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Article

Effect of combined sedation using multiple drugs on inflammatory cytokines in patients with acute respiratory distress syndrome

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The innate immune response plays an important role in the pathophysiology of acute respiratory distress syndrome (ARDS); however, no drug has been proven to be beneficial in the management of ARDS. Therefore, the aim of this study was to investigate the effects of using combined sedatives on systemic inflammatory responses in patients with ARDS. A total of 90 patients with ARDS and an intubation time of > 120 h were randomly divided into the propofol group (group P), midazolam group (group M), and combined sedation group (group U). Patients in groups P and M were sedated with propofol and midazolam, respectively, whereas patients in group U were sedated with a combination of propofol, midazolam, and dexmedetomidine. The dosage of sedatives and vasoactive drugs, duration of mechanical ventilation, and incidence of sedative adverse reactions were documented. The dosage of sedatives and vasoactive drugs, as well as the incidence of sedative adverse reactions in group U, was significantly lower than those in groups P and M. Similarly, the duration of mechanical ventilation in group U was significantly shorter than that in groups P and M. Hence, inducing sedation through a combination of multiple drugs can significantly reduce their adverse effects, improve their sedative effect, inhibit systemic inflammatory responses, and improve oxygenation in patients with ARDS.

Keywords: Acute respiratory distress syndrome. Combined sedation. Propofol. Midazolam. Dexmedetomidine. Cytokines.

INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a common clinical syndrome characterized by progressive hypoxemia and respiratory distress (Papazian *et al*., 2019; Wilson, Calfee, 2020). Despite advances in treatment, the mortality rate of severe ARDS has been reported to be as high as 46% (Grawe, Bennett, Hurford, 2016; Kallet, 2016; Scholten *et al*., 2017; Thompson, Chambers, Liu, 2017; Peck, Hibbert, 2019). Patients with ARDS often require sedation; however, improper sedation can lead to a decrease in treatment compliance and an increase in the incidence of circulatory disturbances, delirium, and other complications, thereby leading to a prolonged duration of mechanical ventilation, extended length of hospitalization, and increased mortality rate (Pearson, Patel, 2020). Currently, most patients with ARDS are sedated using a single drug administered in large doses. As continuous administration of large doses often leads to adverse reactions and complications (Schweickert *et al*., 2009; Devlin *et al*., 2018), we aimed to investigate the effects of combining multiple sedatives on systemic inflammatory responses in patients with ARDS.

MATERIAL AND METHODS

General data

This study enrolled patients with ARDS who were admitted to the intensive care unit (ICU) of the

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Emergency Department of Jiangxi Provincial People's Hospital (Nanchang, China) between September, 2019, and September, 2020. The inclusion criteria were: (1) those whose duration of endotracheal intubation was > 120 h, (2) those whose ages were > 18 years, and (3) those with acute physiology and chronic health evaluation (APACHE) II scores > 12 points. We excluded patients with a history of allergy to propofol, dexmedetomidine, and benzodiazepines, pregnant women, patients in the early stage of recovery, and those with unstable hemodynamics, bradycardia, sinus arrest, or other cardiac arrhythmias. Further, the included patients were randomly assigned to three groups according to their sedation type: propofol group (group P), midazolam group (group M), and combined sedative group (group U), and the attending physicians were not blinded to the treatment. Patient age, sex, and APACHE II scores did not significantly differ among the groups ($P > 0.05$; Table I).

This study was approved by Jiangxi Provincial People's Hospital, and informed consent was obtained from the patients or their families.

TABLE I - Comparison of patient characteristics among the three groups

Group	n	Mean age (years)*	Sex (male/female)*	APACHE II score*
P	30	51.6 ± 24.2	12/18	19.2 ± 3.6
M	30	52.4 ± 23.6	13/17	19.5 ± 3.2
U	30	52.2 ± 23.4	12/18	19.4 ± 3.4

*$P > 0.05$, no significant differences among the groups.

METHODS

All patients were treated using a lung protective ventilation strategy. Fluid intake and output volumes were strictly managed; nutrition support, adequate analgesia, and other comprehensive therapies were provided, including the administration of antibiotics. For sedation, patients in group P received propofol with a loading dose of 0.025–1.000 mg/kg, followed by a maintenance dose of 0.5–4.0 mg/kg/h; patients in group M received midazolam with a loading dose of 0.03–0.30 mg/kg, followed by a maintenance dose of 0.03–0.20 mg/kg/h; and patients in group U received maintenance doses of propofol and midazolam along with that of dexmedetomidine at 0.2–0.7 μg/kg/h. Intravenous infusion of norepinephrine at a concentration of 0.5 mg/kg/min was administered to all the patients. Sedation drug dosages were titrated for all the patients to maintain a Richmond Agitation-Sedation Scale score between −1 and 0.

