Assessment of the sedative effects of dexmedetomidine and propofol treatment in patients undergoing mechanical ventilation in the ICU and relationship between treatment and occurrence of ventilator-associated pneumonia and detection of pathogenic bacteria

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Abstract. The present study aimed to investigate the sedative effects of dexmedetomidine combined with propofol in patients undergoing mechanical ventilation in the intensive care unit (ICU), and to reveal the risk factors of ventilator-associated pneumonia (VAP). A retrospective analysis of 322 patients who had been subject to mechanical ventilation in the ICU ward was performed. Subjects were divided into two groups: A group treated with dexmedetomidine and propofol (combined group) and a group treated with dexmedetomidine alone (monotherapy group). Clinical data, sedative effects, the number of VAP patients and the distribution of VAP pathogens were assessed. Multivariate analysis and receiver operating characteristic (ROC) curves were used to predict VAP. Significant differences in the sedative effects between the two groups were observed (P<0.001). The incidence of VAP was significantly higher in the monotherapy group compared with the combined group (P<0.05). Multivariate logistic regression analysis demonstrated that age, acute physiology chronic health evaluation score, consciousness, invasive operations, recovery time, extubation time and sedation regimen were independent risk factors for VAP in the ICU during mechanical ventilation. ROC curves indicated that the areas under the curve for age, acute physiology chronic health score, consciousness, invasive operations, recovery time, extubation time and sedation regimen were 0.934, 0.870, 0.632, 0.677, 0.865, 0.950 and 0.603, respectively. In summary, dexmedetomidine combined with propofol can shorten the recovery and extubation times of mechanical ventilation patients in the ICU. Different sedation schemes are also independent risk factors for VAP during mechanical ventilation in the ICU.

Introduction

Intensive Care Units (ICUs) treat critically ill patients in hospitals and tracheal intubation is typically required for assisted ventilation in ICU wards. Tracheal intubation primarily consists of mechanical ventilation, to which many patients develop intolerance (1,2). Sedative and analgesic adjuvant therapy is often required during clinical treatment, which reduces the discomfort and stress responses of patients and increases the effectiveness of mechanical ventilation (3). Moreover, studies have shown that appropriate sedation can improve the clinical outcomes of patients (4). The most commonly used sedative in the clinic is dexmedetomidine (5). Dexmedetomidine, as a highly selective α2-adrenergic receptor agonist, inhibits the release of thyroxine by activating α2-adrenergic receptors, reducing sympathetic nervous system activity (6). Patients receiving dexmedetomidine anesthesia do not develop respiratory depression, which is conducive for those with difficulties weaning from mechanical ventilation (7). As a short-acting alkylphenol sedative and hypnotic drug, propofol acts on GABA receptors in the central nervous system and has the characteristics of rapid onset, a short half-life, fast metabolism and a lack of accumulation in the body (8). However, patients may experience memory loss and anti-convulsive effects after propofol use (9).

Ventilator-associated pneumonia (VAP) is a common cause of pulmonary infection in ICU wards. The incidence of pulmonary infections during mechanical ventilation in the ICU is much higher than that in other hospital departments (10). Artificial mechanical ventilation provides a direct route for pathogens to enter the body and damages the physical barrier of the airway, leading to reduced immune resistance, further increasing the risk of infection (11). When patients

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develop pulmonary infections, their condition deteriorates, affecting the treatment of primary diseases. Dexmedetomidine combined with propofol reduces extubation times, however, to the best of our knowledge, whether combination therapy reduces VAP occurrence during mechanical ventilation has not previously been studied (12,13).

In the present study the sedative effects of dexmedetomidine combined with propofol in patients in the ICU undergoing mechanical ventilation were explored and the risk factors of VAP were assessed, in order to provide relevant references for clinicians.

Materials and methods

Patient data. The present study is a retrospective analysis of 322 patients that received mechanical ventilation in the ICU ward of Shanghai Fengxian District Central Hospital from May 2016 to June 2018. According to the use of anesthetics, patients were divided into a combined and monotherapy group. A total of 212 patients were included in the combined group, including 130 males and 82 females, and 110 patients were included in the monotherapy group, including 59 males and 51 females. The current study was approved by the Medical Ethics Committee of Shanghai Fengxian District Central Hospital and the family members of patients signed informed consent forms.

