

Original Article

Clinical outcome analysis of mechanical ventilation combined with dexmedetomidine in patients with traumatic acute lung injury

Xiong Chen^{1*}, Yang Gong^{2*}, Yang He³

Departments of ¹Emergency Surgery, ²Pre-Hospital Emergency, Jingzhou Central Hospital, Jingzhou, Hubei Province, China; ³Department of Medical Insurance, First People's Hospital of Jingzhou, Jingzhou, Hubei Province, China. *Equal contributors and co-first authors.

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Abstract: Objective: To explore the pulmonary protective effect of dexmedetomidine (DEX) in patients with traumatic acute lung injury (ALI). Methods: A prospective study was carried out on 74 patients with traumatic ALI who underwent mechanical ventilation. The patients were divided into an observation group and a control group by random number table (both n=37). The patients in the observation group were treated with DEX before anesthesia, while those in the control group were treated with normal saline. The general data and operation indexes were observed. The expression levels of serum tumor necrosis factor α (TNF- α), interleukin-6 (IL-6), alveolar-arterial oxygen gradient (A-aDO₂) and oxygenation index (OI) were measured at 5 min before anesthesia (T0), 30 min (T1) and 90 min (T2) of one-lung ventilation, and 2 h after surgery (T3). And the postoperative 24 h pain degree measured by the visual analogue scale (VAS) and incidence rate of postoperative complications (atelectasis, pulmonary infection, pleural effusion, hypoxemia, and re-intubation) were recorded. Results: There were no significant differences in age, gender, surgical duration, intraoperative fluid supplement, intraoperative blood loss and mechanical ventilation time between the two groups ($P>0.05$). There was no significant difference in TNF- α , IL-6, A-aDO₂ and OI between the two groups at T0 ($P>0.05$). However, at T1, T2 and T3, the observation group showed lower TNF- α , IL-6 and A-aDO₂ than the control group, but higher OI than the control group ($P<0.05$). Both groups got improved in pain condition after surgery, and the observation group showed better improvement ($P=0.031$). The incidence of postoperative complications in the observation group (5.40%) was lower than that in the control group (27.03%) ($P=0.008$). Conclusion: Compared with mechanical ventilation only, the combination method effectively reduces the level of inflammatory factors in patients with traumatic ALI, stabilizes intraoperative hemodynamics, improves OI, and reduces postoperative pain and postoperative complications.

Keywords: Dexmedetomidine, traumatic acute lung injury, pulmonary protection, clinical research

Introduction

Acute lung injury (ALI) is a clinical syndrome caused by pulmonary diseases or extrapulmonary trauma, with the clinical manifestation of persistent hypoxemia. It is often accompanied by acute respiratory distress syndrome, and the mortality rate can reach 36-44%, up to 46% when combined with severe acute respiratory distress syndrome [1, 2]. Traumatic ALI refers specifically to ALI caused by external trauma. It is mainly characterized by the injury of alveolar epithelial cells caused by a large release of inflammatory factors mediated by tumor necro-

sis factor- α (TNF- α) and interleukin-6 (IL-6) after external trauma [3, 4]. Mechanical ventilation has the effects of improving hypoxia and carbon dioxide retention, improving lung ventilation and increasing oxygenation, which is an effective means of respiratory support and treatment for critical and severe patients [5, 6]. One-lung ventilation anesthesia is not only the most commonly used but also the effective method to treat ALI [7].