Measurements

The I-STAT portable blood gas analyzer (Abbott, Germany) was used to measure the oxygenation index (PaO_2/FiO_2) before and at 24, 48, 72, and 120 h after the administration of the sedatives. PaO_2/FiO_2 is the ratio of arterial oxygen partial pressure (PaO_2 in mmHg) to fractional inspired oxygen (FiO_2 expressed as a fraction, not as a percentage), and it is a widely used clinical indicator of hypoxemia. At sea level, the normal PaO_2/FiO_2 ratio is approximately 400–500 mmHg (~55–65 kPa).

Venous blood samples were centrifuged to obtain plasma, which was stored at a low temperature and later used to measure plasma concentrations of tumor necrosis factor-α (TNF-α), interleukin 6 (IL-6), and high mobility group box 1 (HMGB-1). Sedative doses, vasoactive drug doses, and the incidence of hypotension, bradycardia, ventilator-associated pneumonia, delirium, constipation, diarrhea, and other adverse effects of sedation were recorded.

Statistical analysis

Statistical analyses were conducted using SPSS software version 13.0 (IBM Corp., Armonk, NY, USA). Continuous data were presented as mean ± standard deviation, and they were compared using Student's t-test and analysis of variance. Categorical data were presented as numbers with percentages, and were compared using chi-square test. Statistical significance was set at $P < 0.05$.

RESULTS

Comparison of sedative doses, vasoactive drug doses, and duration of mechanical ventilation

The propofol dose was 1256.2 ± 312.4 mg/d in group P and 1074.9 ± 288.5 mg/d in group U; the dose of midazolam was 122.5 ± 22.7 mg/d in group M and 110.2 ± 20.6 mg/d in group U; the dose of the vasoactive drug noradrenaline was 126.4 ± 28.5 mg/d in group P, 128.2 ± 25.6 mg/d in group M, and 112.5 ± 23.8 mg/d in group U; the duration of mechanical ventilation was 195.6 ± 58.2 h in group P, 211.5 ± 60.4 h in group M, and 167.3 ± 42.7 h in group U. In group U, the doses of propofol, midazolam, and noradrenaline were significantly lower ($P < 0.05$) than those in groups P and M. Likewise, the duration of mechanical ventilation in group U was significantly shorter than that in groups P and M ($P < 0.05$; Table II)

TABLE II - Comparison of sedative doses, vasoactive drug doses, and duration of mechanical ventilation

Group	n	Propofol (mg/d)	Midazolam (mg/d)	Noradrenaline (mg/d)	Duration of mechanical ventilation (h)
P	30	1256.2 ± 312.4	NA	126.4 ± 28.5	195.6 ± 58.2
M	30	NA	122.5 ± 22.7	128.2 ± 25.6	211.5 ± 60.4
U	30	1074.9 ± 288.5*	110.2 ± 20.6#	112.5 ± 23.8*#	167.3 ± 42.7*#

NA, not applicable

*$P < 0.05$ compared with group P; #$P < 0.05$ compared with group M.

Comparison of incidence of adverse effects

The incidence of adverse effects among the groups was 53.3% in group P, 56.7% in group M, and 26.7% in group U. Thus, the incidence of sedative adverse effects was significantly lower in group U than in groups P and M ($P < 0.05$; Table III).

TABLE III - Comparison of incidence of adverse effects

Group	N	Number of adverse reactions (%)
P	30	16 (53.3%)
M	30	17 (56.7%)
U	30	8 (26.7%)*#

*$P < 0.05$ compared with group P; #$P < 0.05$ compared with group M

Comparison of PaO2/FiO2 and concentrations of inflammatory cytokines

No significant differences were observed in PaO_2/FiO_2 and concentrations of inflammatory cytokines among the three groups before the administration of the sedatives (Table IV). However, in group U, the concentrations of plasma TNF-α, IL-6, and HMGB-1 were significantly lower than those in groups P and M at 24, 48, 72, and 120 h after administering the sedatives ($P < 0.05$). In addition, the PaO_2/FiO_2 was significantly higher in group U than in groups P and M at 120 h after sedation initiation ($P < 0.05$; Figures 1 - 4).