Inclusion and exclusion criteria. The patient inclusion criteria were as follows: i) >18 years old; ii) required mechanical ventilation according to a clinician's diagnosis; iii) complete clinical data; iv) mechanical ventilation time <12 h or with an estimated mechanical ventilation time of >24 h; v) received sedative adjuvant therapy. Patient exclusion criteria were as follows: i) Pregnancy; ii) died within 3 days of mechanical ventilation or were transferred to other hospital within 3 days of mechanical ventilation; iii) had undergone digestive tract surgery or had a medical history of digestive disease, immune deficiency, central nervous system disease or cognitive impairment; iv) required renal replacement therapy; v) heart rate <55 beats/min.

Diagnostic criteria for VAP. Patients were diagnosed with VAP if they met the Guidelines for the Diagnosis and Treatment of Hospital-acquired Pneumonia at the Society of Respiratory Diseases of the Chinese Medical Association (14), but also met one of the following laboratory testing conditions: i) Leukocyte counts >$1*10^{11}$/l; ii) leukocyte counts <$4*10^{10}$/l; iii) body temperature >37.5˚C; iv) purulent secretions in respiratory tract; v) isolation of pathogenic bacteria from the airway.

Sedation schemes. Both groups were treated with fentanyl (Jiangsu Nhwa Pharmaceutical Co., Ltd.; cat. no. H20143315; 0.3 μg/kg/h) for continuous intravenous analgesia. In the combined group, dexmedetomidine (Jiangsu Hengrui Medicine Co., Ltd; cat. no. H20090248; 0.5 μg/kg) was injected 10 min prior to fentanyl administration and continuously injected through a micro-injection pump (0.1-0.2 mg/kg/h). Propofol (0.1-0.3 mg/kg/h) was also continuously pumped intravenously. In the monotherapy group, dexmedetomidine (0.5 μg/kg) was slowly injected 10 min prior to fentanyl administration. Dexmedetomidine (0.3-0.6 mg/kg/h) was continuously intravenously injected through a micro-injection pump.

Pathogenic bacteria cultures. An aseptic sputum aspirator was used to collect lower respiratory tract secretions and pharyngeal swabs were used to collect pharyngeal wall specimens every 24 h. Pathogenic bacteria were detected using a BacT/Alert 3d60 automatic bacterial/mycobacterial culture monitoring system (Institut Mérieux).

Observation indicators. The main observation indicator was the number of patients with VAP in both the monotherapy and the combined group. According to VAP occurrence, patients were divided into VAP and non-VAP groups. Independent risk factors for the development of VAP were analyzed using multivariate analysis, and significance indicators were plotted using receiver operating characteristic (ROC) curves.

Secondary observation indicators, including clinical data such as sex, age, body mass index, past medical history, alcohol abuse, smoking history and acute physiology and chronic health evaluation II (APACHE II) scores (15) as well as sedative effects (onset time, waking time and extubation time), were compared between the groups. After extubation, the Ramsay scores (16) of the two groups were compared. The patients were scored as follows: A score of 1 was given if the patient was anxious, restless or, uneasy; a score of 2 was given if the patient was quiet, cooperative and had good directional force; a score of 3 was given if the patient was quiet and only responded to instructions; a score of 4 was given if the patient was in a state of sleep and only responding to light elastic stimulation between the eyebrows; a score of 5 was given if the patient was in a state of sleep and the response to light elastic stimulation between the eyebrows was slow; a score of 6 was given if the patient was in a state of sleep and did not respond to stimulation.

Statistical analysis. SPSS 20.0 software was used to analyze the collected data. GraphPad Prism 7 (GraphPad Software, Inc.) was used for image processing. Counting data were expressed as number (percentage) and assessed through the χ^2 method. Kolmogorov-Smirnov tests were used to analyze data distributions. Measurement data were expressed as the mean ± standard deviation. Independent sample t-tests were used to compare normal distribution data between the two groups. Using VAP as an independent variable and indicators with differences in a single factor as dependent variables, the independent risk factors of VAP were analyzed using the forward stepwise (Wald) method of multi-factor logistic regression. ROC curves were drawn to analyze indicators that had differences in multiple factors. P<0.05 was considered to indicate a statistically significant difference.

