Can albumin administration relieve lung injury in trauma/hemorrhagic shock?

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Abstract

AIM: To study the effect of albumin administration on lung injury in trauma/hemorrhagic shock (T/HS).

METHODS: Sixty experimental animals were randomly divided into three groups: rats undergoing laparotomy without shock (T/SS); rats with T/HS and resuscitation with blood plus twice the volume of shed blood as Ringer’s lactate (RL), and rats with T/HS and resuscitation with blood plus additional 3 mL of 50 g/L human albumin. Expression of polymorphonuclear neutrophil (PMN) CD11b/CD18, intercellular adhesion molecule-1 (ICAM-1) of jugular vein blood and the severity of lung injuries (determined mainly by measuring activity of lung tissue myeloperoxidase (MPO) and lung injury score (LIS)) were measured after a 3-h recovery period.

RESULTS: All three groups showed a significant difference in the expressions of CD11b/CD18, ICAM-1, and severity of lung injury. The expressions of CD11b/CD18 in T/SS group, T/HS + RL group, T/HS + albumin group were 17.76% ± 2.11%, 31.25% ± 3.48%, 20.36% ± 3.21%, respectively (F = 6.25, P < 0.05). The expressions of ICAM-1 (U/mL) in T/SS group, T/HS + RL group, T/HS + albumin group were 258.76 ± 98.23, 356.23 ± 65.6, 301.01 ± 63.21, respectively (F = 5.86, P < 0.05). The expressions of MPO (U/g) in T/SS group, T/HS + RL group, T/HS + albumin group were 2.53 ± 0.11, 4.63 ± 1.31, 4.26 ± 1.12, respectively (F = 6.26, P < 0.05). Moreover, LIS in T/HS + RL group, T/HS + albumin group was 2.62 ± 0.23, 1.25 ± 0.24, respectively. The expressions of CD11b/CD18, ICAM-1 and MPO in T/HS + RL group were significantly increased compared to T/SS group (P = 0.025, P = 0.036, P = 0.028, respectively). However, administration of 3 mL of 50 g/L albumin significantly down-regulated the expressions of CD11b/CD18, ICAM-1 and lung injury index (MPO and LIS) when compared with the T/HS + RL rats (P = 0.035, P = 0.046, P = 0.038, P = 0.012, respectively).

CONCLUSION: The infusion of albumin during resuscitation period can protect lung from injury and decrease the expressions of CD11b/CD18, ICAM-1 in T/HS rats.

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Key words: Albumin; CD11b/CD18; Intercellular adhesion molecule-1; Lung injury; Trauma/hemorrhagic shock

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INTRODUCTION

Previous studies have shown that there is obvious pulmonary microvascular injury at the early stage of trauma/hemorrhagic shock (T/HS)[1]. The polymorphonuclear neutrophils (PMNs) accumulated in lung are closely correlated with lung injury[2]. Endothelial cells can control and regulate the adhesion, recruitment and migration of white blood cells (WBC) through expressing adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1), and ICAM-1 plays an important role in the process of conducting WBC firmly adherent to endothelial cells[3]. Colloid versus crystalloid resuscitation in the acute trauma remains a controversial subject[4]. Although several studies have proved the relative benefits of albumin resuscitation, no consensus has been reached by now[5]. More recently, the immunomodulatory effects of various resuscitation solutions have begun to be revaluated[6].

Trauma/hemorrhagic shock (T/HS) may lead to splanchnic ischemia-reperfusion and to gut barrier failure[7]. This sequence of events gets the gut into an inflammatory cytokine-secreting organ, which contributes to the pathogenesis of shock-induced lung injury[8]. Lung injury generally results when mediators released by systemic...
inflammatory processes up-regulate PMN interactions with endothelial cells (ECs). Endothelial cells play an important role in regulating cells of blood vessel walls in response to injury. ICAM-1 is expressed on endothelial cells and is responsive to numerous inflammatory mediators. It mediates both leukocyte adhesion and migration through the endothelium into tissues. Shock and trauma-induced neutrophil activation have been implicated in the pathogenesis of the adult respiratory distress syndrome (ARDS) and, as a contributory factor, in the development of the multiple organ dysfunction syndrome (MODS). In the study of trauma/hemorrhagic shock-induced organ failure, lung often serves as an ideal model of dysfunction.