Dexmedetomidine (DEX) is a selective α_2 adrenoceptor agonist that was used as an anesthetic agent. It acts on resisting cold, diuresis, and

salivary suppression, as well as on analgesia, anti-anxiety, restraining activity of sympathetic nerve [8, 9]. In the previous study, there were three subtypes of α_2 adrenoceptor: α_2A , α_2B , and α_2C which were widely distributed in human body, including central and peripheral nerves, autonomic nerves, coronary artery, lung, kidney, brain, pancreas, spleen, eyes, and blood vessels, and cause corresponding biological effects after acting on the above parts [10, 11]. The study on pulmonary protection by DEX found that DEX sedated and inhibited sympathetic nervous system after anesthesia. Moreover, it can stabilize the hemodynamics of patients, with no inhibitory effect on respiration [12]. It is reported that DEX has a pulmonary protective effect, and it can reduce airway pressure, improve lung compliance and increase oxygenation index (OI) [13-16]. Its mechanism of pulmonary protection may be related to inhibition of inflammation, reduction of ischemia reperfusion and decrease of oxidative stress response [17, 18]. However, there are few clinical reports on the use of DEX for pulmonary protection in patients with traumatic ALI. Therefore, in this study, the pulmonary protective effect of DEX in patients with traumatic ALI was evaluated.

Material and methods

Clinical data

This study was approved by the Ethics Committee of First People's Hospital of Jingzhou. From March 2017 to December 2018, 74 patients with traumatic ALI treated by mechanical ventilation in intensive care unit were enrolled and randomly divided into an observation group and a control group (both $n=37$). The patients in the observation group were treated with DEX before anesthesia, while those in the control group were treated with normal saline. All patients were over 18 years old, with an average age of 53.5 ± 8.7 years old. All patients included in this study signed the consent form.

Inclusion criteria

Patients diagnosed with traumatic ALI in accordance with the Society of Critical Care Medicine, Chinese Medical Association (2007) [19]; patients undergoing mechanical ventilation; patients with American Society of Anesthesiologist I-III; patients with normal blood coagulation and bone marrow function.

Exclusion criteria

Patients with serious heart and lung diseases; patients with coagulation or bone marrow dysfunctions; patients with hepatic and renal insufficiency; uncooperative patients; patients with allergies to DEX; patients with malignant tumor; pregnant or lactating patients.

Methods

Patients included in the study were treated with mechanical ventilation, and were intravenously injected with penicillin hydrochloride 0.01 mg/kg (Chengdu List Pharmaceutical Co., Ltd.) for general anesthesia. Ten min before anesthesia induction, patients in the observation group received an intravenous injection of DEX 1.0 $\mu\text{g/kg}$ (Jiangsu Enhua Pharmaceutical Co., Ltd.) within 10 min. Afterwards, DEX 0.6 $\mu\text{g}/(\text{kg}\cdot\text{h})$ was administrated (intravenous drip) until mechanical ventilation treatment was finished. The patients in the control group were given an equal amount of normal saline. All patients received intravenous injection of midazolam 2 mg (Jiangsu Enhua Pharmaceutical Co., Ltd.), sufentanil 0.4 $\mu\text{g/kg}$ (Yichang Humanwell Pharmaceutical Co., Ltd.), etomidate 0.2 mg/kg (Jiangsu Enhua Pharmaceutical Co., Ltd.), and cisatracurium 0.2 mg/kg (Jiangsu Hengrui Pharmaceutical Co., Ltd.) for anesthesia induction. After anesthesia was completed, patients were given continuous propofol 3-6 mg/(kg h) (Xi'an Libang Pharmaceutical Co., Ltd.) and intermittent cisatracurium 0.05-0.1 mg/(kg h) for anesthesia maintenance. Mechanical ventilation was performed after double lumen endotracheal intubation and bronchofibroscope localization. Setting parameters: Tidal volume 8-10 mL/kg; end-tidal CO_2 : 35-45 mmHg; respiratory frequency: 12-16 times/min. The patients received no oxygen inhalation before anesthesia, then inhaled pure oxygen using mechanical ventilation, and inhaled oxygen with concentration of 40% 2 h after surgery.

Outcome measures

General information: Surgical duration, intraoperative fluid supplement, intraoperative blood loss and mechanical ventilation time were observed and recorded.