Results

Comparison of clinical data. Through comparison of the clinical data between the groups, no significant differences in sex, age, body mass index, past medical history, history of alcoholism, history of smoking, residence and APACHE II scores were observed (P>0.05; Table I).

Table I. Clinical information.

Characteristic	Monotherapy group (n=110)	Combined group (n=212)	χ^2/t	P-value
Sex			1.764	0.184
Male	59 (53.64)	130 (61.32)		
Female	51 (46.36)	82 (38.68)		
Age	57.20 (7.30)	59.00 (8.40)	1.842	0.067
BMI (kg/m^2)	22.44 (1.55)	22.69 (1.95)	1.167	0.244
Past medical history				
Hypertension	27 (24.55)	60 (28.30)	0.518	0.472
Diabetes	12 (10.91)	27 (12.74)	0.227	0.634
COPD	16 (14.55)	35 (16.51)	0.210	0.647
History of alcoholism			1.179	0.278
Yes	10 (9.09)	28 (13.21)		
No	100 (90.91)	184 (86.79)		
History of smoking			0.151	0.698
Yes	65 (59.09)	130 (61.32)		
No	45 (40.91)	82 (38.68)		
Residence			0.348	0.555
City	69 (62.73)	140 (66.04)		
Country	41 (37.27)	72 (33.96)		
APACHE II score	28.36 (4.25)	27.86 (5.22)	0.939	0.323

Data are presented as (mean ± standard deviation) or frequency (%). BMI, body mass index; COPD, chronic obstructive pulmonary disease; APACHE, acute physiology and chronic health evaluation II.

Comparison of sedative effects. No significant differences in onset times were observed, but the waking and extubation times of the combined group were shorter than those of the monotherapy group. After extubation, the Ramsay score of the combined group was lower than that of the monotherapy group (Table II).

Occurrence of VAP and the distribution of pathogenic bacteria. A total of 54 patients with VAP were identified, 30 in the monotherapy group (27.27%) and 24 in the combined group (11.32%). The incidence of VAP was significantly higher in the monotherapy group (χ^2=16.565; P=0.003; Table III). According to the distribution of pathogenic bacteria detected through microorganisms, 72 pathogenic bacteria were detected in 54 patients. Amongst them, 38 strains (52.78%) were Gram-negative bacteria, 32 strains (44.44%) were Gram-positive and 2 strains (2.78%) were fungi (Table IV).

Univariate analysis of patients with VAP. Patients were re-grouped into VAP (n=54) and non-VAP groups (n=268). Univariate analysis of their clinical data revealed no differences in sex, body mass index, past medical history, history of alcoholism, history of smoking, residence or onset time (P>0.05), whilst differences in age, APACHE II score, consciousness disorders, invasive operations, sedation programs, waking time, and extubation time were significant (P<0.001; Table V).

Multivariate analysis and ROC curves. Single factors with significance were included and assigned (Table VI) for multivariate logistic regression analysis. Age, APACHE II score, consciousness disorders, invasive operations, waking time, extubation time and sedation regimens were independent risk factors for VAP in ICU patients undergoing mechanical ventilation (Table VII). Subsequently, ROC curves were plotted for the indicators of significant difference. The results demonstrated that the area under the curve of age, APACHE II score, consciousness disorders, invasive operations, waking time, extubation time and sedation regimens were 0.934, 0.870, 0.632, 0.677, 0.865, 0.950 and 0.603, respectively (Fig. 1 and Table VIII).