TABLE IV - Comparison of oxygenation and inflammatory cytokines before and after initiating sedation

Group	N	Treatment time (h)	PaO_2/FiO_2	IL-6 (ng/L)	TNF-α (ng/L)	HMGB-1 (ng/mL)
P	30	0	188.2 ± 30.4	34.2 ± 4.6	26.6 ± 3.9	4.2 ± 0.5
		24	176.4 ± 26.2	30.8 ± 4.2	20.5 ± 3.2	9.7 ± 0.8
		48	170.2 ± 25.6	29.5 ± 3.8	18.4 ± 3.2	10.6 ± 1.2
		72	172.6 ± 26.5	26.6 ± 3.8	17.6 ± 2.7	10.2 ± 0.8
		120	180.6 ± 32.8	25.6 ± 3.9	17.2 ± 2.5	9.6 ± 0.6
M	30	0	186.6 ± 34.8	33.8 ± 4.5	26.8 ± 3.8	4.5 ± 0.6
		24	170.4 ± 25.7	30.5 ± 4.1	21.2 ± 3.6	9.9 ± 0.8
		48	168.3 ± 28.5	29.7 ± 3.9	18.5 ± 3.4	10.8 ± 1.4
		72	169.8 ± 27.8	26.9 ± 3.6	17.8 ± 2.8	10.5 ± 1.2
		120	175.2 ± 29.6	26.2 ± 3.5	17.5 ± 2.6	9.8 ± 0.9
U	30	0	189.5 ± 33.2	34.5 ± 4.2	26.5 ± 3.5	4.5 ± 0.5
		24	180.4 ± 32.5	28.4 ± 3.9*#	19.1 ± 2.8*#	10.2 ± 0.6*#
		48	183.3 ± 31.6	27.5 ± 3.2*#	16.6 ± 3.3*#	9.9 ± 0.8*#
		72	184.2 ± 30.2	24.7 ± 3.4*#	16.2 ± 2.6*#	9.8 ± 0.6*#
		120	198.6 ± 33.5*#	24.3 ± 2.7*#	15.9 ± 2.5*#	9.2 ± 0.8*#

PaO_2/FiO_2, oxygenation index; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; HMGB-1, high mobility group box 1; *$P < 0.05$ compared with group P at the same time point; #$P < 0.05$ compared with group M at the same time point.

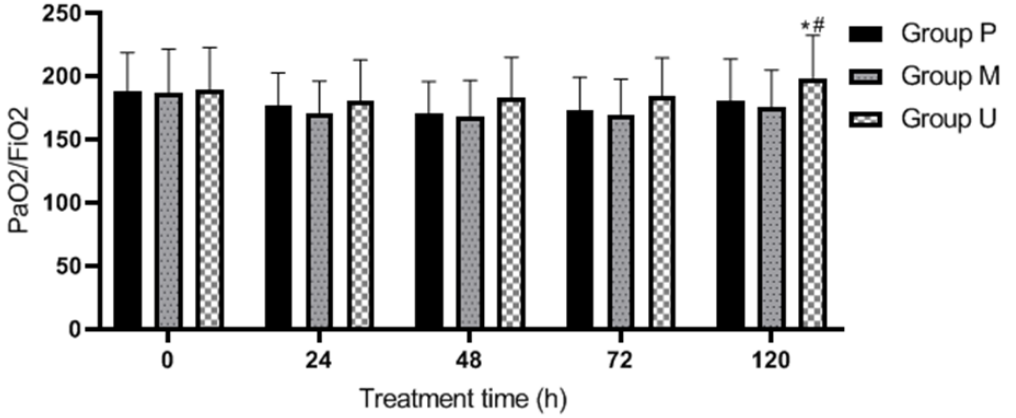

FIGURE 1 - Comparison of PaO_2/FiO_2 among the three groups at different treatment times.

*P < 0.05 compared with group P at the same time point; #P < 0.05 compared with group M at the same time point.

