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Therapeutic experience of the application of anisodamine on acute lung injury

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ABSTRACT

Objective: To investigate the effect of anisodamine combining with conventional therapy on the degree of lung injury and inflammatory reaction of patients with acute pulmonary contusion.

Methods: A total of 48 patients with acute pulmonary contusion treated in our hospital emergency department from April 2011 to October 2015 were enrolled as the research object and were divided into experimental group and control group by using a method of random number table. Experimental group received anisodamine combining with conventional therapy and control group received conventional therapy. In the process of the treatment, the mechanical ventilation time, hospital stays in intensive care unit and the number of cases developed into acute respiratory distress syndrome and multiple organ dysfunction syndromes of patients in two groups were observed. Oxygenation indexes of patients were respectively calculated on Days 1, 2 and 3 after treatment. The contents of inflammatory mediators in serum were detected on Day 3 after treatment.

Results: The mechanical ventilation time and hospital stays in intensive care unit [(9.52 ± 1.41) *vs.* (14.57 ± 2.51) days] of patients in experimental group were significantly shorter than those in control group, and the number of cases developed into acute respiratory distress syndrome [1 (4.17%) *vs.* 9 (37.50%)] and multiple organ dysfunction syndrome [1 (4.17%) *vs.* 7 (29.17%)] was significantly less than those in control group. Oxygenation indexes (294.52 ± 41.26 *vs.* 257.63 ± 38.52; 357.74 ± 47.74 *vs.* 279.87 ± 31.46; 396.71 ± 55.12 *vs.* 279.87 ± 31.46) of patients were respectively calculated on Days 1, 2 and 3 after treatment, which were significantly higher than those in the control group. On Day 3 after treatment, the contents of serum C-reactive protein [(7.94 ± 1.05) *vs.* (14.49 ± 2.97) mg/L], tumor necrosis factor α [(264.69 ± 41.58) *vs.* (417.87 ± 64.51) ng/L], interleukin-6 (IL-6) [(147.72 ± 21.36) *vs.* (257.68 ± 41.54) ng/L], IL-8 [(93.68 ± 12.52) *vs.* (145.62 ± 22.65) ng/L], IL-10 [(205.64 ± 31.56) *vs.* (336.62 ± 51.38) ng/L] and myeloid cells-1 (73.32 ± 10.39 *vs.* 114.45 ± 18.51) of patients in experimental group were significantly lower than those in the control group.

Conclusions: The anisodamine combining with conventional therapy can relieve the degree of lung injury caused by acute pulmonary contusion, improve ventilatory function, lower the incidence of acute respiratory distress syndrome and multiple organ dysfunction syndrome and inhibit the activation of inflammatory reaction and the release of inflammatory mediators.

1. Introduction

Among the emergency trauma patients, more than one-third of patients have blunt chest injury, while pulmonary contusion is the most common complications after blunt chest injury[1,2]. Pulmonary contusion can increase the risk of the incidence of acute respiratory distress syndrome (ARDS) and meanwhile, severe patients need to be assisted breathing with ventilator, which can increase the incidence of ventilator-associated pneumonia. In the pathogenic process

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The study protocol was performed according to the Helsinki declaration and approved by hospital ethical committee (the name of the ethic committee which approved the investigations). Informed written consent was obtained from the objects enrolled.

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of multiple organ dysfunction caused by severe trauma, acute lung injury occurs the earliest and has the highest incidence, which runs through each pathologic stage of multiple organ dysfunction[3–5]. Hence, a reasonable and effective treatment schedule set for acute lung injury can stop further development of illness condition and lower the morbidity and mortality of multiple organ dysfunction syndrome (MODS).

The main pathological features of pulmonary contusion include the bleeding and edema of lung tissue in contusion area combining with a large number of inflammatory cells infiltrations. The activation of inflammatory reaction and the release of inflammatory mediators in local tissues are the critical pathological links for causing lung injury. Inhibiting the inflammatory reaction is an important objective to treat pulmonary contusion and prevent MODS[6–8]. Anisodamine, namely, 654-2, is a kind of alkaloid drug extracted and purified from Solanaceae botany, *Anisodus tanguticus* (Maxim.), which can relieve the bronchospasm, improve the function of pulmonary exchange and ventilation, alleviate microcirculatory disturbance, enhance the effect of microcirculatory blood supply, relieve the local inflammatory reaction of wound tissues and promote the absorption of inflammatory mediators[9–11]. In the following research, we used anisodamine combining with conventional scheme to treat acute lung injury.

2. Materials and methods

2.1. Case data

A total of 48 patients with acute pulmonary contusion treated in our hospital emergency department from April 2011 to October 2015 were enrolled as the research objects. The approval was obtained from the hospital ethical committee and informed consent was obtained from the objects enrolled. All the patients had positive history of chest trauma and were confirmed with pulmonary contusion by the CT examination of chest after admission, and patients with the trauma of other organs or active bleeding and a history of chronic respiratory disease were excluded. A total of 48 patients enrolled included 33 male cases and 15 female cases and their age were 15–68 years with a mean age of (37.6 ± 5.2) years. The causes of injury included traffic accident (33 cases), crush injury (7 cases) and fall injury (8 cases).

