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Original Research Article

Impact of selected sedative agents on inflammatory immune response and clinical outcomes in mechanically-ventilated patients with acute exacerbation of chronic obstructive pulmonary disease complicated by sepsis

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Abstract

Purpose: *To determine the diverse impact of dexmedetomidine (Dex), propofol (Pro), and midazolam (Mid) sedation on immune response, inflammation, and treatment effects in mechanically-ventilated patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) complicated by sepsis.*

Methods: *90 patients with AECOPD complicated by sepsis who were undergoing mechanical ventilation in Xuzhou First People's Hospital, China were randomly divided into Pro, Dex and Mid groups, with 30 patients in each group. Prior to the initiation of mechanical ventilation treatment, participants in each group received a slow intravenous injection of 10 - 40 mg of Pro, Dex (1 μg/kg) or Mid (0.05 mg/kg). Throughout the treatment period, each group underwent continuous intravenous infusion, with Pro, Dex and Mid administered at a rate of 0.3 - 4 mg/kg/h; 0.2 - 0.7 μg/kg/h, and 0.02 - 0.1 mg/kg/h, respectively.*

Results: *On the 6th post-treatment day, concentrations of IL-6, IL-1β, and IL-8 in Pro, Dex and Mid groups were 44.82 ± 25.32, 29.84 ± 26.23, and 43.45 ± 24.57 pg/mL; 12.78 ± 4.48, 9.62 ± 2.28, and 12.19 ± 5.20 pg/mL, and 9.57 ± 3.29, 7.38 ± 2.46, and 10.41 ± 3.66 pg/mL, respectively. The Dex group exhibited significantly lower levels than the pre-treatment levels when compared to others ($p < 0.05$).*

Conclusion: *In patients with AECOPD complicated by sepsis, dexmedetomidine sedation effectively mitigates inflammatory response, enhances immune function, improves oxygenation index, enhances lung static compliance, and decreases hospitalization time. Future studies will require a larger sample size drawn from multiracial populations to validate the findings of this report.*

Keywords: *Dexmedetomidine, Acute exacerbation, Chronic obstructive pulmonary disease, Sepsis, Mechanical ventilation, Inflammatory*

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common respiratory disease, and is currently ranked as the fourth leading cause of death all over the world [1]. In individuals experiencing acute exacerbation of chronic obstructive pulmonary disease (AECOPD), dyspnea symptoms are notably exacerbated, with accompaniment of evident inflammatory reactions, when compared to those with COPD in stable periods. In severe cases, timely administration of anti-infection treatment in combination with mechanical ventilation, is imperative [2]. Patients affected by AECOPD are mostly the elderly with weakened immune system. Infection is the main cause of the disease in these patients. In addition, AECOPD patients have a higher risk of sepsis, and those with sepsis have a higher risk of death than non-septic patients [3-5].

Sedation treatment constitutes an important aspect of overall therapeutic strategies for AECOPD subjects undergoing mechanical ventilation. However, if the sedation drugs are not used properly, the length of stay in intensive care unit (ICU) will be prolonged. Some studies have reported that sedation treatment exhibits an immune regulatory effect by influencing decreased production of inflammatory factors and ameliorating clinical symptoms [6,7]. Nevertheless, there is no standard and optimized sedation regimen for AECOPD. Hence, this study was aimed at investigating the impact of various sedation options on immune inflammation and prognosis in patients undergoing mechanical ventilation due to AECOPD complicated by sepsis.

METHODS

Study design

The study was designed as a prospective, randomized, single blind, controlled, and single center clinical study.

Subjects

Ninety (90) patients with AECOPD complicated by sepsis who underwent mechanical ventilation at the ICU of Xuzhou First People's Hospital, China hospital from December 2019 to November 2022, were selected. The Ethical Authority of Xuzhou First People's Hospital granted approval for this study (approval no. xyll (2020) No. 39), and the study met the criteria in the Declaration of Helsinki [8]. The subjects participated voluntarily and submitted signed informed consent.

