Effect of Propofol and Dexmedetomidine on Pulmonary Injury in Patients with Acute Respiratory Distress Syndrome during Mechanical Ventilation

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Abstract: Objective: This research intended to explore the role of propofol and dexmedetomidine on pulmonary injury in patients with acute respiratory distress syndrome (ARDS) during mechanical ventilation. Methods: A total of 150 ARDS patients undergoing mechanical ventilation in our hospital from January 2017 to May 2019 were randomly grouped into dexmedetomidine group (n=50), propofol group (n=50) and joint group (n=50). The changes of heart rate, systolic blood pressure, diastolic blood pressure in the three groups were compared. Elisa was applied to test the changes of inflammatory factors interleukin -6 (IL-6) and tumor necrosis factor-α (TNF-α) on the first, second and third days after mechanical ventilation. The pulmonary injury score before sedation and after sedation for 2 days (Table 2) was tested. Secondary outcome measures: the incidence of adverse reactions after anesthesia was observed. Results: After sedation, the mean artery pressure and heart rate of the three groups were significantly lower than those before sedation ($P < 0.05$). After sedation, the expressions of IL-6 and TNF-α in joint group were significantly lower than those in propofol and dexmedetomidine group ($P < 0.05$). Two-day pulmonary injury scores of the three groups showed that different sedation schemes had positive effects on improving pulmonary injury scores ($P < 0.05$), and the expressions of IL-6 and TNF-α declined with the decline of pulmonary injury scores. The incidence of adverse reactions in joint group was significantly higher than that in propofol group and dexmedetomidine group ($P < 0.05$). Conclusion: Propofol and dexmedetomidine can effectively improve the effect of pulmonary injury in ARDS patients during mechanical ventilation, and slow down the occurrence of inflammatory reaction, which is an effective scheme of sedation in clinical mechanical ventilation.

Keywords: propofol, dexmedetomidine, acute respiratory distress syndrome, mechanical ventilation, pulmonary injury.
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INTRODUCTION

Acute respiratory distress syndrome (ARDS), also known as pulmonary shock and traumatic moist pulmonary, is a serious acute pulmonary injury [1, 2]. It mainly occurs in critical patients or injured patients, and is characterized by extensive pulmonary inflammation, which will reduce the oxygen intake of patients [3]. Current statistics have shown that [4] more than 30% of ARDS patients die because of treatment failure, and most of the surviving patients are accompanied by respiratory complications caused by pulmonary fibrosis and hypoxia. ARDS is characterized by rapid onset, poor prognosis and high mortality [5]. At present, the main clinical treatment for ARDS is

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mechanical ventilation, which can effectively improve the oxygenation of patients and help the treatment [6]. However, mechanical ventilation is invasive and non-physiological, which easily causes patients to reject machinery, and has anxiety and tension, thus increasing oxygen consumption, which is not conducive to the treatment [7, 8]. Therefore, sedation is applied for patients during mechanical ventilation.

Dexmedetomidine, as a highly selective agonist of α2- adrenoceptor, inhibits the release of thyroxine by activating α2- adrenoceptor, and has the effects of reducing sympathetic activity, tranquilizing and relieving pain [9-11]. Propofol, as a short-acting alkylphenol sedative and hypnotic drug, mainly acts on GABA receptors in the central nervous system, and has the characteristics of quick onset, short half-life, fast metabolism and no accumulation in human body. Both of them are commonly used sedatives in clinical mechanical ventilation [12-14]. However, at present, the clinical sedative effect of a single drug was mainly explored, and there are few studies on the combined effect of the two drugs.

Therefore, this study mainly explored the influence of propofol combined with dexmedetomidine on serum inflammatory factors and pulmonary injury in ARDS patients undergoing mechanical ventilation, and provided a potential scheme for clinical selection of sedation strategy.

MATERIALS AND METHODS

Clinical Data

A total of 150 ARDS patients undergoing mechanical ventilation in our hospital from January 2017 to May 2019 were randomly grouped into dexmedetomidine group (n=50), propofol group (n=50) and joint group (n=50). The guardians of the patients included in this study have signed informed consent. There was no tumor, renal insufficiency and shock in which vasoactive drugs cannot maintain blood pressure, heart rate < 55 beats / min, third degree atrioventricular block without pacemaker, and the time from onset to admission less than 3 hours. This study was approved by the Medical Ethics Committee. The clinical data of the three groups were not statistically significant (P > 0.05), as shown in Table 1.

