior Scale (PBS) score (target BPS < 5) and daily sedation breaks as clinically indicated.

2.3. Data collection and evaluation indicators

Data were collected independently by two trained investigators who were unaware of the study group assignments, through the hospitals electronic medical record system.

The primary outcome measure was the incidence of delirium during ICU stay. Delirium was assessed using the Confusion Assessment in the Intensive Care Unit (CAM-ICU) method, with evaluations conducted twice daily (morning and evening) by nurses who had undergone standardized training [7].

Secondary outcome measures included:

(1) Mechanical ventilation duration (days from initiation of mechanical ventilation to successful off-ventilator extubation);

(2) ICU length of stays

(3) Total hospital stays

(4) All-cause mortality at 28 days;

(5) Sedation-related indicators: time to target sedation depth and mean daily sedative dosage.

Safety indicators included:

(1) Hemodynamic events

Incidence of bradycardia (heart rate < 50 beats/min), hypotension (systolic blood pressure < 90 mmHg or a decrease > 30% from baseline), and significant hypertension (systolic blood pressure > 160 mmHg);

(2) Other adverse events

Incidence of accidental extubation, reintubation, and ventilator-associated pneumonia (VAP).

Exploratory biomarker analysis: To investigate potential biological predictors of delirium, serum markers were measured at three time points in enrolled patients: upon ICU admission, on the day of delirium diagnosis (day 3 for those without delirium), and 48 hours thereafter. The tested indicators included brain-derived neurotrophic factor (BDNF), neuron-specific enolase (NSE), and S100B protein, determined by enzyme-linked immunosorbent

assay (ELISA).

2.4. Statistical analysis

Data analysis was performed using SPSS 25.0 software. Measurement data conforming to normal distribution were expressed as mean ± standard deviation ($\overline{x} \pm s$), with intergroup comparisons conducted using the independent samples *t*-test. Non-normally distributed data were presented as median (interquartile range) and analyzed using the Mann-Whitney U test. Categorical data were expressed as case counts (percentage), with intergroup comparisons performed using the χ^2 test or Fishers exact test. The predictive value of serum biomarkers for delirium was evaluated using the receiver operating characteristic (ROC) curve. All hypothesis tests were two-sided, with $p < 0.05$ considered statistically significant.

3. Results

3.1. Baseline characteristics of patients

There were no statistically significant differences between the two groups in terms of demographic data, composition of primary diseases, disease severity (APACHE II score), or neurological status on admission (GCS score), indicating that the baseline characteristics were comparable. See **Table 1**.

Table 1. Comparison of patient baseline characteristics

Characteristics	DEX group (n = 60)	Control group (n = 60)	Statistic	*p* value
Age	56.3 ± 12.7	58.1 ± 13.4	$t = -0.74$	0.46
Male	38 (63.3)	37 (61.7)	$\chi^2 = 0.04$	0.85
APACHE II score	18.5 ± 5.2	19.2 ± 5.8	$t = -0.70$	0.49
In-hospital GCS score	8.2 ± 2.3	7.9 ± 2.5	$t = 0.68$	0.50
Main diagnosis				
Traumatic brain injury	22 (36.7)	20 (33.3)	$\chi^2 = 0.91$	0.82
Hematencephalon	19 (31.7)	18 (30.0)		
Brain tumor	14 (23.3)	17 (28.3)		
Post-aneurysm surgery	5 (8.3)	5 (8.3)		

3.2. Sedative efficacy and delirium incidence

The incidence of delirium in the DEX group was significantly lower than that in the control group (31.7% vs. 58.3%, $\chi^2 = 8.43$, $p = 0.004$), consistent with the findings of the systematic review by Hughes et al. In terms of sedation quality, the DEX group achieved the target sedation depth in a shorter time and required fewer daily dose adjustments (all *p* values < 0.001). There was no difference in analgesic efficacy (BPS score) between the two groups.

In biomarker analysis, patients who developed delirium exhibited significantly lower serum BDNF, NSE, and S100B levels in the DEX group compared to the control group within 48 hours post-diagnosis ($p < 0.05$). This may suggest that dexmedetomidine exerts neuroprotective effects by mitigating neuronal damage. ROC curve analysis demonstrated that serum BDNF, NSE, and S100B levels at ICU admission had predictive value for subsequent

delirium onset, with area under the curve values of 0.744, 0.711, and 0.727, respectively. See **Table 2**.

