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WORD COUNT 4411
TIME SUBMITTED 11-JAN-2024 07:46PM
PAPER ID 106081705

Brain protective effect of dexmedetomidine *vs* propofol for sedation during prolonged mechanical ventilation in non-brain injured patients

Abstract

BACKGROUND

Dexmedetomidine and propofol are two sedatives used for long-term sedation. It remains unclear whether dexmedetomidine provides superior cerebral protection for patients undergoing long-term mechanical ventilation.

AIM

To compare the neuroprotective effects of dexmedetomidine and propofol for sedation during prolonged mechanical ventilation in patients without brain injury.

METHODS

Patients who underwent mechanical ventilation for > 72 h were randomly assigned to receive sedation with dexmedetomidine or propofol. The Richmond Agitation and Sedation Scale (RASS) was used to evaluate sedation effects, with a target range of -3 to 0. The primary outcomes were serum levels of S100-β and neuron-specific enolase (NSE) every 24 h. The secondary outcomes were remifentanil dosage, the proportion of patients requiring rescue sedation, and the time and frequency of RASS scores within the target range.

RESULTS

A total of 52 and 63 patients were allocated to the dexmedetomidine group and propofol group, respectively. Baseline data were comparable between groups. No significant differences were identified between groups within the median duration of study drug infusion [52.0 (IQR: 36.0-73.5) h *vs* 53.0 (IQR: 37.0-72.0) h, *P* = 0.958], the median dose of remifentanil [4.5 (IQR: 4.0-5.0) μg/kg/h *vs* 4.6 (IQR: 4.0-5.0) μg/kg/h, *P*

= 0.395], the median percentage of time in the target RASS range without rescue sedation [85.6% (IQR: 65.8%-96.6%) *vs* 86.7% (IQR: 72.3%-95.3), *P* = 0.592], and the median frequency within the target RASS range without rescue sedation [72.2% (60.8%-91.7%) *vs* 73.3% (60.0%-100.0%), *P* = 0.880]. The proportion of patients in the dexmedetomidine group who required rescue sedation was higher than in the propofol group with statistical significance (69.2% *vs* 50.8%, *P* = 0.045). Serum S100-β and NSE levels in the propofol group were higher than in the dexmedetomidine group with statistical significance during the first six and five days of mechanical ventilation, respectively (all *P* < 0.05).

CONCLUSION

Dexmedetomidine demonstrated stronger protective effects on the brain compared to propofol for long-term mechanical ventilation in patients without brain injury.

Key Words: Dexmedetomidine; Propofol; Sedation; Prolonged mechanical ventilation; Brain protective

Yuan HX, Zhang LN, Li G, Qiao L. Brain protective effect of dexmedetomidine *vs* propofol for sedation during prolonged mechanical ventilation in non-brain injured patients. *World J Psychiatry* 2024; In press

Core Tip: In this study, we designed a single center, prospective, randomized controlled study to compare the brain protective effect of dexmedetomidine *vs* propofol for sedation during prolonged mechanical ventilation in non-brain injured patients.

INTRODUCTION

Patients who require intensive care may experience a strong stress response due to their own serious illness, leading to long-term negative emotions such as anxiety and irritability. In addition, most of these patients also necessitate mechanical ventilation,

which can readily result in conflict between the individual and the machine, thereby affecting the efficacy of mechanical ventilation[1,2]. Analgesic and sedative therapies can alleviate pain, anxiety, and restlessness in patients, reduce oxygen consumption, reduce stress reactions, playing a crucial role in intensive care unit (ICU) treatment[3]. However, long-term sedation may cause serious adverse reactions, including extended mechanical ventilation, impaired cognitive function, coma, and post-traumatic stress disorder. These outcomes are closely related to the choice of sedation regimen.

Dexmedetomidine and propofol are two sedatives used for long-term sedation[4]. Dexmedetomidine, an adrenergic receptor agonist, possesses analgesic, sedative, and inhibitory effects on sympathetic nervous activity[5,6]., contributing to enhanced patient safety and comfort during long-term sedation[5,6]. Previous studies have demonstrated that compared to propofol or midazolam, dexmedetomidine can reduce the incidence of coma and delirium, as well as decrease mechanical ventilation time in ICU patients[6,7]. A multicenter randomized controlled trial from Europe revealed that in ICU patients undergoing long-term mechanical ventilation, dexmedetomidine is non-inferior to midazolam or propofol in maintaining mild to moderate sedation, while also shortening the duration of mechanical ventilation and improving patients' ability to communicate pain[4]. Additionally, several clinical trials[8,9] and animal studies[10,11] have confirmed the brain-protective effects of dexmedetomidine. Nevertheless, it remains unclear whether dexmedetomidine provides superior cerebral protection for patients undergoing long-term mechanical ventilation.