Table 1 Comparison of baseline data

Factor		Dexmedetomidine group (n=50)	Propofol group (n=50)	Joint group (n=50)	F/c^2	P
Gender						
	Male	21	27	25	1.494	0.473
	Female	29	23	25		
Age (years)		58.4±3.8	59.4±4.2	60.5±4.7	3.055	0.051
BMI（kg/m^2）		22.4±1.84	23.1±2.12	22.8±2.58	1.273	0.283
ASA grading						
	I	35	40	37	1.339	0.512
	II	15	10	13		

Anesthesia Method

All patients were given midazolam (0. 03mg /kg), etomidate (0. 3mg/kg), sufentanil (0. 5μg/kg) and rocuronium (0. 6mg/kg) intravenously to induce basic anesthesia. After anesthesia induction, a double-lumen tube was inserted, and after successful intubation, mechanical ventilation was performed. Anesthesia was maintained in three groups: Dexmedetomidine group was given dexmedetomidine with a load of 1μg/kg for analgesia, and 0. 5μg/(kg*h) dexmedetomidine was injected intravenously at a constant speed 10 minutes later until 30 minutes before the end of operation. Propofol group was given propofol at a maintenance dose of 4 ~ 12mg/kg. In the joint group, dexmedetomidine (1 μ g/kg) was injected intravenously, 10 minutes later, intravenous infusion of 5 μ g/(kg h) was performed at a constant speed until 30 minutes before the end of operation, and propofol (4 ~ 6mg/kg) was pumped at the same time, and the dose of dexmedetomidine and propofol was adjusted during operation to maintain BIS to 40 ~ 60. Remifentanil and rocuronium bromide were injected intravenously at the same time. After the operation, they were

transferred to the anesthesia recovery room for routine examination under oxygen inhalation.

Elisa Detection

TNF-α and IL-6 in patients' serum were tested using Elisa kit. The fasting venous blood of patients after admission and venous blood in the morning after treatment for 4 weeks were collected, and centrifuged at 1509.3*g for 10min. The serum was obtained for later use. Elisa detection was carried out according to the kit instructions. The steps were as follows: the collected serum was put into 50μL standard solutions with different concentrations in blank micropores; 50μL of distilled water and 50μL antibody were put into the blank control well; 40μL of sample and then 10μL of biotin-labeled antibody were put into other micro-wells. Then, the plate was sealed and incubated at 37℃ for 30min. When rinsing the plate, the washing liquid in each hole should be kept full without overflowing for 30 seconds, discarded, dried for 5 times, and 50μL of enzyme-labeled solution was added to each well, the plate was sealed again for 60min at 37℃ and rinsed again for 5 times, dried thoroughly with absorbent paper for the last time. Horseradish peroxidase (100μL/ well) was added to seal the plate, incubated in dark at 37 ℃ for 15 min, added with hromogenic substrate TMB (100μL/ well), incubated for 20 minutes at room temperature in the dark, and finally added with 50μL/ well of stopping solution, and then the microplate reader was applied within 15 minutes to test the maximum absorption wavelength at 450nm. Three groups of repeated wells were set, and the experiment was repeated three times.

Outcome Measures

Main outcome measures: the changes of heart rate, systolic blood pressure, diastolic blood pressure in the three groups after medication were observed. Elisa was used to detect the changes of inflammatory factors interleukin -6 (IL-6) and tumor necrosis factor-α (TNF-α) on the first, second and third days after mechanical ventilation. The pulmonary injury score before sedation and after sedation for 2 days (Table 2) was tested. Secondary outcome measures: the incidence of adverse reactions after anesthesia was observed.