Discussion

The ICU treats an array of critically ill patients (17). Due to their serious condition, many patients in the ICU have difficulties breathing. In the clinic, mechanical ventilation can assist breathing to keep the airways open, improving ventilation and oxygenation, to prevent hypoxia and carbon dioxide accumulation (18). However, patients in the ICU often suffer from intolerance to mechanical ventilation, as a result, sedatives are commonly used for assisted ventilation (19). The side effects of opioid use in the ICU include prolonged ventilation, psychiatric effects (such as irritability or hallucination), asceticism and urinary retention, which can reduce the patient compliance to treatment (20). According to the guidelines on analgesia, sedation and delirium issued by the American Society of Critical Care Medicine in 2013, patients in the ICU should try to treated to 'shallow sedation', where the patient is still responsive to language instructions, but where cognitive functions and

Table II. Comparison of sedative effects.

Group	Monotherapy group (n=110)	Combined group (n=212)	t value	P-value
Onset time (s)	16.25 (4.88)	17.54 (6.24)	1.889	0.060
Waking time (min)	20.31 (5.22)	8.51 (4.33)	20.349	P<0.001
Extubation time (h)	7.84 (0.59)	5.36 (0.38)	39.977	P<0.001
Ramsay score after extubation	3.35±0.68	2.62±0.49	11.054	P<0.001

Data are presented as (mean ± standard deviation).

Table III. Comparison of ventilator-associated pneumonia incidence.

Group	Occurred	Not occurred	χ^2 value	P-value
Monotherapy group (n=110)	30	80	16.565	0.003
Combined group (n=212)	24	188		

Table IV. Comparison of distribution of pathogenic bacteria in VAP patients.

Pathogenic bacteria	n	Constituent ratio (%)
Gram-negative bacterium		
Staphylococcus aureus	27	37.50
Staphylococcus epidermidis	8	11.11
Enterococcus	3	4.17
Gram-positive bacterium		
Pseudomonas aeruginosa	23	31.94
Klebsiella pneumoniae	4	5.56
Escherichia coli	3	4.17
Acinetobacter baumannii	2	2.78
Fungus		
Candida albicans	1	1.39
Candida tropicalis	1	1.39

VAP, ventilator-associated pneumonia.

coordination abilities are affected, without impacting on the breathing and circulation. Regardless of the sedation duration, dexmedetomidine or propofol are recommended for sedation, whilst benzodiazepines are not recommended (21).

As a common short-acting intravenous anesthetic, propofol provides anesthesia and sedation by acting on GABA receptors. However, propofol has clear inhibitory effects on the circulation and respiration, leading to lower blood pressure and slower heart rates in patients (22). As a highly selective $\alpha 2$ receptor agonist, dexmedetomidine has analgesic, sedative and anti-anxiety effects by promoting the secretion of GABA; compared with propofol, dexmedetomidine was not observed not cause respiratory depression, which was conducive to extubation (23). The sedative effects of dexmedetomidine used alone or in combination with propofol were compared in the present study. The results indicated that, although the

dose of the two drugs was lower in the combined group, the two groups had similar onset times of anesthesia with the combined group showing significantly shorter waking times and extubation times compared with the monotherapy group. In studies by Xia *et al* (24), the sedative effects of propofol and dexmedetomidine alone on mechanical ventilation in the ICU were compared. The recovery and extubation times following dexmedetomidine treatment alone were significantly shorter than those of propofol. In the present study, shorter recovery and extubation times in response to the combination of dexmedetomidine and propofol were also observed, suggesting a good sedative effect. It can be speculated that the reason for this may be that the dose of the two drugs is reduced compared with that of the single drug, resulting in a shortening of the recovery time.

VAP is a common complication of mechanical ventilation in the ICU. The incidence of VAP in ICU patients after mechanical ventilation is high, which not only aggravates the condition, but also significantly increases mortality rates, which prolongs ICU residence times and increases costs (22,23). The incidence of VAP was compared between monotherapy and combined groups and a significantly lower incidence of VAP was observed in the combined group compared with the monotherapy group, indicating that the sedation impacted the occurrence of VAP after mechanical ventilation in the ICU. However, to the best of our knowledge, no relevant studies on different sedation regimens as independent factors for VAP have been performed. In the present study clinical data was collected and were patients divided into VAP and non-VAP groups. Multivariate analysis indicated that age, APACHE II score, the disturbance of consciousness, invasive operations, waking time, extubation time and sedation programs were independent factors affecting VAP after mechanical ventilation in ICU patients. With increased patient age, body functions gradually weaken, and older patients have more basic diseases, such as hypertension, hyperlipidemia and diabetes, which often aggravates the condition (25). This is likely to be the main reason for the increased incidence of VAP after mechanical ventilation.