Main outcome measures: A 5 mL volume of elbow venous blood was extracted from each patient at four time points: before anesthesia

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Table 1. Comparison of general data and baseline data ($\bar{x} \pm sd$)

Item	Observation group (n=37)	Control group (n=37)	χ^2/t	P
Gender (male:female)	17:20	15:22	0.220	0.639
Age (year)	52.9±4.8	54.3±5.8	1.070	0.288
Surgical duration (min)	176.08±13.30	175.04±12.74	0.353	0.752
Intraoperative blood loss (mL)	321.43±42.82	324.02±32.83	0.272	0.787
Intraoperative fluid supplement (mL)	1203.40±190.54	1207.03±191.65	0.082	0.935
Mechanical ventilation time (min)	107.49±45.57	101.03±50.82	0.576	0.567
Body mass index (kg/m ²)	25.21±3.62	24.82±3.54	0.412	0.684

Table 2. Comparison of TNF- α at different time points ($\bar{x} \pm sd$)

Group	T0	T1	T2	T3
Observation group (n=37)	4.92±1.07	10.29±1.52	21.87±4.35	30.51±5.07
Control group (n=37)	5.02±1.33	15.27±2.22	39.87±7.95	44.25±6.15
t	0.349	11.478	12.081	10.489
P	0.728	0.000	0.000	0.000

Note: T0, before anesthesia; T2 and T3, 30 min and 90 min of one-lung ventilation, respectively; T3, 2 h after surgery. TNF- α , tumor necrosis factor α .

hypoxemia and secondary intubation.

Statistical analysis

SPSS 17.0 statistical software was used to analyze the collected data. The continuous variables were analyzed by normal distribution

and homogeneity of variance, then expressed as the mean $\pm$ standard deviation ($\bar{x} \pm sd$), and were compared by independent sample t-test. Counting data expressed as percentage were analyzed by Pearson Chi-square test. A value of $P < 0.05$ was considered statistically different.

Results

General data and baseline data

There was no significant difference in age, gender, surgical duration, intraoperative fluid supplement, intraoperative blood loss, mechanical ventilation time and body mass index between the two groups ($P > 0.05$) as shown in **Table 1**.

Significantly decreased concentration of TNF- α and IL-6 after combined with DEX

There was no significant difference in TNF- α and IL-6 between the two groups at T0 ($P > 0.05$). During the surgery, TNF- α and IL-6 were gradually increased. At T1, T2 and T3, the TNF- α in the observation group were 10.29±1.52, 21.87±4.35, 30.51±5.07, and IL-6 were 18.58±5.42, 33.58±8.49, 41.62±5.23, respectively, which were significantly lower than those in the control group, which were 15.27±2.22, 39.87±7.95, 44.25±6.15, and 29.51±7.31, 42.95±9.17, 54.31±7.15 correspondingly ($P < 0.05$). See **Tables 2** and **3**.

(T0), 30 min (T1) and 90 min (T2) of one-lung ventilation, 2 h after surgery (T3), respectively. The collected blood samples were stored in sterile tubes containing ethylene diamine tetra acetic acid (Shanghai Generay Biotech Co., Ltd.). After stored in refrigerator at 4°C for 15 min, serum and plasma were separated by a centrifuge with a speed of 3,300 rpm/min. The separated plasma was added with 40 μ L phosphate buffer solution containing protease inhibitor (Lianyungang Duanfeng Biotechnology Co., Ltd.) and stored in a refrigerator at -80°C. The TNF- α and IL-6 were tested by an enzyme-linked immunosorbent assay (ELISA) kit (Shanghai Generay Biotech Co., Ltd.).

Alveolar-arterial oxygen gradient (A-aDO₂) and OI at T0-T3 were recorded respectively.

Secondary outcome measures: Postoperative pain: Subjective pain was quantified using the linear visual analog scale (VAS) method. A 10 cm long ruler with two end points 0 and 10 was applied, where 0 meant no pain and 10 meant the most severe pain. The patients selected a point between 0 and 10 according to the degree of pain, and the measured value of the point at 2 h after surgery was the score of visual analog scale [20].