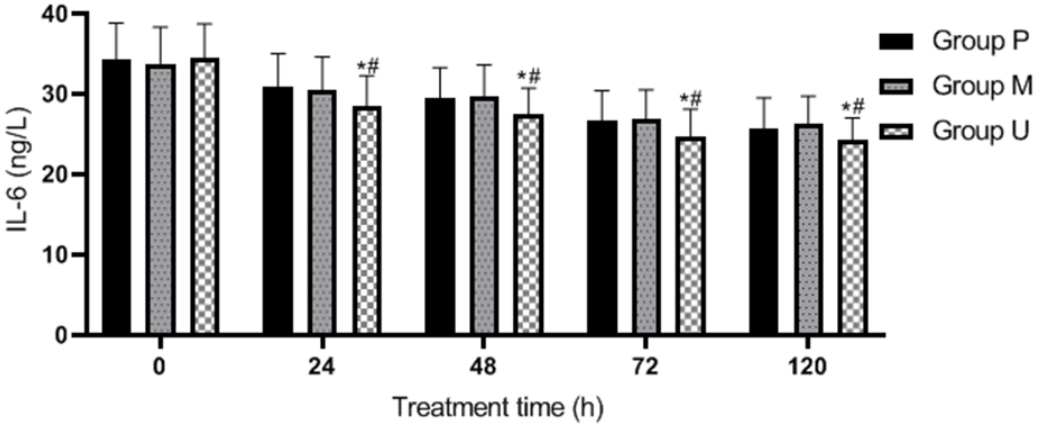

FIGURE 2 - Comparison of IL-6 levels among the three groups at different treatment times.

*P < 0.05 compared with group P at the same time point; #P < 0.05 compared with group M at the same time point.

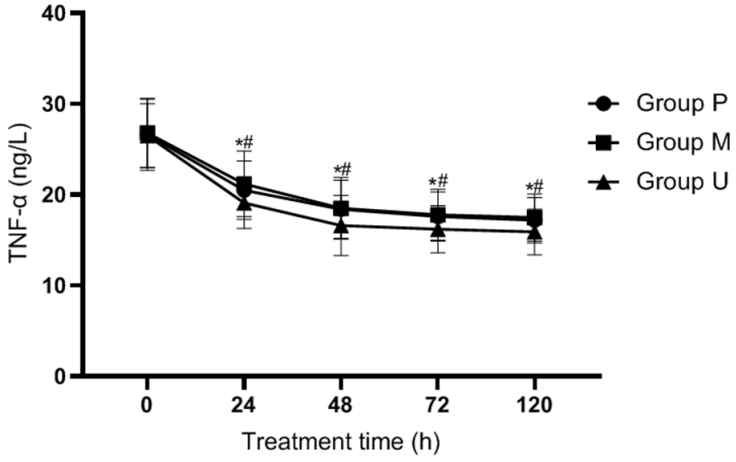

FIGURE 3 - Comparison of TNF-α levels among the three groups at different treatment times.

*P < 0.05 compared with group P at the same time point; #P < 0.05 compared with group M at the same time point.

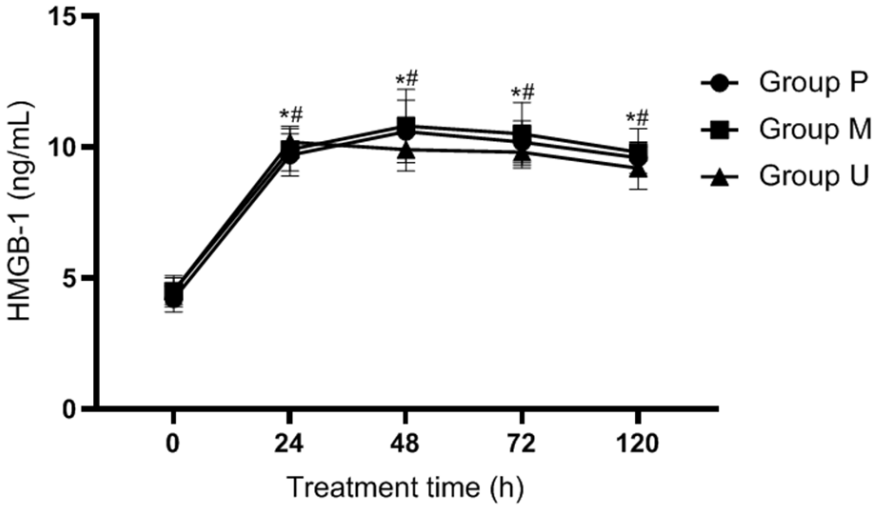

FIGURE 4 - Comparison of HMGB-1 levels among the three groups at different treatment times.

*P < 0.05 compared with group P at the same time point; #P < 0.05 compared with group M at the same time point.

DISCUSSION

We investigated the effect of using combined multiple sedatives on the systemic inflammatory response of patients with ARDS. Combining sedatives significantly reduced the required sedative doses, vasoactive drug dose, and incidence of adverse effects associated with sedative treatment. Furthermore, the duration of mechanical ventilation was significantly shortened, concentrations of plasma inflammatory cytokines was significantly lowered, and the oxygenation index was significantly improved.