Table V. Univariate analysis.

Factor	VAP group (n=54)	Non-VAP group (n=268)	χ^2/t value	P-value
Sex			2.977	0.084
Male	26 (48.15)	163 (60.82)		
Female	28 (51.85)	105 (39.18)		
Age	65.54 (3.25)	58.41 (3.65)	13.326	P<0.001
BMI (kg/m^2)	22.54 (1.52)	22.69 (1.84)	0.561	0.575
Past medical history				
Hypertension	13 (24.07)	74 (27.61)	0.182	0.671
Diabetes	8 (14.81)	31 (11.57)	0.445	0.505
COPD	10 (18.52)	41 (15.30)	0.350	0.554
History of alcoholism			0.084	0.772
Yes	7 (12.96)	31 (15.57)		
No	47 (87.04)	237 (88.43)		
History of smoking			1.013	0.314
Yes	36 (66.67)	159 (59.33)		
No	18 (33.33)	109 (40.67)		
Place of residence			0.850	0.357
City	38 (70.37)	171 (63.81)		
Country	16 (29.63)	97 (36.19)		
APACHE II score	31.55 (2.58)	25.33 (3.84)	11.389	P<0.001
Disturbance of consciousness			22.381	P<0.001
Yes	22 (40.74)	38 (13.67)		
No	32 (59.26)	240 (86.33)		
Invasive operation			30.719	P<0.001
Yes	29 (53.70)	49 (18.28)		
No	25 (46.30)	219 (81.72)		
Sedation scheme			19.822	P<0.001
Monotherapy	30 (55.56)	70 (25.18)		
Combined therapy	24 (44.44)	208 (74.82)		
Onset time (sec)	17.25 (4.48)	18.54 (5.44)	1.634	0.103
Recovery time (min)	18.54 (4.25)	12.58 (3.98)	9.925	P<0.001
Extubation time (h)	8.54 (0.74)	5.32 (1.25)	18.281	P<0.001

Data are presented as mean ± standard deviation), or frequency (%). VAP, ventilator-associated pneumonia; BMI, body mass index; COPD, chronic obstructive pulmonary disease; APACHE, acute physiology and chronic health evaluation.

Table VI. Logistic regression factor assignment table.

Factor	n
Age (X)	<50 years old=1, 51-55 years old=2, 56-60 years old=3, >61 years old=4
APACHE scores (X)	Using original data as it belongs to continuous variable
Conscious disturbance (X)	Yes=1, No=2
Invasive operation	Yes=1, No=2
Onset time (X)	Using original data as it belongs to continuous variable
Extubation time (X)	The average extubation time is 5.85; ≤5.85=1, >5.85=2
Sedation scheme (X)	Monotherapy=1, combined therapy=2
VAP situation (Y)	VAP patient=1, non-VAP patient=2

X, independent variable; Y, dependent variable. VAP, ventilator-associated pneumonia; APACHE, acute physiology and chronic health evaluation.

Table VII. Multivariate logistic regression analysis.

| | | | | | | 95% CI of Exp (β) | |
Factor	β	SEM	Wals	P-value	Exp (β)	Low limit	Upper limit
Age	-2.172	0.571	14.459	<0.001	0.114	0.037	0.349
APACHE II scores	-0.449	0.130	11.889	0.001	0.638	0.494	0.824
Disorder of consciousness	2.630	1.066	6.090	0.014	13.870	1.718	111.973
Invasive operation	2.950	1.003	8.655	0.003	19.099	2.677	136.289
Waking time	-0.302	0.128	5.571	0.018	0.740	0.576	0.950
Extubation time	-5.451	1.540	12.394	<0.001	0.004	0.000	0.089
Sedation scheme	1.825	0.818	4.983	0.026	6.204	1.249	30.805

APACHE, acute physiology and chronic health evaluation; Exp, expectation; CI, confidence interval.

