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Journal of Acute Disease

journal homepage: www.jadweb.org

Original article http://dx.doi.org/10.1016/j.joad.2016.07.001

A clinical study of multiple trauma combined with acute lung injury

Tao Liang[1], Yong-Fu Ma[2], Jian Zhu[1], Dao-Xi Wang[1], Yang Liu[2*]

[1]*Department of Thoracic Surgery, the General Hospital of the PLA Rocket Force, Beijing, 100088, China*

[2]*Department of Thoracic Surgery, General Hospital of Chinese People's Liberation Army, Beijing, 100853, China*

ARTICLE INFO

Article history:
Received 20 Jun 2016
Accepted 3 Jul 2016
Available online 21 Sep 2016

Keywords:
Multiple trauma
Acute lung injury
Inflammatory mediators
Blood gas analysis

ABSTRACT

Objective: To study the changes of the contents of inflammatory mediators in serum of polytrauma patients with acute lung injury (ALI) and their correlation with the disease.
Methods: Patients suffering from multiple trauma combined with ALI were selected as ALI group (n = 54). Patients suffering from multiple trauma without ALI were considered as the control group (n = 117). The severity of the disease of patients in the two groups was assessed. Arterial blood was extracted for blood gas analysis. Venous blood was extracted to detect the contents of inflammatory mediators tumor necrosis factor-α, interleukin-1β (IL-1β), IL-10, granulocyte-macrophage colony stimulating factor, NO, endothelin-1.
Results: The scores of injury severity score [(25.42 ± 3.58) *vs.* (17.03 ± 2.25)], systemic inflammatory response syndrome [(3.85 ± 0.52) *vs.* (2.20 ± 0.36)] and acute physiology and chronic health evaluation II [(92.63 ± 11.04) *vs.* (60.46 ± 8.87)] in patients in ALI group were all significantly higher than those in the control group and its correcting shock time [(8.39 ± 1.05) *vs.* (5.15 ± 0.72) h] was longer than that of the control group. The amount of blood transfusion [(674.69 ± 93.52) *vs.* (402.55 ± 57.65) mL] was greater than that in the control group. The contents of the arterial partial pressure of oxygen [(76.65 ± 9.68) vs. (86.51 ± 10.56) mmHg], arterial blood pressure of carbon dioxide [(27.76 ± 4.82) *vs.* (36.78 ± 5.82) mmHg] and arterial partial pressure of oxygen/fraction of inspired oxygen [(236.94 ± 36.49) *vs.* (353.95 ± 47.76)] were all significantly lower than those in the control group. The contents of serum tumor necrosis factor-α, IL-1β, IL-10, granulocyte-macrophage colony stimulating factor, NO and endothelin-1 were obviously higher than those of control group and also positively correlated with the scores of injury severity score, systemic inflammatory response syndrome and acute physiology and chronic health evaluation II.
Conclusions: The activation of the inflammatory reactions and the excessive release of inflammatory mediators are the key link causing multiple trauma combined with ALI. The content of serum inflammatory mediators is closely related to the severity of the disease.

1. Introduction

The treatment of multiple trauma has been a hotspot of the department of traumatology and a difficult problem as well. In recent years, with the increase of unintentional injuries caused by traffic accidents and construction accidents, the incidence rate of multiple trauma has been increasing year by year. Acute lung injury (ALI) refers to dyspnea and refractory hypoxemia induced by many intrapulmonary or extrapulmonary pathogenic factors. Multiple trauma combined with ALI is an important factor causing deaths for patients[1–3]. Multiple trauma combined with ALI will advance to be acute respiratory distress syndrome, increase the occurrence risk of multiple organ dysfunction syndrome (MODS) and then cause deaths for patients with multiple trauma[4–6]. Therefore, the prevention of the occurrence of ALI in patients with multiple trauma and the protection of pulmonary function can improve the prognosis of the disease.

*Corresponding author: Yang Liu, Department of Thoracic Surgery, General Hospital of Chinese People's Liberation Army, Beijing, 100853, China.
Tel: +86 13501009331
E-mail: liangabcde@yeah.net

The study protocol was performed according to the Helsinki declaration and approved by the ethic committee of the General Hospital of the PLA Rocket Force. Informed written consent was obtained from patients.