Lung injury following T/HS is a well-accepted phenomenon; the exact mechanisms of injury are not yet defined. Albumin, a broadly binding protein, has been characterized as a scavenger in addition to being an anti-apoptotic agent and an antioxidant. A recent study showed that albumin protected endothelial cells in vitro from the injury by hematin. We hypothesize that albumin would protect against lung injury induced by activation of PMN in our T/HS model.

**MATERIALS AND METHODS**

**Experiment design**
The aim of this experiment was to determine the protective effects of albumin on lung injury in a T/HS model. Rats were randomly divided into three groups: rats undergoing laparotomy without shock (T/SS), rats with T/HS and resuscitation with blood plus 50 g/L human albumin (Aventis Behring GmbH, Germany), Rats of the albumin group received 3 mL of 50 g/L human albumin (150 mg of albumin) in addition to their shed blood. In a 400-g rat, with a circulating blood volume of about 24 mL, this dose is 6 g/L, approximating the distribution of a 25-g dose of albumin in the approximately 4 L blood volume of a 60-kg man. Polymorphonuclear neutrophil (PMN) CD11b/CD18, ICAM-1 in jugular vein blood and the severity of lung injuries [determined by myeloperoxidase (MPO) and lung injury score (LIS)] were measured after a 3-h recovery period.

**Subjects**
Sixty adults Sprague-Dawley (SD) rats, weighing 300-350 g, were used after a minimum acclimatization period of 7 d. These animals were randomly divided into three groups according to aforementioned experimental design. The animals were allowed free access to food and water. The animals and their diet were provided by the Laboratory Animal Center, Collage of Medicine, Zhejiang University. The animals were maintained in accordance with the guideline of the National Guide for the Care and Use of Laboratory Animals, and the experiment was approved by Local Ethical Committee of the College of Medicine, Zhejiang University.

**T/HS model**
As described above, rats were anesthetized using intraperitoneal sodium pentobarbital (50 mg/kg). A heparinized polyethylene catheter (PE-50) was introduced into the femoral artery for measuring the arterial pressure. A right jugular vein catheter was similarly inserted for blood withdrawal and resuscitation. Laparotomy (trauma) was performed to the animals through a 5-cm midline incision with two-layer closure using 3-0 silk in a running suture. The T/HS rats were subjected to T/HS (90 min at a mean artery pressure of 30 mmHg) by withdrawing blood through the jugular vein catheter in a heparinized syringe until the pressure reached 30 mmHg. The blood pressure was maintained for 90 min by withdrawing or re-infusing the shed blood. At the end of the 90-min shock period, the HS rats were resuscitated by their shed blood (average 18 mL). The RL group received an additional crystalloid (average 18 mL) and the albumin group received an additional 3 mL of 50 g/L albumin. Sham (T/SS) animal underwent vascular cannulation and laparotomy, but had no blood withdrawn and received no resuscitation. The animals’ body temperature during the experimental period was maintained at about 37°C by using a heating pad.

**Assay of blood CD11b/CD18 and ICAM-1**
After the 3-h resuscitation period, each 1 mL of blood sample from the jugular vein was taken and treated with anti-coagulant EDTA.Na2. The 100-μL blood sample was put into a tube with size of 12 mm × 75 mm and then 10 μL of either anti-rat CD11b or CD18 fluorescent-labeled monoclonal antibody (BD Pharmingen) was added into the tube. The samples were gently vortexed for 10 min and then placed into a dark place for 40 min. And then the red blood cells of the sample were lysed and the sample was fixed with Coahem.Q-PREP equipment (Couletr Company, USA) for 15 min on ice. After being treated with centrifugation and washed for 3 times, PMN cells obtained were analyzed for detection of adhesion molecule expression using flow cytometer (ESPLL-XL, BECKMAN, USA) according to the manufacturer’s recommendation. The amounts of these neutrophils labeled with monoclonal antibody among each 10000 neutrophils were counted and the percentage was evaluated.

The expression of serum ICAM-1 in the venous blood was detected using a special Regent Box (Jianqing Company, Nanjing, China) with ELISA methods following manufacturer’s instructions.