Postoperative complications included atelectasis, pleural effusion, pulmonary infection,

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Table 3. Comparison of IL-6 at different time points ($\bar{x} \pm sd$)

Group	T0	T1	T2	T3
Observation group (n=37)	11.48±1.58	18.58±5.42	33.58±8.49	41.62±5.23
Control group (n=37)	10.95±1.72	29.51±7.31	42.95±9.17	54.31±7.15
t	1.380	7.036	4.385	8.713
P	0.172	0.000	0.000	0.000

Note: T0, before anesthesia; T2 and T3, 30 min and 90 min of one-lung ventilation, respectively; T3, 2 h after surgery. IL-6, interleukin-6.

Table 4. Comparison of A-aDO₂ at different time points ($\bar{x} \pm sd$)

Group	T0	T1	T2	T3
Observation group (n=37)	28.59±2.07	399.68±4.24	414.68±5.37	118.58±1.82
Control group (n=37)	28.76±1.89	413.29±7.42	429.64±3.32	125.47±1.03
t	0.375	9.687	14.415	8.713
P	0.709	0.000	0.000	0.000

Note: T0, before anesthesia; T2 and T3, 30 min and 90 min of one-lung ventilation, respectively; T3, 2 h after surgery. A-aDO₂, alveolar-arterial oxygen gradient.

Table 5. Comparison of OI at different time points ($\bar{x} \pm sd$)

Group	T0	T1	T2	T3
Observation group (n=37)	393.58±16.59	193.78±15.42	168.37±11.27	224.08±13.25
Control group (n=37)	393.61±17.18	173.67±11.06	132.59±11.36	175.39±11.27
t	0.262	6.442	13.600	17.066
P	0.794	0.000	0.000	0.000

Note: T0, before anesthesia; T2 and T3, 30 min and 90 min of one-lung ventilation, respectively; T3, 2 h after surgery. OI, oxygenation index.

More significant changes of A-aDO₂ and OI at different time points were shown in the observation group

There was no significant difference in the alveolar arterial partial pressure and oxygenation index between the observation group and the control group at T0 ($P>0.05$). At T1, the alveolar arterial pressure was significantly higher than that at T0 in the control group. The increasing extent of the control group was more obvious ($P<0.05$). At T2, the alveolar arterial pressure still showed an upward trend compared with that at T1. The increase of the control group was more significantly higher than that of the observation group ($P<0.05$). At T3, the alveolar arterial pressure decreased significantly compared with T2, and the degree of decline in the observation group was more obvious than the control group ($P<0.05$). At T1, the oxygenation index decreased significantly compared with T0. The degree of decline was

more obvious in the observation group ($P<0.05$). The oxygenation index at T2 was further decreased than that at T1, and the degree of decline in the control group was more significant than that of the observation group ($P<0.05$); the oxygenation index of T3 was higher than that of T2, and the increase of observation group was more significant than that of the control group ($P<0.05$). See **Tables 4 and 5**.

Lower postoperative pain evaluation scores in the observation group than control group

Pain in both group patients were alleviated after surgery ($P<0.05$), and the alleviation was more obvious in the observation group ($P<0.05$). See **Table 6**.

Comparison of postoperative complications

The incidence of postoperative complications in the observation group (5.40%) was signifi-

Table 6. Comparison of postoperative pain condition at different time points ($\bar{x} \pm sd$)

Group	VAS scores
Before surgery	
Observation group (n=37)	5.30±1.16
Control group (n=37)	5.24±1.09
t	0.221
P	0.826
After surgery	
Observation group (n=37)	1.54±1.42 [#]
Control group (n=37)	2.25±1.30 [#]
t	2.201
P	0.031

Note: Compared with before surgery, [#]P<0.05. VAS, visual analog scale.

cantly lower than that in the control group (27.03%) (P<0.05). See **Table 7**.