Table 2 pulmonary injury score

Score	0	1	2	3	4
PO2/FiO2	≥300	225-299	175-224	100-174	＜100
Pulmonary consolidation	NA	1/4	2/4	3/4	All
PEEP(cmH2O)	≤5	6-8	9-11	12-14	≥15
Pulmonary compliance	≥80	60-79	40-59	20-39	≤19

Statistical Analysis

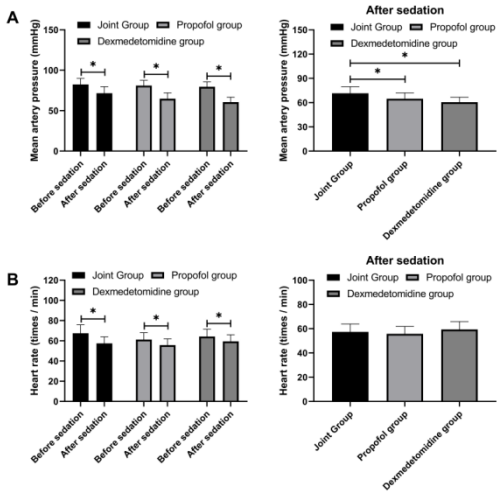
SPSS19.0 (IBM Corp, Armonk, NY, USA) was applied for statistical analysis, and the rate between the two groups was tested by Chi-square test. The measurement data were expressed by means ± standard deviation (x±SD), and compared by independent sample t-test. Repeated measurement variance analysis was applied for comparison at multiple time points, and Bonferroni method was applied for pairwise comparison at different time points. The correlation between pulmonary injury score and inflammatory factors was analyzed by Spearman and expressed by r. When P<0.05, the difference was statistically significant.

RESULTS

Heart Rate Changes

Firstly, the changes of mean arterial pressure and heart rate were compared before sedation and after sedation for 30min in ARDS patients. There was no significant difference in mean arterial pressure and heart rate before sedation among the three groups (P > 0.05), but there was a significant difference in mean artery pressure and heart rate after sedation (P < 0.05). Further comparison showed that MAP of patients in joint group after sedation was significantly higher than that of propofol group and dexmedetomidine group, but there was no significant difference in heart rate (P > 0.05) (Figure 1).

Figure 1 Changes of mean artery pressure and heart rate before and after sedation in 3 groups.

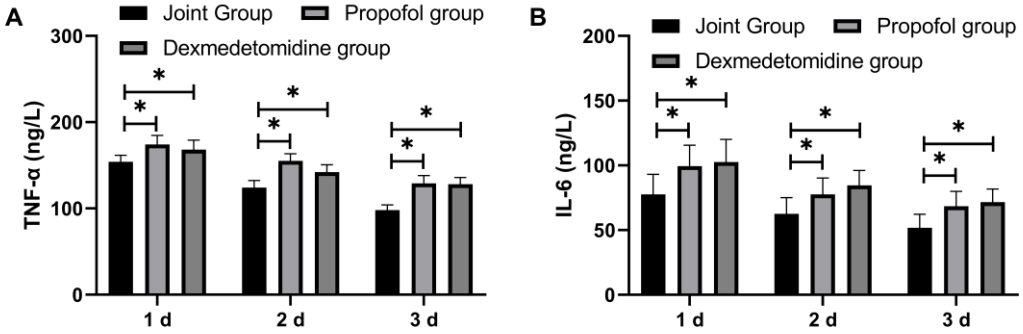


A. Mean artery pressure before and after sedation in 3 groups. B. Changes of heart rate before and after sedation in three groups. * indicates P<0.05.

Changes of Serum Inflammatory Factors

The changes of inflammatory factors IL-6 and TNF-α in ARDS patients were observed within 3 days after treatment. By comparison, we found that IL-6 and TNF-α in joint group were significantly lower than that in propofol and dexmedetomidine group after 1 day of sedation (P < 0.05), and the concentration of IL-6 and TNF-α in combined sedation group was lower than that in the single application group within 2 and 3 days after sedation (P<0.05).

Figure 2 Changes of inflammatory factors in 3 days after sedation in 3 groups.