In this study, we designed a single-center, prospective, randomized controlled study to compare the brain-protective effects of dexmedetomidine versus propofol for sedation during prolonged mechanical ventilation in non-brain-injured patients.

MATERIALS AND METHODS

Patients and ethical statement

This single-center, prospective, randomized controlled study was approved by the Ethics Committee of Peking University International Hospital (Approval No. 2021-KY-

0037-01). Patients or their legal representatives signed an agreement to voluntarily participate in the present study.

The inclusion criteria of patients included: (1) Age ≥ 18 years and ≤ 75 years; (2) mechanical ventilation time ≥ 72 h and sedation time ≥ 24 h; and (3) patients without brain injuries.

Exclusion criteria: (1) Body mass index (BMI) < 18 kg/m^2 or > 30 kg/m^2; (2) acute severe neurological disorders; (3) brain injury, including head trauma, cerebral hemorrhage, cerebral infarction, and neurosurgery; and (4) acute hepatitis or serious hepatic dysfunction (Child-Pugh class C); (5) chronic kidney disease with glomerular filtration rate < 60 mL/min/1.73 m^2; (6) alcohol consumption or drug addiction; (7) myasthenia gravis, pregnancy or lactation, study drug allergies, or contraindications; and (8) patients with malignant tumors.

Randomization and intervention

Eligible patients received sedative drugs by doctors who were blind to the research details. The patients were unaware of the sedative medications administered as well.

All patients received analgesia at a dosage ranging from 4.0 to 9.0 μg/kg/h. Patients in the dexmedetomidine group received dexmedetomidine hydrochloride injection (0.1-1.2 μg/kg/h) (H20183219, Yangzijiang Pharmaceutical Group Co., Ltd, China) for sedation, while patients in the propofol group were given propofol medium long chain fat emulsion injection (0.3-4.0 mg/kg/h) (HJ20150655, Beijing Feisenyuskabi Pharmaceutical Co., Ltd, China) for sedation.

Primary outcome

Serum S100-β and neuron-specific enolase (NSE) levels were measured to assess brain function. Briefly, venous blood was collected every 24 h during mechanical ventilation, followed by centrifugation (1000 × g, room temperature, 10 min) to separate the serum. The central laboratory detects serum S100-β and NSE levels using enzyme-linked immunosorbent assay.

Secondary outcomes

The secondary outcomes included the remifentanil dosage, the proportion of patients receiving rescue sedation, and the time and frequency of Richmond Agitation Sedation Scale (RASS) within the target range. Briefly, patients eventually included in the analysis recorded the dose of remifentanil used during the study. If a patient's RASS score was above the target range (-3 to 0) and required rescue sedation, the patient was recorded as requiring rescue sedation. RASS scores were assessed every 4 h prior to any administration of rescue therapy.

Statistical analysis

Due to a lack of assumptions, sample size estimation was not conducted in this study. Data were collected using an Excel table and analyzed by SPSS 25.0 (IBM, United States). Continuous data were presented as median and interquartile range (IQR). Differences between groups were compared utilizing Student's *t*-test or the Mann-Whitney *U* test, based on the results of the Kolmogorov-Smirnov test. Count data were expressed as percentages (%), and differences between groups were compared utilizing the chi-square test or Fisher's exact test. Statistical significance was set at $P < 0.05$.

RESULTS

Demographics and diagnostic results at baseline

We screened 3047 ICU patients and ultimately included 115 patients in the final analysis: 52 in the dexmedetomidine group and 63 in the propofol group (Figure 1). Their median age was 61.0 years (IQR: 54.00-65.00), with 69 male patients (60.0%) and a median BMI of 21.32 kg/m² (IQR: 19.35-22.98). No significant differences were observed in the baseline clinical characteristics between groups, such as the SAPS II score, the main reason for ICU admission, infection at ICU admission, SOFA score of organs (including respiratory, cardiovascular, renal, coagulation, and liver), total SOFA score, RASS score at enrollment, and time from ICU admission to drug initiation (Table 1).