**Assay of MPO and LIS**
After the 3-h resuscitation period with aforementioned different methods, rats were killed immediately, and the right lobe lung was taken. One part of lung tissue was frozen, homogenized and processed for detection of MPO with special Regent-Box (Jiancheng Bio-Technology Company, Nanjing, China) according to the manufacturer’s recommendation. One unit of MPO activity represents the amount of enzyme that will reduce 1 μmol/L peroxide per minute. The other part of lung tissue was fixed by...
Table 1  Comparisons of the expressions of CD11b/CD18, ICAM-1, MPO, and LIS among the three groups (mean ± SD)

| Group (n)           | CD11b/CD18 (%) | ICAM-1 (U/mL) | MPO (U/g) | LIS |
|---------------------|----------------|---------------|-----------|-----|
| T/SS (20)           | 17.76 ± 2.11   | 258.76 ± 98.23| 2.53 ± 0.11| -   |
| T/HS + RL (20)      | 31.25 ± 3.48   | 356.23 ± 65.6 | 4.63 ± 1.31| 2.62 ± 0.23|
| T/HS + albumin (20) | 20.36 ± 3.21   | 301.01 ± 63.21| 4.26 ± 1.12| 1.25 ± 0.24|
| F                   | 6.25'          | 5.86'         | 6.26'     | -   |

ICAM-1: Intercellular adhesion molecule-1; MPO: Myeloperoxidase; LIS: Lung injury score. 'p < 0.05 vs T/SS group; 'p < 0.05 vs T/HS + RL group; 'p < 0.05 comparison among the three groups (ANOVA).

The present study showed that PMNs infiltrated and aggregated in the lung after trauma/hemorrhagic shock (T/HS) [17]. Up-regulation of CD11b/CD18 on PMNs and ICAM-1 in endothelial cells are the molecular basis of PMNs adhering to the endothelium [18]. Trauma/ hemorrhagic shock is associated with the generation of reactive oxygen species, which may contribute to delayed multiple organ system failure and death [19]. It has been shown the phenomenon of neutrophil activation is often accompanied with T/HS. In addition, the activated neutrophil may play an important role in the pathogenesis of lung injury or multiple organ dysfunction (MOD), multiple organ failure (MOF) in T/HS [20]. The activation of neutrophil and lung injury are often chosen as ideal quantifiable indices to assess the severity of trauma in an animal model and patients. In this study, CD11b/CD18 was chosen as the marker of PMN activation; MPO and LIS were chosen as the markers of lung injury [21].

The integrins CD11b/CD18 have been found to be involved in monocyte adhesion to endothelial cells and transendothelial migration [22,23], release of hydrogen peroxide [24,25], and oxidative activity [26]. ICAM-1 is expressed on endothelial cells and is responsive to numerous inflammatory mediators [27]. It mediates both leukocyte adhesion and migration through the endothelium into tissues [28].

The potential advantages and disadvantages of colloids during resuscitation in T/HS have been long debated [29]. Some animal experiments showed that albumin was linked with increased mortality, but which did not accord with some clinical findings that albumin could decrease mortality in the trauma population [30]. However, a more recent study has demonstrated that early albumin infusion during resuscitation period may decrease neutrophil activation in animal model [31]. Some studies indicated that resuscitation with 250 g/L albumin significantly reduced transpulmonary protein flux, bronchoalveolar lavage fluid neutrophil counts, and the degree of histopathological injury compared to resuscitation with Ringer’s lactate [32].

The exact mechanism by which albumin does benefit to alleviate lung injury and down-regulate CD11b/CD18 expression is still uncertain. In addition to colloid oncotic effects during resuscitation period, a variety of other properties of albumin have been described [33]. Albumin has been shown to have antioxidant properties and proven to inhibit apoptosis in certain cell lines [34]. As a broad binding protein, albumin may bind and neutralize toxic factors and inflammatory mediators, including cytokines, eicosanoids, oxidants, platelet-activating factors, complement fragments, and endotoxin [34,35]. And many of these mediators can prime or activate neutrophils and endothelial cells and cause lung injury directly or indirectly. Although the exact function and identity of the toxic factors in T/HS lymph/plasma remain unknown, it is clearly that albumin has a neutralizing effect [36].

Based on our results, the beneficial effect of albumin infusion occurred during the resuscitation period in T/HS. The results showed that up-regulated expression of PMN CD11b/CD18, ICAM-1 and the lung injury induced by T/ HS could be alleviated by the infusion of albumin during resuscitation period. On the other hand, considering the ability of albumin to bind and neutralize the toxic factors,
our study further supports the hypothesis of organ injury induced by some factors released or produced by the post-ischemic intestine through mesenteric lymph pathway in T/HS[13].

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