Sedation has been used as conventional therapy for patients with severe ARDS because it reduces metabolism and oxygen consumption, thereby preventing organ injury and facilitating the recovery of organ function (Devlin *et al*., 2018). Currently, patients are often sedated with a single drug, and large doses are often required to achieve an adequate sedative effect. However, continuous administration of large doses often causes adverse effects and complications. High-dose midazolam may cause respiratory depression, drug accumulation, and delirium, while high-dose propofol may cause hypotension, hyperlipidemia, and even fatal propofol infusion syndrome (Hemphill *et al*., 2019). Continuous use of high-dose dexmedetomidine may cause bradycardia. Moreover, high-dose sedatives generally affect gastroenteric functions and may cause ICU-acquired weakness (Zorowitz, 2016). Furthermore, adjusting sedation depth and implementing the current recommended strategy of light sedation in patients with mild to moderate ARDS are difficult when sedating with a single drug (Shah, Girard, Yende, 2017).

Sedatives commonly used today include benzodiazepines, propofol, and dexmedetomidine. Midazolam is a γ-aminobutyric acid receptor agonist in the central nervous system (CNS), and dexmedetomidine is a selective α_2 receptor agonist (Nelson *et al*., 2015; Prommer, 2020). The specific sedative mechanism of propofol is unclear; however, it may affect multiple CNS receptors and ion channels. Since different drugs have different targets and mechanisms, previous studies have investigated sedation induced by combining multiple drugs. A previous study (Angsuwatcharakon *et al*., 2012) showed that a combination of propofol, midazolam, and pethidine during endoscopic retrograde cholangiopancreatography improves sedation and shortens the waking time. Lin *et al.* (2020) administered propofol, midazolam, and fentanyl to patients undergoing gastroenteroscopy and reported a significantly shorter waking time, shorter length of stay, and reduced incidence of adverse effects than with the traditional administration

of propofol alone. Another study (Amini *et al*., 2018) showed that the combined use of propofol, midazolam, ketamine, and fentanyl in emergency patients could achieve adequate sedation more rapidly. Consistent with these studies, the sedation achieved in our study using a combination of multiple drugs significantly reduced the required sedative and vasoactive drug doses as well as the incidence of the sedatives' adverse effects. Furthermore, the duration of mechanical ventilation recorded was shortened. Thus, these findings indicate that inducing sedation through a combination of multiple drugs improves sedation in patients with ARDS.

Uncontrolled inflammation is considered the primary cause of ARDS, and inflammatory cytokines significantly affect the pathogenesis of ARDS (Zhao *et al*., 2016). Inflammatory cytokine concentrations are significantly high in patients with ARDS and reflect the severity of lung injury. When these cytokine concentrations decrease, patient condition and respiratory indicators significantly improve (Sharp, Millar, Medford, 2015). Therefore, in addition to treating ARDS etiology and providing ventilation support, controlling inflammation and inhibiting the cytokine cascade are imperative to improve treatment outcomes. Common sedatives exert anti-inflammatory effects through various mechanisms of action (Guo *et al*., 2018). According to a previous report (Xiao *et al*., 2015), midazolam significantly inhibits inflammation and reduces inflammatory factor concentrations in mice with sepsis. Further, another study (Yu, Li, 2019) showed that propofol significantly inhibited inflammation and oxidative stress by regulating the P38MAPK/NF-KB signaling pathway, thus reducing acute lung injury caused by lipopolysaccharides. Moreover, dexmedetomidine inhibits inflammation by regulating the MAPK signaling pathway and exerts a protective effect on lung tissue (Xu *et al*., 2015). Chen *et al.* (2018) also showed that inducing sedation through a combination of dexmedetomidine and propofol significantly reduced the concentrations of plasma IL-6, TNF-α, and other inflammatory factors in patients with ARDS. Consistent with the studies above, our study showed that inducing sedation using a combination of propofol, midazolam, and dexmedetomidine significantly lowered plasma inflammatory cytokine concentrations and improved PaO_2/FiO_2, which means that inducing sedation using a combination of multiple drugs facilitates the inhibition of systemic inflammatory responses and improves oxygenation in patients with ARDS.

In conclusion, our study showed that inducing sedation using a combination of multiple drugs could significantly reduce their adverse effects, improved their sedative effect, inhibited the systemic inflammatory response, and improved oxygenation in patients with ARDS.

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None.

DECLARATION OF CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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AUTHOR CONTRIBUTIONS

Xiangbi Nie and Zenggeng Wang conceived the study and designed the experiments. Liqiong Lou, Hui Xu, and Wei Xiong contributed to the data collection, performed the data analysis, and interpreted the results. Xiangbi Nie wrote the manuscript, and Zenggeng Wang contributed to the critical revision of the article. All authors read and approved the final manuscript.

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