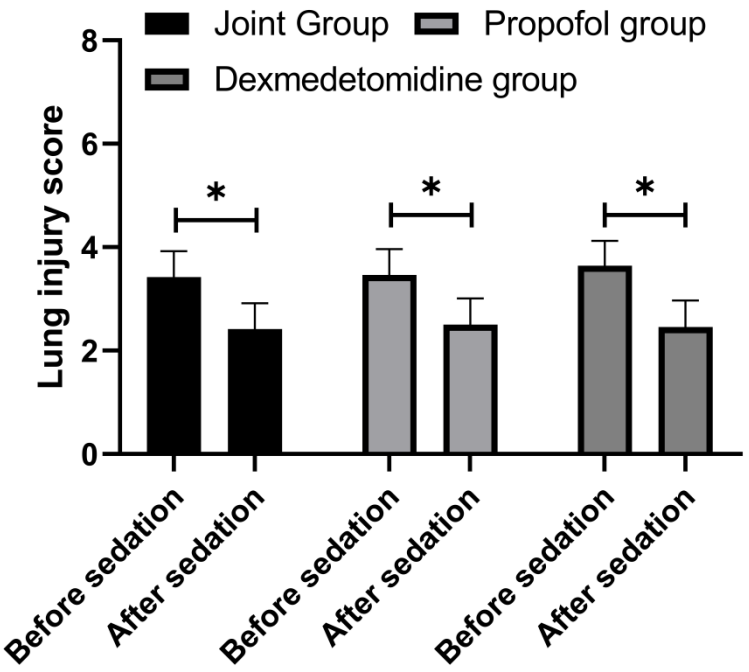


A. Changes of TNF-α concentration in 3 days after sedation in 3 groups. B. Changes of IL-6 in 3 days after sedation. * indicates P<0.05.

Pulmonary Injury Score

By comparison of the pulmonary injury, we found that there was no significant difference in the pre-sedation injury scores among the three groups (P > 0.05). By comparing the two-day pulmonary injury scores of the three groups, it was found that different sedation schemes had positive effects on the pulmonary injury scores of patients (P < 0.05), but there was no significant difference among the three groups (P > 0.05).

Figure 3 Changes of pulmonary injury scores before and after sedation.

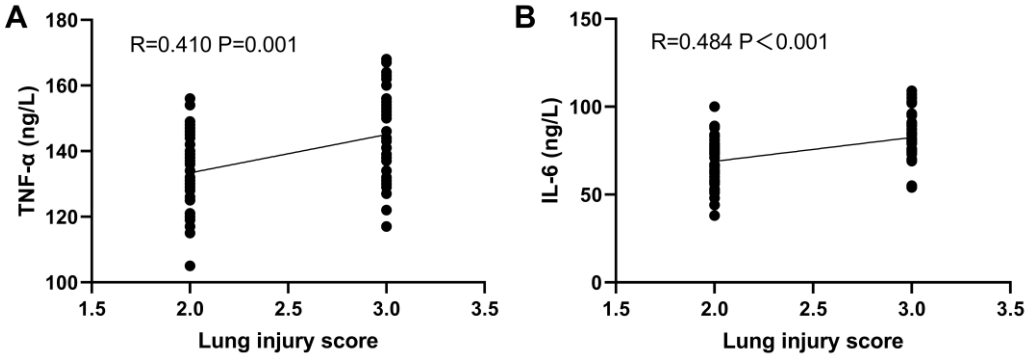


Comparison of pulmonary injury scores of patients before and after sedation. * indicates P<0.05.

Correlation of Inflammatory Factors with Pulmonary Injury Score

We selected the pulmonary injury score on the 2nd day after sedation and analyzed the correlation of it with IL-6 and TNF-α data. Spearman analysis showed that IL-6 and TNF-α declined with the decline of pulmonary injury score, suggesting that IL-6 and TNF-α could be applied as potential indicators for evaluating pulmonary injury.

Figure 4 Correlation of inflammatory factors with pulmonary injury score.



A. Correlation between TNF-α and pulmonary injury score. B. Correlation between IL-6 and pulmonary injury.

Adverse Reactions of Patients

At the end of the study, we analyzed the incidence of adverse reactions during sedation, and found that the incidence of adverse reactions in the joint group was significantly higher than that in propofol group and dexmedetomidine group (P < 0.05).