Discussion

In the study, at T1, T2 and T3, it was found that the TNF- α and IL-6 in the observation group were lower than those of the control group, indicating that DEX can significantly reduce the inflammatory reaction in the body, which may be due to damage to the pulmonary blood vessels and bronchi caused by the external trauma of the lung causes, a large amount of vasoactive substances are released into the bloodstream, thereby slowing down the blood flow and increasing the intravascular pressure, eventually reducing the amount of active substances attached to the alveoli [21, 22]. A study shows that during mechanical ventilation, macrophages and neutrophils are abundantly produced in the lung of patients with lung injury, which promotes the synthesis and release of pro-inflammatory factors [23]. It has been found that the DEX can reduce the level of inflammatory factors and low the occurrence of oxidative stress in surgical patients [24-26]. In this study, it showed that TNF- α and IL-6 in the observation group were lower than those in the control group at T1, T2 and T3, with statistical differences, indicating that DEX significantly reduced the inflammatory response in vivo, which was consistent with the above researches. Hence, it was suggested that DEX is likely to produce protection by weakening inflammation responses in patients with lung injury.

In our study, the A-aDO₂ and OI of patients were dynamically observed. At T1, T2 and T3, the

observation group showed lower A-aDO₂ than the control group, but higher OI with statistical differences, indicating that DEX could stabilize the blood flow and improve the OI of patients. The cause of pulmonary arterial pressure and oxygenation index changes was mainly including the lung atrophy in patients with lung injury due to injury, ischemia and hypoxia in the lung tissue resulted by the blood shunt in the lung [27]. With the improvement of technology, mechanical ventilation effectively improves the oxygen supply of patients, but still 10% of the patients suffer from hypoxemia [27]. Researches also reveal that DEX can effectively improve the OI of surgical patients and reduce blood flow shunt in lung [16, 28]. Which were consistent with our results, suggesting that DEX can improve oxygen supply and stabilize blood flow in patients.

In this study, it was found that the alleviation of pain in the observation group using DEX was more obvious than that in the control group, which was related to the good analgesic effect of DEX. One previous published study reported that the sedative effect of DEX is a biological effect through the stimulation of locus coeruleus α 2 receptor, but its analgesic mechanism is not clear, which may be related to the combined action of central analgesia and peripheral analgesia [29-31]. Since the analgesia of DEX can be achieved by a variety of mechanisms, its clinical analgesic effect is satisfactory.

Our study demonstrated that the incidence of postoperative complications in the observation group (5.40%) was lower than that in the control group (27.03%), suggesting that DEX effectively reduced the occurrence of postoperative complications. In terms of postoperative complications, previous studies have found that high-dose DEX can significantly improve the tidal volume, reduce inflammatory response of surgical patients, and thus reduce pulmonary edema and pulmonary infection [32]. Another study also demonstrated that DEX plays roles in reducing the duration of ischemia reperfusion of lung tissue, reducing inflammatory response and decreasing postoperative complications [11].

The sample size of this study is small and needs to be further enlarged to at least 80 cases in each group. Besides, it is necessary to further prolong the observation duration to study the

Table 7. Comparison of postoperative complications (n, %)

Item	Observation group (n=37)	Control group (n=37)	χ^2/t	P
Atelectasis	0 (0.00)	2 (5.40)		
Pulmonary infection	1 (2.70)	2 (5.40)		
Pleural effusion	1 (2.70)	3 (8.11)		
Hypoxemia	0 (0.00)	2 (5.40)		
Secondary intubation	0 (0.00)	1 (2.70)		
Total occurrence rate	2 (5.40)	10 (27.03)	6.950	0.008

postoperative recovery of the patients for 5 years.

To sum up, compared with singly use of mechanical ventilation, DEX combination therapy effectively reduces the level of inflammatory factors in patients with traumatic ALI, stabilizes intraoperative hemodynamics, improves OI, and reduces postoperative pain and postoperative complications. Therefore, it is worthy of clinical application.

Disclosure of conflict of interest

None.

Address correspondence to: Yang He, Department of Medical Insurance, First People's Hospital of Jingzhou, No. 40 Jinlong Road, Shashi District, Jingzhou 434000, Hubei Province, China. Tel: +86-0716-8515610; Fax: +86-0716-8515610; E-mail: heyang3wf8@163.com

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