Details of dexmedetomidine and propofol administered

The median infusion time of dexmedetomidine in the dexmedetomidine group was 52.0 (IQR: 36.0-73.5) hours, and the median infusion time of propofol in the propofol group was 53.0 (IQR: 37.0-72.0) hours, with no significant difference between groups (P = 0.958) (Table 2). Meanwhile, there was also no significant difference in the dose of remifentanil between groups (P = 0.395). However, the proportion of patients undergoing rescue sedation in the dexmedetomidine group was significantly higher in contrast with that in the propofol group (69.2% *vs* 50.8%, P = 0.045, Table 2).

Sedative effects

During the absence of rescue sedation, the median percentage of time within the target RASS in the dexmedetomidine group was similar to the propofol group [85.6% (IQR: 65.8%-96.6%) *vs* 86.7% (IQR: 72.3%-95.3%), P = 0.592] (Table 3). Patients in the dexmedetomidine group underwent 1428 RASS evaluations, with 1031 (72.2%) reaching the target RASS range (-3 to 0) (Figure 2A), and patients in the propofol group underwent a total of 1740 RASS evaluations, with 1297 (74.5%) patients in the target RASS range (Figure 2B). The median percentage of the target RASS score in the dexmedetomidine group was different from the propofol group without statistical significance [72.2% (60.8%-91.7%) *vs* 73.3% (60.0%-100.0%)], P = 0.880] (Table 3).

Brain function index levels

Starting with mechanical ventilation, sedation, and analgesia, we evaluated the brain function of all patients every 24 h by measuring serum S100-β and NSE levels. Serum S100-β levels in patients in the propofol group were higher in contrast with those in the dexmedetomidine group during the first 7 d of mechanical ventilation and were significantly higher from day 1 to day 6, with no significant difference on day 7 (Table 4, Figure 3A). The levels of serum NSE in patients in the propofol group were also higher in contrast with those in the dexmedetomidine group during the first 7 d of mechanical

ventilation and were significantly higher from day 1 to day 5, with no significant difference from day 6 to day 7 (Table 5, Figure 3B).

DISCUSSION

In this study, we initially observed that the sedative effects of dexmedetomidine and propofol during prolonged mechanical ventilation in patients without brain injury were similar. There were no significant differences in remifentanil dosage, RASS target range time ratio, and frequency. However, it is important to note that the proportion of patients in the dexmedetomidine group requiring rescue sedation was significantly higher than that in the propofol group. These research results were in accordance with previous studies; for instance, Jakob *et al*[4] found that the dexmedetomidine/propofol ratio in time at target sedation was 1.00 (95% confidence interval: 0.92-1.08), and the proportion of patients undergoing rescue sedation in the dexmedetomidine group was significantly higher in contrast with that in the propofol group (72.5% *vs* 64.4%, P = 0.05).

In addition, we found some unreported results: Serum S100-β and NSE levels in the propofol group were higher in contrast with those in the dexmedetomidine group during prolonged mechanical ventilation in patients without brain injury. As a marker of glial cells, S100-β protein is a calcium-binding protein mainly present in mature perivascular astrocytes. It is primarily found in glial cells and Schwann cells, released from the cytoplasm into the cerebrospinal fluid after central nervous system cell injury, and then enters the bloodstream *via* the damaged blood-brain barrier[12,13]. NSE represents a marker enzyme for neuronal damage and is a key enzyme in the glycolytic pathway. It is specifically localized within neurons and predominantly exists in the cytoplasm of brain nerve cells as well as neuroendocrine cells[14,15]. The content of NSE in body fluids is very low under normal circumstances, but a large amount of NSE quickly leaks out of damaged neurons in the case of nerve cell damage and passes through the blood-brain barrier, entering the cerebrospinal fluid and bloodstream[16,17]. Therefore, serum S100-β and NSE levels can be utilized to evaluate the degree of brain

injury, particularly the brain-protective effects of anesthetic drugs in non-cerebral injury[18,19].