Table VIII. ROC parameters.

Parameter	AUC	95% CI	Specificity %	Sensitivity %	Youden index %	Cut-off
Age	0.934	0.904-0.964	92.59	80.59	73.19	<61.00
APACHE II scores	0.870	0.826-0.915	79.63	80.59	60.23	<29.00
Disorder of consciousness	0.632	0.545-0.721	59.26	85.82	26.56	1
Invasive operation	0.677	0.592-0.762	53.70	81.72	35.42	1
Waking time	0.865	0.814-0.915	74.07	84.70	58.78	<16.47
Extubation time	0.950	0.914-0.986	94.44	92.54	86.98	<7.11
Sedation scheme	0.603	0.518-0.687	51.85	68.66	20.51	1

APACHE, acute physiology and chronic health evaluation; AUC, area under the curve; CI, confidence interval.
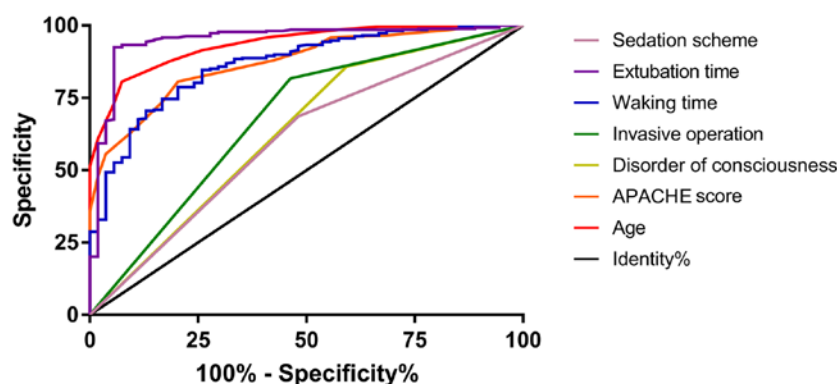

Figure 1. Receiver operating characteristic curve of ventilator-associated pneumonia occurrence, predicted by multi factor analysis difference index. ROC, receiver operating characteristic; APACHE, acute physiology and chronic health evaluation.

APACHE II scores are important comprehensive scores to assess the severity of the patients' condition. Higher scores indicate a higher risk of VAP. Invasive manipulation provides a direct channel for pathogens to enter the body. Moreover, invasive manipulations damage the respiratory mucosa and increase VAP incidence (11). In the different sedation schemes, the waking and extubation times of the monotherapy group were lower compared with the combined group. If the patient exhibited no consciousness disturbance after awakening, the machine was withdrawn ahead of schedule. Extubation times have been shown to be directly related to the incidence of VAP, mainly due to the fact tracheal insertion establishes a channel that increases infections by pathogenic bacteria infection. The shorter the extubation time, the lower the incidence of VAP (26).

The results of the present study indicated that a combination of drugs can shorten the waking and extubation times of patients with mechanical ventilation in the ICU. Multivariate analysis also suggests that different sedation schemes are independent risk factors for VAP. However, there are some

limitations to the present study. As a retrospective analysis, selection bias can occur. Additionally patients treated with propofol only anesthesia were not included in the current study and their impact on the study findings requires assessment. Finally, statistics were not gathered regarding the adverse reactions of patients to the drugs. It is not clear whether the two schemes affect the adverse reactions of patients. Further prospective randomized controlled trials and other sedation regimens are now required to confirm these results.

In conclusion, dexmedetomidine combined with propofol may shorten the recovery and extubation time of patients with mechanical ventilation in the ICU compared with dexmedetomidine treatment alone. Different sedation schemes are also suggested to be independent risk factors for VAP in patients with mechanical ventilation in the ICU.

Availability of data and materials

The datasets use and/or anlayzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

HD was responsible for the research and analyzed the data;FH drafted the manuscript and analyzed the data.; WW and LL collected cases; DW and FL collected data.

Ethics approval and consent to participate

The present study was approved by the Medical Ethics Committee of Shanghai Fengxian District Central Hospital and all patients signed informed consent forms.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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