2.2. Grouping methods

The 48 patients enrolled were divided into experimental group and control group with a method of random number table and each group included 24 cases. After admission, the patients of experimental group and control group were actively disposed and treated at the original injury locations to keep unobstructed respiratory tract, and ventilator should be offered for the severe patients to assist breathing. Also the antibiotics were used to prevent pulmonary infection. Hormone and appropriate volume of human serum albumin or blood component transfusion were used as needed. The patients of experimental group received anisodamine treatment based on the above treatment and the method was listed as follow: 1.0 mg/kg anisodamine injection was used for intravenous injection for continuous 3 days (3 times/day).

2.3. Evaluation methods of clinical indexes

In the process of treatment, the mechanical ventilation time, hospital stays in intensive care unit (ICU) and the number of cases developed into ARDS and MODS of patients in two groups were observed. Oxygenation indexes of patients were respectively calculated on Days 1, 2 and 3 after injecting anisodamine. About 5–10 mL peripheral-blood specimens of patients in two groups were collected. After getting serum centrifuged, ELISA was used to detect the contents of serum C-reactive protein (CRP), tumor necrosis factor α (TNF-α), α interleukin-6 (IL-6), IL-10 and myeloid cells-1 (sTREM-1) on Day 3 after treatment.

2.4. Statistics process methods

The data were inputted by using SPSS 22.0 software and measurement data underwent homogeneity test for variance, which fitted normal distribution were expressed as mean ± SD. The measurement data of normal distribution between two groups were analyzed by using *t*-test. Enumeration data were expressed by using frequency number and were analyzed by *Chi*-square test. Differences were considered statistically significant when $P < 0.05$.

3. Results

3.1. General clinical data

The gender, age, respiratory frequency, oxygenation index, APACHE II score and the contents of serum creatinine, urea nitrogen, alanine aminotransferase and aspartate aminotransferase had no significant difference (Table 1).

Table 1
The general data of patients in the two groups.

General data	Experimental group (n = 24)	Control group (n = 24)
Gender (male/female)	17/7	16/8
Age (years)	38.5 ± 5.9	37.1 ± 4.4
BMI (kg/m^2)	22.19 ± 3.14	22.68 ± 2.95
Respiratory frequency (times/min)	26.52 ± 3.12	26.18 ± 3.32
Oxygenation index	239.52 ± 42.29	242.45 ± 39.45
APACHE II score	17.69 ± 2.96	17.14 ± 2.64
BUN (mmol/L)	8.51 ± 0.92	9.14 ± 1.26
Scr (μmol/L)	94.33 ± 14.25	96.18 ± 12.77
ALT (IU/L)	32.85 ± 5.69	34.12 ± 4.86
AST (IU/L)	29.38 ± 4.72	30.52 ± 4.24

3.2. General conditions of treatment

The mechanical ventilation time and hospital stays in ICU of patients in experimental group were significantly shorter than those in control group, and the number of cases developed into ARDS and MODS cases was significantly less than those in control group (Table 2). Oxygenation indexes (294.52 ± 41.26 *vs.* 257.63 ± 38.52; 357.74 ± 47.74 *vs.* 279.87 ± 31.46; 396.71 ± 55.12 *vs.* 279.87 ± 31.46) of patients were respectively calculated on Days 1, 2 and 3 after treatment, which were significantly higher than those in the control group (Table 2).

Table 2
The general conditions of treatment of patients in two groups.

General condition	Experimental group (n = 24)	Control group (n = 24)
Mechanical ventilation time (day)	4.28 ± 0.61*	6.65 ± 0.91
Hospital stays in ICU (day)	9.52 ± 1.41*	14.57 ± 2.51
ARDS cases	1 (4.17%)*	9 (37.50%)
MODS cases	1 (4.17%)*	7 (29.17%)
Oxygenation indexes		
Day 1 after treatment	294.52 ± 41.26*	257.63 ± 38.52
Day 2 after treatment	357.74 ± 47.74*	279.87 ± 31.46
Day 3 after treatment	396.71 ± 55.12*	301.35 ± 40.29

*: $P < 0.05$ compared with control group.

3.3. Contents of serum inflammatory mediators

On Day 3 after treatment, the contents of serum CRP, TNF-α, IL-6, IL-8, IL-10 and sTREM-1 of patients in experimental group were significantly lower than those in the control group (Table 3).

Table 3
The contents of serum inflammatory mediators of patients in two groups.

Serum inflammatory mediator	Experimental group (n = 24)	Control group (n = 24)
CRP (mg/L)	7.94 ± 1.05*	14.49 ± 2.97
TNF-α (ng/L)	264.69 ± 41.58*	417.87 ± 64.51
IL-6 (ng/L)	147.72 ± 21.36*	257.68 ± 41.54
IL-8 (ng/L)	93.68 ± 12.52*	145.62 ± 22.65
IL-10 (ng/L)	205.64 ± 31.56*	336.62 ± 51.38
sTREM-1 (ng/L)	73.32 ± 10.39*	114.45 ± 18.51

*: $P < 0.05$ compared with control group.