Inclusion criteria

All enrolled patients met the diagnostic criteria for acute exacerbation of chronic obstructive pulmonary disease (AECOPD) [9] and sepsis [10]. Additionally, they exhibited indications for endotracheal intubation and mechanical ventilation [9]. The inclusion criteria were as follows: patients with acute onset time not exceeding 1 week; patients who did not take glucocorticoids in the previous 2 weeks before the study; those aged 50 years and above, and patients who provided informed consent.

Exclusion criteria

Patients in the following categories were excluded from the study: those aged 85 years or more; patients with severe circulatory failure requiring high-dose vasoactive drugs; patients with comorbid systemic underlying diseases that might negatively impact respiratory function and prognosis; patients with comorbid diseases that might affect immune indices of inflammation; those with a history of allergy or contraindication to the sedative and analgesic drugs used in the study, as well as patients expected to be treated in the ICU for less than 6 days.

Drugs, reagents and instruments

Drugs and reagents

The sedative drugs utilized in this study were Dexmedetomidine (Dex) injection (Yangtze River Pharmaceutical Group Co. Ltd; specification: 0.2 mg/2 mL; lot numbers 19081432, 21051131, 22011832; Registration Certificate No. OTC H20183219); Propofol (Pro) (Sichuan Guorui Pharmaceutical Co. Ltd; specification: 0.10 g/10 mL; lot numbers 19062811, 21062811, 22070913; Registration Certificate No. OTC H20050079). Additionally, Midazolam (Mid) (Jiangsu Nhwa Pharmaceutical Co. Ltd; specification: 10 mg/2 mL; lot numbers: MZ190701, MZ211205, MZ221005; Registration Certificate no. OTC H19990027) was used.

The enzyme-linked immunosorbent assay (ELISA) kits employed for the analysis of IL-6, IL-1β, IL-8, IgA, IgM, and IgG were procured from Multi Sciences (Lianke) Biotech Co. Ltd.

Instruments

DxFLEX flow cytometer was produced by Beckman Coulter Life Sciences. GEM Premier

3000 automatic blood gas analyzer was product of National Instruments, USA. Spirit wisdom ventilator eVolution 3e was produced by VentMedical Ltd., Ireland.

Grouping and treatments

Based on variations in sedative drug choices, the study participants were divided into three groups: Dex, Pro and Mid groups. All patients in the three groups received comprehensive rescue measures such as active anti-infection, endotracheal intubation, mechanical ventilation, analgesia, fluid replacement, stabilization of circulation, protection of organ function and maintenance of homeostasis after admission to ICU.

In all three groups, a slow intravenous injection was administered before mechanical ventilation. It consisted of Pro at a dose range of 10 - 40 mg, Dex (1 μg/kg), and Mid (0.05 mg/kg). Subsequently, during mechanical ventilation, continuous intravenous infusion of Pro was implemented at rate of 0.3 - 4 mg/kg/h, Dex and Mid at rates of 0.2 - 0.7 μg/kg/h and 0.02 -0.1 mg/kg/h, respectively [11].

The sedation score was rated with Richmond agitation-sedation scale (RASS), which was maintained at -1 to 2 points. The arousal test was performed daily to adjust the doses of sedative drugs [11]. Patients in the three groups were continuously sedated for more than 6 days.

Evaluation of parameters/indices

Inflammatory and immune indicators

Peripheral blood (4 mL) was drawn from the vein of each subject prior to treatment (T0), on the 3rd day of treatment (T3d) and on the 6th day of the treatment (T6d). After separation of serum, it was placed in the freezer at -70 ℃ prior to use. The concentrations of IL-6, IL-1β, IL-8, IgA, IgM, and IgG were quantified using ELISA as per the provided instructions.

Pulmonary function parameters

At T0, T3d, and T6d, arterial blood samples were collected for blood gas analysis to determine the partial pressure of oxygen (PaO_2). Subsequently, the oxygenation index (PaO_2/FiO_2) was calculated for patients based on the fraction of inspired oxygen (FiO_2). Concurrently, static lung compliance (Cst) levels were assessed using a respiratory function monitor at the afore-mentioned time points.

Evaluation of clinical efficacy

On the 6th day of treatment, Acute Physiology and Chronic Health Scoring System II (APACHE II) and Sequential Organ Failure Assessment (SOFA) scores were computed for each group. Additionally, the times spent in ICU and mechanical ventilation were meticulously recorded for comprehensive evaluation.