Peer review under responsibility of Hainan Medical College. The journal implements double-blind peer review practiced by specially invited international editorial board members.

A number of clinical studies on ALI confirmed that inflammation reaction caused by serious infection, toxicosis and shock is an important link for the occurrence of ALI. A variety of inflammatory mediators involve in the development and occurrence of ALI[7,8]. However, molecular mechanism of multiple trauma patients combined with ALI is not fully clear. It is not clear that whether inflammatory reaction is the pivotal step of concomitant ALI or not after multiple trauma. In the process of the development of ALI, numerous substances have involved in the inflammation reactions. Inflammatory factors such as tumor necrosis factor-α (TNF-α) and interleukin (IL), gas signaling molecule NO and endothelial-related molecular endothelin-1 (ET-1) are associated with inflammatory reactions. In the following studies, we explored the changes of the contents of inflammatory mediators in serum of multiple trauma patients combined with ALI and their correlation with the disease.

2. Materials and methods

2.1. General materials

The research objects were multiple trauma patients treated in our hospital from April 2012 to August 2015. According to CRASHPLAN sequence, patients were diagnosed with multiple trauma. Multiple trauma patients found to be combined with ALI within 72 h after admission to hospital were included in ALI group, while patients without ALI were assigned to the control group. Patients in ALI group met the following diagnostic criteria: hypoxemia, oxygenation index (PaO_2/FiO_2) 200–300, pulmonary artery wedge pressure $\leq$ 18 mmHg and chest X-ray showing bilateral pulmonary infiltrates without cardiogenic pulmonary edema. Patients with severe infections or other diseases involved vital organs such as heart, liver and kidney were excluded.

2.2. Research methods

2.2.1. Assessment of the severity of the disease

All enrolled patients received tests of injury severity score (ISS), systemic inflammatory response syndrome (SIRS), acute physiology and chronic health evaluation II (APACHE II). The number of organ damage, cases of gastrointestinal bleeding, traumatic shock, blood transfusion, blood transfusion and transfusion volume were recorded.

2.2.2. Assessment methods of respiratory function

Peripheral arterial blood of patients of the two groups were collected immediately once they were admitted to the hospital. The arterial partial pressure of oxygen (PaO_2) and arterial blood pressure of carbon dioxide ($PaCO_2$) were measured and PaO_2/fraction of inspired oxygen (FiO_2) was calculated.

2.2.3. Detection methods of serum inflammatory mediators

Peripheral venous blood of patients of the two groups was collected immediately once the patients were admitted to the hospital and stored in a cryogenic refrigerator at −80 °C after centrifugation. The contents of TNF-α, IL-1β, IL-10, granulocyte-macrophage colony stimulating factor (GM-CSF), NO, ET-1 were tested by ELISA.

2.2.4. Statistical methods

Data were input and analyzed by SPSS20.0 software. Analysis of measurement data was tested by *t*-test. Correlation analysis was tested by used Pearson correlation test. Differences were statistically significant when $P < 0.05$.

3. Results

3.1. Severity of patient's condition

The scores of ISS [(25.42 ± 3.58) *vs.* (17.03 ± 2.25)], SIRS [(3.85 ± 0.52) *vs.* (2.20 ± 0.36)] and APACHE II [(92.63 ± 11.04) *vs.* (60.46 ± 8.87)] in patients of ALI group were significantly higher than those of the control group. Correcting shock time [(8.39 ± 1.05) *vs.* (5.15 ± 0.72) h] was longer than that of the control group. The amount of blood transfusion [(674.69 ± 93.52) *vs.* (402.55 ± 57.65) mL] was greater than that of the control group. The number of organic damage [(2.06 ± 0.26) *vs.* (2.10 ± 0.29)] had no significantly difference as compared with the control group ($P > 0.05$) (Table 1).

3.2. Indexes of respiratory function

The amount of PaO_2 [(76.65 ± 9.68) *vs.* (86.51 ± 10.56) mmHg], $PaCO_2$ [(27.76 ± 4.82) *vs.* (36.78 ± 5.82) mmHg] and PaO_2/FiO_2 [(236.94 ± 36.49) *vs.* (353.95 ± 47.76)] were all significantly lower than those of the control group (Table 2).