Table 3

Group	Endotracheal intubation shows positive	Hypotension	Bradycardia	Total
Joint group (n=50)	2	2	2	6
Propofol group (n=50)	6	9	6	21
Dexmedetomidine group (n=50)	5	7	6	17
$\chi 2$	2.190	4.924	2.521	11.645
P	0.335	0.085	0.284	0.003

DISCUSSION

ARDS is the most critical organ dysfunction disease in clinic. There are many causes of the disease, including chronic obstructive pulmonary disease, infectious shock, pulmonary infection, and craniocerebral injury. At present, the main clinical treatment for ARDS is mechanical ventilation. However, patients will have man-machine counteraction, ventilator-associated pneumonia and pulmonary injury, so sedation is essential during ventilation [16, 17]. At present, propofol and dexmedetomidine are commonly used in clinical mechanical ventilation [18, 19], but it is not clear whether the combined use of propofol and dexmedetomidine has any influence on the sedative effect of patients and the improvement of inflammatory factors. In this study, we found that combined medication can effectively improve the inflammatory factors, reduce the incidence of adverse reactions, and adjust the mean artery pressure of patients, which is a potential sedative scheme.

Propofol, as a common clinical short-acting intravenous anesthetic, has anesthetic and sedative effects through GABA receptor, but studies have shown that propofol has obvious inhibitory effect on circulation and respiration, which can decline the blood pressure and slow down the heart rate in patients [20, 21]. Dexmedetomidine, as a highly selective α2 receptor agonist, has analgesic, sedative and anti-anxiety effects by promoting GABA secretion. Compared with propofol, dexmedetomidine does not show respiratory depression, which is beneficial to tracheal extubation [20, 22]. In this study, we found that the mean artery pressure of patients was significantly improved by using the two drugs alone, and that of patients in the joint group was lower than that in the single drug group, indicating that dexmedetomidine had a greater impact on heart rate deceleration, while propofol had a smaller impact, and the combined use could avoid the occurrence of complications of bradycardia.

Inflammatory reaction is one of the main mechanisms of pulmonary injury during one-lung ventilation, and the occurrence of inflammatory reaction may be related to the mechanical pulling effect of tidal volume and airway pressure on alveoli during one-lung ventilation [23]. Early studies have found that proper use of sedatives can alleviate patients' pain, and have an impact on immune cells and inflammatory response factors in patients. For example, in the research of Tasdogan et al. [26], propofol and dexmedetomidine effectively inhibited the inflammatory reaction of severe sepsis after operation, and Cui et al. [27] found that dexmedetomidine improved the pulmonary function of patients undergoing total thoracoscopic cardiac surgery by promoting inflammation regression. IL-6, a key member of interleukins, participates in many inflammatory reactions and diseases in human body [28]. TNF-α, an immune regulatory factor, is highly expressed in serum and can cause the reduction of killing tumor cells, mediate various diseases, and cause the body to have inflammatory reactions [29]. In this study, it was found that the concentrations of IL-6 and TNF-α were significantly inhibited after combined sedation, and we also found that there was no significant difference in pulmonary injury scores among the three groups during sedation, suggesting that combined sedation could reduce the inflammatory reaction of patients and had no effect on pulmonary injury.

We also analyzed the correlation of inflammatory factors with pulmonary injury score in this study. As pulmonary injury score needs multiple indicators, if we can find the correlation of a certain indicator with pulmonary injury score, we can reduce the evaluation time and facilitate doctors to evaluate patients' condition. In this research, the decrease of pulmonary injury score was related to the decline of IL-6 and TNF-α, and Spearman analysis showed that IL-6 and TNF-α were positively correlated with pulmonary injury score. This suggested that IL-6 and TNF-α can be used as potential indicators to evaluate pulmonary injury in patients. At the end of the study, we compared the patients' adverse reactions, and found that the incidence of adverse reactions in the

joint group was significantly reduced, suggesting that sedation with combined medication could improve the occurrence of adverse reactions.

However, we still have some limitations in this study. The small sample size may have an impact on the statistical results. Secondly, the sample we included in this study is mainly elderly patients, and whether the results are consistent among young patients needs further verification. Therefore, we hope to improve our research results by increasing the sample size.

To sum up, propofol and dexmedetomidine can effectively improve the effects of pulmonary injury in ARDS patients during mechanical ventilation, and slow down the occurrence of inflammatory reaction, which is an effective scheme for clinical mechanical ventilation sedation.

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