Safety analysis

The occurrences of adverse drug reactions throughout the treatment period were systematically documented for each of the three groups.

Statistical analysis

The data collected were subjected to analysis and processing with SPSS 22.0 statistical software. Normality tests and homogeneity of variance analyses were conducted for different groups of data. Counting data are expressed as numbers and percentages (n (%)). Comparisons between groups were conducted with χ^2. Measurement data are expressed as mean ± standard deviation (SD). Comparisons of means amongst groups were performed with ANOVA. Statistical significance was assumed at $p < 0.05$.

RESULTS

General data

After screening, 113 subjects were included, while 23 participants were lost due to transfer or automatic discharge. The effective population comprised 90 subjects who were distributed equally amongst the 3 groups. General characteristics were comparable amongst the groups, as presented in Table 1.

Inflammatory indices

Before treatment, there were no statistical significance in differences in concentrations of IL-6, IL-1β, and IL-8 amongst the three groups. However, IL-6 and IL-1 levels decreased on the 3rd and 6th days of treatment, when compared to those before treatment, but there were lower levels in the Dex group than in the Pro group and the Mid group, with statistically significant differences ($p < 0.05$). On the 6th day of treatment, the level of IL-8 was lesser in Dex group than in Pro and Mid groups ($p < 0.05$), as shown in Table 2.

Table 1: Main clinical characteristics of study groups (n = 30)

Variable	Pro	Dex	Mid
Sex (male/female)	20/10	22/8	21/9
Age (years)	75.10±8.11	74.53±8.96	75.03±8.47
Duration of COPD (years)	13.33±5.47	12.87±4.72	13.67±4.38
$PaCO_2$ (mmHg)	70.53±12.51	69.17±12.81	68.97±11.46
WBC ($\times 10^9$/L)	13.89±4.37	14.24±4.68	13.16±3.72
PLT ($\times 10^9$/L)	141.53±36.59	148.16±35.17	149.90±38.41
TBIL (μmol/L)	19.75±5.68	19.10±5.45	18.43±6.78
APTT (sec)	44.73±8.38	44.92±7.81	43.83±8.56
T (℃)	38.19±0.83	37.93±0.81	38.08±0.83
Lac (mmol/L)	2.77±0.69	2.66±0.67	2.61±0.63
SOFA score	10.43±2.51	11.23±2.83	10.77±2.95
APACHE Ⅱ score	22.26±2.53	21.97±2.31	20.37±2.65

Pro group: Propofol infusion; Dex group: Dexmedetomidine infusion, Mid group: Midazolam infusion, COPD: Chronic obstructive pulmonary disease, $PaCO_2$: Partial pressure of carbon dioxide (mmHg); WBC: white blood cells, PLT: Platelet, T: temperature, Lac: lactic acid

Table 2: Interleukin levels in the three groups

Group	IL-6 (pg/mL)			IL-1β (pg/mL)			IL-8 (pg/mL)		
	T0	*T3d*	*T6*	*T0*	*T3d*	*T6d*	*T0*	*T3d*	*T6d*
Pro	79.13±41.38	62.25±32.30*	44.82±25.32*	21.50±10.35	16.68±8.18*	12.78±4.48*	16.28±8.57	12.41±5.60	9.57±3.29*
Dex	82.91±41.72	44.28±22.84	29.84±26.23	19.79±9.76	12.55±4.18	9.62±2.28	16.80±9.42	11.58±4.48	7.38±2.46
Mid	78.43±40.81	69.37±29.29#	43.45±24.57#	20.37±9.67	17.42±8.20#	12.19±5.20#	17.76±9.19	13.29±5.98	10.41±3.66#

*#$P < 0.05$, vs. Dex.