3.3. Contents of serum inflammatory mediators

The analysis of the contents of serum inflammatory mediators in patients of the two groups was shown in Table 3. The contents of serum TNF-α, IL-1β, IL-10, GM-CSF, NO and ET-1 in ALI group were obviously higher than those of control group. The analysis of the correlation between contents of serum inflammatory mediators and disease severity was shown in

Table 1
Comparison of the severity of the disease in patients of the two groups.

Items	ALI group (n = 54)	Control group (n = 117)	P
ISS	25.42 ± 3.58	17.03 ± 2.25	< 0.05
SIRS	3.85 ± 0.52	2.20 ± 0.36	< 0.05
APACHE II	92.63 ± 11.04	60.46 ± 8.87	< 0.05
Numbers of organic damage	2.06 ± 0.26	2.10 ± 0.29	> 0.05
Numbers of traumatic shock	22 (40.74%)	21 (17.94%)	< 0.05
Numbers of correcting shock time (h)	8.39 ± 1.05	5.15 ± 0.72	< 0.05
Blood transfusion (mL)	674.69 ± 93.52	402.55 ± 57.65	< 0.05

Table 2
Comparison of the respiratory function in patients of the two groups.

Items	ALI group (n = 54)	Control group (n = 117)	P
PaO_2 (mmHg)	76.65 ± 9.68	86.51 ± 10.56	< 0.05
$PaCO_2$ (mmHg)	27.76 ± 4.82	36.78 ± 5.82	< 0.05
PaO_2/FiO_2	236.94 ± 36.49	353.95 ± 47.76	< 0.05

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

Mediators	ALI group (n = 54)	Control group (n = 117)	P
TNF-α (pg/mL)	89.48 ± 10.58	39.65 ± 5.27	< 0.05
IL-1β (ng/mL)	1.84 ± 0.22	0.48 ± 0.06	< 0.05
IL-10 (pg/mL)	78.72 ± 9.24	24.54 ± 4.84	< 0.05
GM-CSF (pg/mL)	55.28 ± 8.22	15.32 ± 1.96	< 0.05
NO (μmol/L)	47.79 ± 5.72	16.68 ± 2.05	< 0.05
ET-1 (pg/mL)	42.32 ± 5.47	12.54 ± 1.94	< 0.05

Table 4. The contents of serum TNF-α, IL-1β, IL-10, GM-CSF, NO and ET-1 correlated positively with the scores of ISS, SIRS and APACHE II.

Table 4
The correlation of the contents of serum inflammatory mediators and disease severity.

Mediators	ISS scores		SIRS scores		APACHE II scores	
	r	P	r	P	r	P
TNF-α	0.665	< 0.05	0.596	< 0.05	0.808	< 0.05
IL-1β	0.671	< 0.05	0.704	< 0.05	0.704	< 0.05
IL-10	0.703	< 0.05	0.684	< 0.05	0.774	< 0.05
GM-CSF	0.596	< 0.05	0.691	< 0.05	0.715	< 0.05
NO	0.738	< 0.05	0.834	< 0.05	0.654	< 0.05
ET-1	0.639	< 0.05	0.687	< 0.05	0.628	< 0.05

4. Discussion

ALI is the acute progressive respiratory failure resulting from intrapulmonary and extrapulmonary factors other than cardiogenic factors. Multiple trauma patients accompanied with ALI have poor prognosis and a higher mortality rate[9,10]. The pathological and physiological basis of ALI is the infiltration of mononuclear macrophages, neutrophils, eosinophils, lymphocytes and other inflammatory cells in the lung tissue and capillary damage caused by uncontrolled inflammatory reaction, which further results in the great exudation and aggregation of protein-rich liquid in the alveoli causing non cardiogenic pulmonary edema[11–13]. ALI can advance to be acute respiratory distress syndrome and induce refractory hypoxemia and systemic inflammatory reaction syndrome. Severe cases will be further developed into MODS[2,14,15]. In recent years, a growing number of studies have confirmed that ALI is the initial step of MODS in multiple trauma patients, while inflammatory cell infiltration in lung tissue and the activation of systemic inflammatory reaction are important steps to connect ALI and MODS[16,17].

