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Original Contribution

A fresh frozen plasma to red blood cell transfusion ratio of 1:1 mitigates lung injury in a rat model of damage control resuscitation for hemorrhagic shock☆,☆☆

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ABSTRACT

Background: We aimed to evaluate the effects of resuscitation with different ratios of fresh frozen plasma (FFP) to red blood cells (RBCs) on pulmonary inflammatory injury and to illuminate the beneficial effects of FFP on lung protection compared with lactated ringers (LR) using a rat model of hemorrhagic shock.

Methods: Rats underwent pressure-controlled hemorrhage for 60 minutes and were then transfused with LR for initial resuscitation. Thereafter, the rats were transfused with varying ratios of FFP:RBC (1:4, 1:2, 1:1, and 2:1) or LR:RBC (1:1) to hold their mean arterial pressure (MAP) at 100 ± 3 mm Hg for 30 minutes. After 4 hours of observation, lung tissue was harvested to determine the wet/dry weight, myeloperoxidase levels, tumor necrosis factor α levels, macrophage inflammatory protein 2 (MIP-2) levels, inducible nitric oxide synthase activity, and the nuclear factor κB p65 DNA-binding activity.

Results: With an increase in the FFP:RBC ratio, the volume of required RBC to maintain the target MAP decreased. The MAP value in each group was not significantly different during the whole experiment period. The values of the wet/dry weights and MIP-2 were significantly lower in the FFP:RBC = 1:1 group than the other groups ($P < .05$). All parameters detected above were predominantly lower in the FFP:RBC = 1:1 group than the FFP:RBC = 1:2 group and the LR:RBC = 1:1 group ($P < .05$). In addition, all parameter values were lower in the FFP:RBC = 1:1 group than in the FFP:RBC = 2:1 group, but only the wet/dry weight, myeloperoxidase, and MIP-2 values were significantly different ($P < .05$).

Conclusions: Resuscitation with a 1:1 ratio of FFP to RBC results in decreased lung inflammation. Compared with LR, FFP could further mitigate lung inflammatory injury.

1. Introduction

According to data obtained from both the military and the clinic, the damage control resuscitation (DCR) strategy as a structured intervention begins immediately after rapid initial assessment in the emergency department (ED). Thus, DCR represents a potential opportunity to reduce mortality further. For a severely injured casualty, DCR consists of 2 parts and is initiated within minutes of arrival in the ED. First, resuscitation is limited to keep systolic blood pressure at approximately 80 to 90 mm Hg, which prevents renewed bleeding from recently clotted vessels. Second, intravascular volume restoration is accomplished using thawed plasma as a primary resuscitation fluid in a high ratio with red blood cells (RBCs) [1,2]. Based on previous civilian clinical and military studies, Borgman et al [3,4] reviewed massively transfused (≥10 U RBC/24 hours) combatants and demonstrated that the mortality reduction was impressive in patients with a higher FFP:RBC ratio (1:1.4) and that they had a longer median time to death than those with a lower ratio. The study by Holcomb et al [5] examined trauma patients at 16 trauma centers who required massive transfusion, and the study determined that an FFP:packed red blood cell ratio of 1:2 or higher compared with lower ratios was associated with improved 30-day survival. Sperry et al [6] found mortality differences in those patients who received ratios of plasma to packed red blood cell of approximately 1:1.5. Therefore, increasing the ratio of fresh frozen plasma (FFP) to RBCs is beneficial in clinical situations associated with traumatic hemorrhage.

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However, the currently available evidence supporting higher FFP:RBC ratios for resuscitation is inconclusive. The present civilian clinical and military studies are not randomized controlled trials that account for survivorship bias [7,8]. The survivorship bias arises because the patients who were not expected to live long enough to receive FFP were categorized (without randomization) to the low FFP:RBC cohorts in observational studies. However, patients surviving long enough to receive sufficient FFP were categorized to the high FFP:RBC cohorts [7].