Table 3: IgA, IgM and IgG in three groups

Group	IgA (pg/mL)			IgM (pg/mL)			IgG (pg/mL)		
	T0	*T3d*	*T 6d*	*T0*	*T3d*	*T 6d*	*T0*	*T3d*	*T 6d*
Pro	2.74±0.89	3.14±0.88	3.17±1.14	0.91±0.47	1.06±0.63	1.11±0.49*	11.77±2.18	12.04±2.26	12.64±2.45*
Dex	2.83±0.91	3.09±0.85	3.25±1.13	0.95±0.54	1.08±0.59	1.47±0.52	11.64±2.31	12.19±2.24	14.05±2.56
Mid	2.79±0.97	3.06±0.94	3.15±1.11	0.91±0.48	1.04±0.54	1.09±0.47#	11.58±2.25	11.89±2.51	12.52±2.38#

*#$P < 0.05$, compared with Dex group

Table 4: PaO_2/FiO_2 and Cst in three groups

Group	PaO_2/FiO_2 (mm Hg)			Cst (mL/cm H_2O)		
	T0	*T3d*	*T 6d*	*T0*	*T3d*	*T 6d*
Pro	159.50±38.86	165.67±43.42*	181.27±59.53*	32.92±7.25	37.67±7.56*	44.56±7.11*
Dex	162.73±35.77	193.13±47.14	220.40±62.31	31.77±7.14	42.13±9.69	49.57±8.98
Mid	166.76±33.12	167.30±50.36#	186.46±65.33#	31.85±7.07	35.84±8.38#	43.94±8.81#

*#$P < 0.05$, vs. Dex

Inflammatory and immune indicators

Prior to treatment, the concentrations of IgA, IgM, and IgG were comparable among the three cohorts. However, on day 6, IgM and IgG levels in Dex group exhibited significant increases surpassing those in the Pro and Mid groups. Conversely, IgA levels were comparable in the 3 cohorts on both the 3rd and 6th days of treatment, as detailed in Table 3.

Pulmonary function parameters

Prior to treatment, no statistically significant differences were observed in the oxygenation index and lung static compliance amongst the three groups ($p > 0.05$). However, on the 3rd and 6th days of treatment, there were significant increases in the oxygenation index and lung static compliance in the Dex group, when compared to the Pro and Mid groups ($p < 0.05$), as shown in Table 4.

Efficacy

On the 6th day of treatment, the Dex cohort exhibited marked reductions in APACHE II and SOFA scores, relative to Pro and Mid groups ($p < 0.05$). Additionally, there were markedly shorter lengths of ICU stay and mechanical ventilation times in Dex group than in the Pro and Mid cohorts, as detailed in Table 5.

Table 5: Clinical efficacy in the three groups

Group	SOFA score	APACHE Ⅱ score	Duration of mechanical ventilation (h)	LOS in ICU (h)
Pro	8.06+1.48*	17.36+2.31	163.33+23.97*	196.18+23.97*
Dex	6.67+1.61	15.30+2.15	145.47+24.67	183.44+25.33
Mid	7.83+1.69#	17.15+2.62	168.15+26.92#	200.15+24.08#

*#*P* < 0.05, vs. Dex. (LOS: Length of stay)

Safety evaluation of the study drugs

Throughout the treatment course, the Pro group exhibited adverse drug reactions comprising 7 cases of hypotension, 3 cases of bradycardia, and 2 cases of respiratory depression, resulting in an overall incidence of 40.00% (12 patients out of 30). In the Dex group, adverse drug reactions were observed in 3 incidents of hypotension, 3 incidents of bradycardia, and 1 incident of tachycardia, leading to total incidence of 23.33 % (7 patients out of 30). The Mid group experienced adverse reactions consisting of 3 cases of hypotension, 2 cases of bradycardia, and 8 cases of respiratory depression, resulting in 43.33 % incidence of adverse drug reactions (13 patients out of 30). A comparison of the incidence of adverse reactions amongst the three groups showed that there were no statistically significant differences ($p > 0.05$).

DISCUSSION

Elevated levels of inflammatory factors and immune dysfunction are the main mechanisms that underlie the occurrence and development of AECOPD [12,13].

Sepsis, characterized as the uncontrolled response of the body to infection, represents a prevalent cause of death in ICU [14]. In AECOPD subjects, the occurrence of sepsis leads to an imbalance in inflammation and immune response, resulting in a sustained decline in overall immune function. This, in turn, renders the control of infection more challenging. When patients with AECOPD have respiratory dysfunction, they often need mechanical ventilation. The administration of sedative drugs is effective in diminishing the contact between man and machine, thereby concurrently reducing oxygen consumption.