ISS and APACHE II rating scales are the major ways to assess disease severity for trauma patients, which can provide the basis for medical improvement and prognosis evaluation. The analysis of the disease severity of multiple patients accompanied with ALL confirmed that ISS and APACHE II scores of patients in ALI group were higher than those of the control group, which demonstrated that the condition of multiple trauma patients combined with ALL will be worse with affected prognosis. Further analysis of specific clinical parameters revealed that the number of organ damage of patients in the two groups had no significant difference. However, patients in ALI group have more cases of gastrointestinal bleeding and traumatic shock, longer time of correcting shock and larger blood transfusion. These showed that the condition of multiple trauma patients combined with ALI was more severe with longer shock time and more serious bleeding. But there is no difference in the number of organ damage, which also confirmed that ALI aggravating multiple trauma has no direct relationship with organ damage in patients. The changing of basic pathology of ALI is the gathering of inflammatory cells in lung tissue. Inflammation reaction is considered as the critical link to connect ALI and MODS, but the changes of inflammatory reaction in patients suffering from multiple trauma combined with ALI are not yet clear. The degree of systemic inflammatory response was assessed by SIRS scores. The result showed that SIRS scores of ALI group were significantly higher than those of the control group, which suggested that multiple trauma patients combined with ALI may aggravate the disease by activating the inflammatory response.

In order to clarify the degree of inflammatory reaction in multiple trauma patients combined with ALI, the contents of inflammatory mediators in serum were analyzed. NO is a kind of gaseous signal molecule. Inflammatory cells recruited from the pulmonary alveoli can express NO synthase and increase the production of NO, and then mediate the inflammatory damage and oxidative stress damage of lung tissue through the downstream signaling pathway[18]. ET-1 comes mainly from alveolar epithelial cells and macrophages, which can affect vascular permeability and promote the collection of inflammatory cells in lung tissue, and further mediate the acute and chronic inflammation[19]. TNF-α, IL-1β and GM-CSF are cytokines with pro-inflammatory effects, which can promote the degranulation of granulocytes and the activation and migration of inflammatory cells and can also directly cause alveolar epithelial injury and lung edema[20]. IL-10 is an important anti-inflammatory factor in the body, which shows a compensatory increase in the process of the occurrence of ALI[21]. The analysis of the contents of serum inflammatory mediators of patients suffering from multiple trauma combined with ALI confirmed that the contents of serum TNF-α, IL-1β, IL-10, GM-CSF, NO and ET-1 of patients in ALI group were significantly higher than those of the control group and correlated positively with scores of ISS, SIRS and APACHE II, which showed that the inflammatory reaction was obviously activated and the secretion of inflammatory mediators significantly increased in patients suffering from multiple trauma combined with ALI and the contents of serum inflammatory mediators were closely related to the disease severity in patients.

In conclusion, the activation of inflammatory reactions and over release of inflammatory mediators are the key links causing multiple trauma combined ALI, and the contents of serum inflammatory mediators correlate positively with the severity of the disease.

Conflict of interest statement

The authors report no conflict of interest.

References

[1] Fair KA, Gordon NT, Barbosa RR, Rowell SE, Watters JM, Schreiber MA. Traumatic diaphragmatic injury in the American College of Surgeons National Trauma Data Bank: a new examination of a rare diagnosis. *Am J Surg* 2015; **209**(5): 864-8.