We observed that serum levels of S100-β (first 6 d) as well as NSE (first 5 d) in the propofol group were obviously higher in contrast with those in the dexmedetomidine group during the early stage of mechanical ventilation and sedation. However, as the 7-d mechanical ventilation observation period progressed, although these levels remained higher in the propofol group compared to the dexmedetomidine group, the difference was not statistically significant. Therefore, our results indicate that dexmedetomidine has a stronger brain protective effect in the early stages of prolonged mechanical ventilation and sedation compared to propofol in patients. Studies have demonstrated that dexmedetomidine are neuroprotective based on various pathways, including binding to α2-adrenal receptor subtype binding[20], reducing the brain metabolic rate[21,22], curtailing excitatory amino acid release[23], mitigating intracellular calcium overload[24], and regulating apoptotic protein expression to inhibit neuronal apoptosis[25,26]. On one hand, uncontrolled inflammation is the main cause of neuronal apoptosis/necrosis, and dexmedetomidine has been proven to exert anti-inflammatory effects by inhibiting the production of pro-inflammatory factors and microglial M1 phenotype, inhibiting neuroinflammation, and protecting neurons from apoptosis caused by inflammatory factors[27,28]. On the other hand, dexmedetomidine can inhibit oxidative stress and cell apoptosis by regulating the NRF2/ARE pathway and Trx1 dependent Akt pathway. Dexmedetomidine can also eliminate excess oxygen free radicals in the body by reducing the content of malondialdehyde and reactive oxygen species, increasing the activity of superoxide dismutase, and alleviating the damage caused by the chain reaction caused by oxygen free radicals, It has a protective effect on oxidative stress and neuronal apoptosis triggered by ischemia-reperfusion injury[29,30]. Moreover, our results suggested that the brain-protective effect of dexmedetomidine was not markedly superior to that of propofol in the later stages of mechanical ventilation and sedation. However, given that only a small number of patients (10 in the dexmedetomidine group and 14 in the propofol group) completed the full 7-d

mechanical ventilation, we believe that the findings regarding the brain protective effect in the later stage of mechanical ventilation and sedation may be biased.

There were several limitations in this study. Firstly, as a single-center randomized controlled study, its generalizability is limited, and the results require further validation with a larger sample size from multiple centers. Secondly, hundreds of nursing staff members randomly participated in the care of all patients, eliminating the impact of nursing practices. Lastly, due to the distinct nature of propofol, patient allocation was not blinded to healthcare professionals.

CONCLUSION

Overall, dexmedetomidine exhibited stronger protective effects on the brain than propofol for long-term mechanical ventilation in patients without brain injury.

ARTICLE HIGHLIGHTS

Research background

Dexmedetomidine and propofol are two sedatives used for long-term sedation. It remains unclear whether dexmedetomidine provides superior cerebral protection for patients undergoing long-term mechanical ventilation.

Research motivation

In this study, we designed a single-center, prospective, randomized controlled study to compare the brain-protective effects of dexmedetomidine versus propofol for sedation during prolonged mechanical ventilation in non-brain-injured patients.

Research objectives

To compare the neuroprotective effects of dexmedetomidine and propofol for sedation during prolonged mechanical ventilation in patients without brain injury.

Research methods

Patients who underwent mechanical ventilation for > 72 h were randomly assigned to receive sedation with dexmedetomidine or propofol. The Richmond Agitation and Sedation Scale (RASS) was used to evaluate sedation effects, with a target range of -3 to 0. The primary outcomes were serum levels of S100-β neuron-specific enolase (NSE) every 24 h. The secondary outcomes were remifentanil dosage, the proportion of patients requiring rescue sedation, and the time and frequency of RASS scores within the target range.

Research results

The sedative effects of dexmedetomidine and propofol during prolonged mechanical ventilation in patients without brain injury were similar. Serum S100-β and NSE levels in the propofol group were higher in contrast with those in the dexmedetomidine group during prolonged mechanical ventilation in patients without brain injury. Serum levels of S100-β (first 6 d) as well as NSE (first 5 d) levels in the propofol group were obviously higher in contrast with-those in the dexmedetomidine group during the early stage of mechanical ventilation and sedation.

Research conclusions

Dexmedetomidine exhibited stronger protective effects on the brain than propofol for long-term mechanical ventilation in patients without brain injury.

Research perspectives

We believe that the findings regarding the brain protective effect in the later stage of mechanical ventilation and sedation may be biased.

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Figure 1 Flow diagrams for the trials. BMI: Body mass index; GFR: Glomerular filtration rate.

Figure 2 Number of times Richmond Agitation Sedation Scale scores in and out the target range. A: Dexmedetomidine group; B: Propofol group. RASS: Richmond Agitation Sedation Scale scores.

Figure 3 Dynamic changes of serum S100-β and neuron-specific enolase levels in patients with mechanical ventilation. A: S100-β; B: Neuron-specific enolase. NSE: Neuron-specific enolase; NS: Not significant. $^{a}P < 0.05$; $^{b}P < 0.01$; $^{c}P < 0.001$.