Recently, a study found that appropriate sedation regulates the inflammatory response and metabolism, and protects organ function, and it is also an important component of the treatment of patients with sepsis [15]. Presently, the primary established pro-inflammatory mediators implicated in sepsis include IL-6, IL-8, IL-1β, and TNF-α. The elicited inflammation is intricately linked to the severity of the disease and clinical prognosis [16-18]. Earlier study on a sepsis mouse model has indicated that dexmedetomidine down-regulated IL-1β, TNF-α and IL-6, leading to an improvement in the survival rate of mice [19, 20]. In the present investigation, more pronounced reductions in inflammatory factors were observed in Dex cohort than in non-Dex cohorts, indicating the potential of Dex to attenuate inflammation in subjects with AECOPD complicated by sepsis.

Immunoglobulin levels serve as crucial indicators reflecting the body's immune function. Specifically, IgA inhibits the proliferation of pathogenic bacteria; IgM demonstrates efficient defensive effects, and IgG neutralizes endotoxins, thereby exhibiting a robust inhibitory effect on endotoxemia commonly associated with patients with AECOPD complicated by sepsis [21]. In the current study, more significant increases in peripheral blood levels of IgM and IgG were observed in the Dex group, suggesting that Dex may enhance the immune function of patients with AECOPD complicated by sepsis. The assessment of lung static compliance gauges the elastic state of lung tissue under mechanical ventilation, while the oxygenation index accurately reflects lung oxygenation function [22]. Furthermore, bronchial mucosa and ganglia harbor α1 and α2 adrenergic receptors: Dex is a specific α2 adrenergic receptor agonist. This property expands bronchoconstriction induced by histamine and suppresses ischemic pulmonary vasoconstriction, thereby mitigating impairment of pulmonary function [23]. A recent animal study found that intraperitoneal injection of Dex in a murine sepsis model of acute lung injury attenuated lung pathological injury and decreased the oxidative stress index, thereby improving lung function [24]. The findings in the present study suggest that Dex significantly enhances the oxygenation index and lung static compliance in patients with AECOPD complicated by sepsis.

Dexmedetomidine (Dex) is effective in reducing inflammatory factors, modulating immune function, and safeguarding certain organ functions. Notably, the Dex group exhibited more pronounced score reductions in SOFA and

APACHE II, accompanied by more substantial decreases in mechanical ventilation time and length of stay in the ICU. Furthermore, the drug demonstrated a high safety profile, suggesting a favorable role for Dex in mitigating the disease. Hence, in the context of mechanical ventilation for AECOPD complicated with sepsis, dexmedetomidine exhibits not only sedative properties but also exerts regulatory effects on the body's inflammatory immune response. This dual action contributes to the improvement of lung oxygenation function, fostering recovery from the disease, and notably reducing both the mechanical ventilation time and duration of hospitalization in the ICU.

Study limitations

This study has some limitations. Firstly, considering the racial disparities in the incidence of AECOPD, the results may be applicable primarily to the Asian population. Secondly, the sample size is relatively small, thereby necessitating the assessment of a larger number of patients to gain further insights. Lastly, the study participants were AECOPD patients from China. This potentially introduced selection bias.

CONCLUSION

The administration of dexmedetomidine sedation to patients undergoing mechanical ventilation due to AECOPD complicated by sepsis lead to decreases in concentrations of inflammation indices, i.e., IL-8, IL-1β, and IL-6. Additionally, it lead to elevation in the levels of immunoglobulins IgM and IgG, along with improvements in oxygenation index and lung static compliance. This pharmacological intervention is relatively safe, and it exerts a positive impact on disease progression, patient prognosis, and overall clinical outcomes. Future studies will require a larger sample size drawn from multiracial sources to validate the findings in this report.

DECLARATIONS

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Ethical approval

The study was approved by the Ethical Authority of Xuzhou First People's Hospital, China (approval no. xyII (2020) No. 39),

Availability of data and materials

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

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Weitao Shi and Yuliang Zhao conceived and designed the study, and drafted the manuscript. Weitao Shi, Yuliang Zhao, Xudong Wang and Jiani Yu collected, analyzed and interpreted the experimental data. Xudong Wang and Jiani Yu revised the manuscript for important intellectual content. All authors read and approved the final manuscript for publication.

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