[2] Howard BM, Kornblith LZ, Hendrickson CM, Redick BJ, Conroy AS, Nelson MF, et al. Differences in degree, differences in kind: characterizing lung injury in trauma. *J Trauma Acute Care Surg* 2015; **78**(4): 735-41.
[3] Jin H, Tang LQ, Pan ZG, Peng N, Wen Q, Tang YQ, et al. Ten-year retrospective analysis of multiple trauma complicated by pulmonary contusion. *Mil Med Res* 2014; **1**: 7.
[4] Sehgal IS, Dhooria S, Behera D, Agarwal R. Acute respiratory distress syndrome: pulmonary and extrapulmonary not so similar. *Indian J Crit Care Med* 2016; **20**(3): 194-7.
[5] Chiumello D, Chidini G, Calderini E, Colombo A, Crimella F, Brioni M. Respiratory mechanics and lung stress/strain in children with acute respiratory distress syndrome. *Ann Intensive Care* 2016; **6**(1): 11.
[6] Gong MN, Thompson BT. Acute respiratory distress syndrome: shifting the emphasis from treatment to prevention. *Curr Opin Crit Care* 2016; **22**(1): 21-37.
[7] Afshar M, Smith GS, Cooper RS, Murthi S, Netzer G. Trauma indices for prediction of acute respiratory distress syndrome. *J Surg Res* 2016; **201**(2): 394-401.
[8] Butt Y, Kurdowska A, Allen TC. Acute lung injury: a clinical and molecular review. *Arch Pathol Lab Med* 2016; **140**(4): 345-50.
[9] Chen X, Song Y, Liu Z, Zhang J, Sun T. Ultrastructural lung pathology following brain injury combined with femur shaft fracture in a rat model. *J Trauma Acute Care Surg* 2015; **78**(3): 558-64.
[10] Schreiber MA, Meier EN, Tisherman SA, Kerby JD, Newgard CD, Brasel K, et al. A controlled resuscitation strategy is feasible and safe in hypotensive trauma patients: results of a prospective randomized pilot trial. *J Trauma Acute Care Surg* 2015; **78**(4): 687-95.
[11] Zhang Y, Wen Z, Guan L, Jiang P, Gu T, Zhao J, et al. Extracellular histones play an inflammatory role in acid aspiration-induced acute respiratory distress syndrome. *Anesthesiology* 2015; **122**(1): 127-39.
[12] Xiao XG, Zu HG, Li QG, Huang P. Sivelestat sodium hydrate attenuates acute lung injury by decreasing systemic inflammation in a rat model of severe burns. *Eur Rev Med Pharmacol Sci* 2016; **20**(3): 528-36.
[13] Ji WJ, Ma YQ, Zhang X, Zhang L, Zhang YD, Su CC, et al. Inflammatory monocyte/macrophage modulation by liposome-entrapped spironolactone ameliorates acute lung injury in mice. *Nanomedicine (Lond)* 2016; **11**(11): 1393-406.
[14] John S, Willam C. [Lung and kidney failure. Pathogenesis, interactions, and therapy]. *Med Klin Intensivmed Notfmed* 2015; **110**(6): 452-8. German.
[15] Sauaia A, Moore EE, Johnson JL, Chin TL, Banerjee A, Sperry JL, et al. Temporal trends of postinjury multiple-organ failure: still resource intensive, morbid, and lethal. *J Trauma Acute Care Surg* 2014; **76**(3): 582-92.
[16] Weckbach S, Hohmann C, Braumueller S, Denk S, Klohs B, Stahel PF, et al. Inflammatory and apoptotic alterations in serum and injured tissue after experimental polytrauma in mice: distinct early response compared with single trauma or "double-hit" injury. *J Trauma Acute Care Surg* 2013; **74**(2): 489-98.
[17] Hatakeyama N, Matsuda N. Alert cell strategy: mechanisms of inflammatory response and organ protection. *Curr Pharm Des* 2014; **20**(36): 5766-78.
[18] Gross CM, Rafikov R, Kumar S, Aggarwal S, Ham PB 3rd, Meadows ML, et al. Endothelial nitric oxide synthase deficient mice are protected from lipopolysaccharide induced acute lung injury. *PLoS One* 2015; **10**(3): e0119918.
[19] Lin CC, Lin WN, Hou WC, Hsiao LD, Yang CM. Endothelin-1 induces VCAM-1 expression-mediated inflammation via receptor tyrosine kinases and Elk/p300 in human tracheal smooth muscle cells. *Am J Physiol Lung Cell Mol Physiol* 2015; **309**(3): L211-25.
[20] Wang HT, Fang YQ, Bao XC, Yuan HR, Ma J, Wang FF, et al. Expression changes of TNF-α, IL-1β and IL-6 in the rat lung of decompression sickness induced by fast buoyancy ascent escape. *Undersea Hyperb Med* 2015; **42**(1): 23-31.
[21] Xu S, Xu M, Li GG, Wang C, Song H, Bai J. Early recruitment of IL-10-producing B cells into alveoli improved the resolution of acute lung injury. *Cell Physiol Biochem* 2016; **38**(5): 1752-60.