4. Discussion

Acute pulmonary contusion is the common concurrent change after blunt chest trauma, which results in the bleeding and edema of lung tissue and the activation of inflammatory reaction in contusion area, and further causes the relevant change of acute lung injury and significantly increases the risk of incidence of ARDS and MODS.

Acute lung injury is the initial factor to cause ARDS and MODS and also is an important pathologic change of multiple pathological links throughout multiple organ damage. The infiltration of local injured inflammatory cells and the release of inflammatory mediators are the most important pathological features of acute lung injury and the pathological basis for acute lung injury developing into ARDS and MODS[12]. Therefore, a treatment schedule set for the inflammatory reaction of acute lung injury to prevent the activation of inflammatory reaction and the release of inflammatory mediators can effectively delay the progress of disease, prevent the occurrence of ARDS and MODS and improve the prognosis of disease.

Anisodamine can resist the function of M acetylcholine receptor and exert the effect of relieving smooth muscle spasm, improving the function of pulmonary exchange and ventilation, alleviating microcirculatory disturbance and increasing the blood supply of microcirculation. Removing the vasospasm of arteriole and venule system in lesser and systemic circulation is the main pharmacological effects of anisodamine, which can transfer the blood in lung into systemic circulation. A large dose of anisodamine can promote the spontaneous vasomotion of arteriole and venule, which is helpful to dredge microcirculation. Meanwhile, anisodamine can inhibit the aggregation of blood platelets and granulocytes and the synthesis of thromboxane A2, decrease the incidence of thrombus of lesser circulation, stabilize lysosomal membrane, improve capillary permeability, activate and dredge microcirculation and accelerate the absorption of pulmonary edema, which reduces intrapulmonary shunt, enhances lung compliance, increases pulmonary ventilation, improves pulmonary exchange and ventilation and elevates oxygen partial pressure. The relief of states of airways spasm and the improvement of function of pulmonary exchange and ventilation can effectively reverse the impairment of lung function caused by pulmonary contusion, and the improvement of microcirculation can relieve the activation of inflammatory reaction and promote the absorption of local inflammatory factors[13–15]. In recent years, pharmacological research also confirmed that anisodamine can regulate the expression of aquaporin-1 and aquaporin-5, enhance the permeability of cytomembrane for water molecule, accelerate the backflow of vascular system and alleviate the state of pulmonary edema caused by trauma, which are helpful to the improvement of lung function. In this research, the vein was injected with anisodamine based on conventional therapy and according to general condition of treatment, we observed that the mechanical ventilation time and hospital stays in ICU of patients in experimental group were significantly shorter than those in control group, and the number of cases developed into ARDS and MODS was significantly less than those in control group. Oxygenation indexes of patients were respectively calculated on Days 1, 2 and 3 after treatment, which were significantly higher than those in the control group, which indicated that treatment with anisodamine can promote the recovery of illness condition, reduce the incidence of ARDS and MODS, and improve the function of pulmonary exchange and ventilation.

Inflammatory reaction is an important pathologic basis of acute lung injury caused by pulmonary contusion and its process is mediated by a variety of inflammatory mediators[7]. CRP is a kind of acute phase proteins synthetised and secreted by hepatic cells. Hepatic cells, which are effected by pro-inflammatory cytokines, such as IL-1β, TNF-α, can massively produce CRP and secrete into blood circulation. There is a good coincidence between the content of serum CRP and the degree of body's inflammatory response[16,17]. TNF-α changes the earliest among inflammatory mediators in the process of inflammatory reaction, which participates in inflammatory injury of tissues and the cascade amplification of inflammatory reaction[18]. The cytokines IL-6 and IL-8 possess many biological activities, which participate in the regulations of inflammatory reaction and immune response and enhance the inflammatory reaction of systemic organs caused by acute lung injury. IL-10 is an important anti-inflammatory cytokine in body, which exerts the inhibiting effect on the activation of mononuclear macrophage and the synthesis of inflammatory mediators. The compensatory increase of the content of serum IL-10 in the process of acute lung injury is the self-protective mechanism of body. While, sTREM-1 is the new-found trigger factor of inflammatory reaction in the recent years, which activates the synthesis and secretion of many inflammatory mediators through the passageway of TREM-1/DAP12[19]. We analyzed the contents of inflammatory mediators of patients with pulmonary contusion after treatment and the results showed that on Day 3 after

treatment, the contents of serum CRP, TNF-α, IL-6, IL-8, IL-10 and sTREM-1 of patients in experimental group were obviously lower than those in control group, which showed that anisodamine had inhibiting effect on the inflammatory reaction of patients with acute pulmonary contusion and can inhibit the synthesis and secretion of inflammatory mediators in the course of disease.

In conclusion, anisodamine combining with conventional therapy can relieve the degree of lung injury caused by acute pulmonary contusion, improve ventilatory function, lower the incidence of ARDS and MODS and inhibit the activation of inflammatory reaction and the release of inflammatory mediators.

Conflict of interest statement

The author reports no conflict of interest.

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