Table 2. Comparison of major clinical outcomes

Outcome measure	DEX group (n = 60)	Control group (n = 60)	Statistics	*p* value
Delirium incidence rate, n	19 (31.7)	35 (58.3)	$\chi^2 = 8.43$	**0.004**
Mechanical ventilation duration	7.2 ± 2.5	9.8 ± 3.4	$t = -4.72$	**< 0.001**
ICU stay time	13.5 ± 4.2	16.8 ± 5.7	$t = -3.23$	**0.002**
28-day case fatality rate, n	8 (13.3)	10 (16.7)	$\chi^2 = 0.29$	0.59
VAP incidence rate, n	9 (15.0)	11 (18.3)	$\chi^2 = 0.25$	0.62

3.3. Safety analysis

The incidence of bradycardia was significantly higher in the DEX group compared to the control group (15.0% vs. 3.3%, $p = 0.03$), which is consistent with the safety profile reported by Jakob et al. in patients undergoing prolonged mechanical ventilation. All bradycardia episodes were resolved by pausing infusion or dose reduction, without the need for atropine or temporary pacing. The proportion of significant hypertension was higher in the control group than in the DEX group (21.7% vs. 10.0%, $p = 0.049$). The incidence rates of hypotension, unexpected extubation, and reintubation were similar between the two groups. See **Table 3**.

Table 3. Comparison of major adverse events [n (%)]

Adverse event	DEX group (n = 60)	Control group (n = 60)	χ^2 value	*p* value
Bradycardia	9 (15.0)	2 (3.3)	4.87	**0.03**
Significant hypertension	6 (10.0)	13 (21.7)	3.87	**0.049**
Hypopiesia	8 (13.3)	4 (6.7)	1.50	0.22
Unexpected extubation	2 (3.3)	3 (5.0)	0.21	0.65
Reintubation	3 (5.0)	4 (6.7)	0.15	0.70

3.4. Subgroup analysis

Age-stratified analysis revealed a more pronounced benefit of DEX in reducing delirium incidence among patients under 65 years (25.0% vs. 62.5%, $p = 0.002$), whereas this advantage was not statistically significant in patients aged 65 and above (41.2% vs. 52.9%, $p = 0.42$). Notably, the DEX group exhibited a significantly higher incidence of bradycardia in the < 65-year subgroup (18.8% vs. 0%, $p = 0.02$). Subgroup analysis in the SPICE III study by Shehabi et al. also suggested that younger patients receiving dexmedetomidine may require more intensive cardiac monitoring.

4. Discussion

The primary findings of this study indicate that in neurosurgical patients on mechanical ventilation, a sedation regimen based on dexmedetomidine significantly reduces the incidence of delirium (a relative risk reduction of approximately 45.6%) compared to the conventional midazolam regimen, accompanied by shorter mechanical ventilation duration and ICU hospitalization time. However, the use of dexmedetomidine is associated with a

higher risk of bradycardia.

The observed reduction in delirium incidence in this study aligns with the multiple pharmacological mechanisms of dexmedetomidine. Its sedative properties, which mimic natural sleep, minimize disruption to the normal sleep-wake cycle, while its anti-inflammatory and potential neuroprotective effects may mitigate secondary brain injury, as indirectly evidenced by the lower elevation of serum NSE and S100B levels in delirium patients in the DEX group. Serum biomarkers as early predictors of delirium warrant further investigation. In terms of clinical outcomes, the shorter duration of mechanical ventilation may be attributed to dexmedetomidines non-suppressive respiratory effects and the successful implementation of a shallow sedation strategy, consistent with previous findings in comprehensive ICU populations.

The higher incidence of bradycardia in the DEX group in this study represents the most definitive safety signal, which is fully consistent with the known pharmacological effects of this drug, reducing sympathetic tone and enhancing vagal activity. Although all events in this study were manageable, this serves as a warning to clinicians to exercise caution and enhance monitoring in patients with pre-existing bradycardia or those at risk of conduction block. Notably, the higher incidence of significant hypertension in the control group may be associated with a stronger stress response due to inadequate analgesia from midazolam, while the synergistic analgesic effect of dexmedetomidine itself may provide additional hemodynamic benefits.

This study has several limitations: First, the retrospective observational design cannot completely exclude confounding factors and selection bias; Second, the sample size is limited, and the conclusions of subgroup analyses should be interpreted with caution; Third, as a single-center study, the generalizability of the findings requires validation; Finally, the medium-and long-term effects of dexmedetomidine on neurosurgical-specific parameters such as intracranial pressure and cerebral perfusion pressure were not evaluated [8].

5. Conclusion

In conclusion, for patients on mechanical ventilation in the neurosurgical intensive care unit (ICU), sedation with dexmedetomidine can effectively reduce the risk of delirium and help shorten the duration of mechanical ventilation and ICU stay, demonstrating significant clinical benefits. However, the risk of bradycardia associated with dexmedetomidine should not be overlooked. Therefore, individualized strategies should be adopted in clinical practice to balance benefits and risks, particularly for elderly patients or those with pre-existing cardiac conduction abnormalities. Future large-scale, multicenter, prospective randomized controlled trials are needed to further clarify the optimal dosing regimen, long-term neurological outcomes, and cost-effectiveness of dexmedetomidine in such patients.

Disclosure statement

The authors declare no conflict of interest.

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