Table 1 Baseline characteristics of non-brain injured patients, *n* (%)

	Dexmedetomidine (*n* = 52)	**Propofol (*n* = 63)**	***P* value**
Age (yr), median (IQR)	61.0 (55.0-64.0)	61.0 (53.0-66.0)	0.663
Male	30 (57.7)	39 (61.9)	0.646
BMI (kg/m^2), median (IQR)	21.8 (19.6-24.3)	21.1 (19.0-22.3)	0.191
SAPS II, median (IQR)	46.0 (38.0-54.0)	46.0 (36.0-53.0)	0.675
Main reason for ICU			
Medical	37 (71.2)	44 (69.9)	0.983
Surgical	10 (19.2)	13 (20.6)	
Trauma	5 (9.6)	6 (9.5)	
Infection at ICU admission	24 (46.2)	30 (47.6)	0.875
SOFA score of organ > 2			
Respiratory	30 (57.7)	35 (55.6)	0.818
Cardiovascular	26 (50.0)	27 (42.9)	0.444
Renal	8 (15.4)	10 (15.9)	0.943
Coagulation	4 (7.7)	6 (9.5)	0.729
Liver	1 (1.9)	1 (1.6)	0.891
Total SOFA score, median (IQR)	7.0 (4.0-9.0)	6.0 (3.0-9.0)	0.954
RASS score at enrollment, median (IQR)	-2 (-3 to -1)	-3 (-3 to -1)	0.247
Time from ICU admission to drug initiation (h), median (IQR)	32.0 (20.0-35.0)	31.0 (20.0-42.0)	0.798

ICU: Intensive care unit.

Table 2 Dosage of study drugs during mechanical ventilation

	Dexmedetomidine (*n* = 52)	**Propofol (*n* = 63)**	***P* value**
Duration of study drug infusion (h), median (IQR)	52.0 (36.0-73.5)	53.0 (37.0-72.0)	0.958
Dose of study drug (μg or mg/kg/h), median (IQR)	0.58 (0.34-0.79)	0.82 (0.65-1.32)	-
Dose of remifentanil (μg/kg/h), median (IQR)	4.5 (4.0-5.0)	4.6 (4.0-5.0)	0.395
Receiving rescue sedation, *n* (%)	36.0 (69.2)	32.0 (50.8)	0.045

Table 3 Comparison of sedative effect between the two groups

	Dexmedetomidine (*n* = 52)	**Propofol (*n* = 63)**	***P* value**
Percentage of time within the target RASS (%), median (IQR)	85.6 (65.8-96.6)	86.7 (72.3-95.3)	0.592
Percentage of target RASS score (%), median (IQR)	72.2 (60.8-91.7)	73.3 (60.0-100.0)	0.880

RASS: Richmond Agitation and Sedation Scale.

Table 4 Comparison of S100-β serum levels between the two groups

Time	Dexmedetomidine		Propofol		*P* value
	n	S100-β	*n*	S100-β	
Day 0	52	0.12 (0.06-0.18)	63	0.14 (0.08-0.23)	0.408
Day 1	52	2.12 (2.03-2.22)	63	3.02 (2.92-3.18)	< 0.001
Day 2	52	2.30 (2.18-2.48)	63	3.53 (3.32-3.85)	< 0.001
Day 3	52	2.88 (2.67-3.05)	63	3.62 (3.39-4.06)	< 0.001
Day 4	35	3.58 (3.36-3.85)	40	4.70 (4.35-4.97)	< 0.001
Day 5	22	4.46 (4.34-4.58)	28	4.98 (4.86-5.44)	< 0.001
Day 6	15	4.83 (4.68-5.03)	19	5.33 (4.98-5.65)	0.0026
Day 7	10	5.06 (4.81-5.32)	14	5.38 (5.19-5.67)	0.0562

Table 5 Comparison of neuron-specific enolase serum levels between the two groups

Time	Dexmedetomidine		Propofol		*P* value
	n	NSE	*n*	NSE	
Day 0	52	9.95 (9.08-10.65)	63	9.86 (9.35-10.56)	0.9570
Day 1	52	20.09 (17.63-21.43)	63	21.42 (20.71-23.08)	< 0.0010
Day 2	52	20.35 (17.96-21.50)	63	22.35 (21.38-23.92)	< 0.0010
Day 3	52	24.89 (21.87-26.85)	63	26.25 (25.15-27.35)	< 0.0010
Day 4	35	26.62 (23.43-29.35)	40	29.17 (26.61-31.14)	0.0082
Day 5	22	26.75 (24.93-29.37)	28	29.66 (27.72-31.14)	0.0047
Day 6	15	28.93 (26.35-30.52)	19	30.72 (28.65-31.98)	0.0774
Day 7	10	28.34 (26.95-31.23)	14	30.54 (28.90-32.46)	0.2060

NSE: Neuron-specific enolase.

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