Fresh frozen plasma is usually used as a volume expander and is currently indicated for the management and prevention of bleeding in coagulopathic patients [1,8]. Recently, Letourneau et al [9,10] demonstrated that treatment with FFP stabilized the endothelium. The overall beneficial effect of FFP may be decreased endothelium permeability, which could contribute to vascular instability, edema, and other detrimental effects of injury and resuscitation, despite increased leukocyte-endothelial binding. Therefore, the beneficial effects of FFP on lung tissue protection besides coagulopathy should be further investigated.

In the present study, we examined the effect of transfusing various ratios of FFP:RBC on lung injury with the goal of identifying the appropriate FFP:RBC ratio for DCR. In addition, we aimed to find the association between FFP with transfusion-related lung injury in a rat model of hemorrhagic shock.

2. Materials and methods

All animal studies were approved by the Ethics Committee of the Institute of Transfusion Medicine, Academy of Military Medical Sciences. The care and handling of the animals were in accordance with the National Institutes of Health guidelines. All efforts were made to minimize the number of animals used and animal suffering.

2.1. Animal preparation

Fifty-six male Wistar rats (280-300 g; Vital River Laboratories, Beijing, China) were anesthetized with an intraperitoneal injection of 50 mg/kg sodium pentobarbital (Peking Chemical Agent Co, Peking, China) and placed on a warming pad (TMS-202; Softron, Beijing, China) in a supine position that was maintained at 37 ± 0.1°C throughout the experiment [11]. Supplemental doses of 10 mg/kg sodium pentobarbital were given per hour after the start of resuscitation.

The left carotid artery, right femoral artery, and vein were exposed, isolated, and cannulated with polyethylene catheters (PE-50). Four hundred units per kilogram heparin (Chinese Medicine Group Chemical Agent Co, Peking, China) was administered intravenously to inhibit the coagulation of blood in the experimental equipment. The left carotid artery was used for continuous monitoring of blood pressure. The right femoral artery was used to achieve bleeding using a withdrawal pump (LZS-AJ10; Softron) and to sample the arterial blood for blood gas analysis. The right femoral vein was used for the administration of fluids.

2.2. Collection of blood components

Donor male rats were anesthetized and heparinized. The femoral artery was isolated and cannulated to obtain the whole blood. Anticoagulated whole blood was centrifuged at 1000g for 10 minutes immediately after collection to obtain plasma and fresh RBC. Plasma was stored at −80°C to prepare the FFP for future use. Fresh RBC was gently mixed with thawed FFP in the ratio specified for blood transfusion.

2.3. Experimental protocols

Fig. 1 depicts the experimental protocol. After the operation and instrumentation, the rat hemorrhagic shock model was prepared as described previously [12] with several modifications. A volume-controlled hemorrhage of 21 mL/kg (~35% of total blood volume) was performed for 20 minutes through the right femoral arterial catheter, and the animals were stabilized for 10 minutes. Subsequently, the animals were subjected to a slower hemorrhage of 10 mL/kg (~10% of total blood volume) for 15 minutes, and hemorrhaging was continued as needed to maintain a MAP at 50 ± 5 mm Hg for 15 minutes. The total amount of blood withdrawn was recorded. Resuscitation with lactated ringers (LR) (equal to the maximum blood volume withdrawn) was performed, and the animals were stabilized for 30 minutes (R"). Subsequently, all of the rats were divided into 5 groups (n = 8/group) and were resuscitated with the varying ratios of FFP (LR) and RBC to hold their MAP at 100 ± 3 mm Hg for 30 minutes (R0): (1) an FFP to RBC ratio of 1:4 (1:4), (2) an FFP to RBC ratio of 1:2 (1:2), (3) an FFP to RBC ratio of 1:1 (1:1), (4) an FFP to RBC ratio of 2:1 (2:1), and (5) an LR to RBC ratio of 1:1 (LR1:1). All infusions were performed using a pump driven at a constant rate of 0.33 mL/min in all groups. Thereafter, all rats were monitored for 240 minutes, and the MAP was recorded at intervals of 30 minutes (R30, R60, R90, R120, R150, R180, and R240). Sham animals underwent cannulation and anesthesia for an identical period as the resuscitation animals but were not bled (sham) (n = 8). Shock animals underwent hemorrhage but not resuscitation (shock) (n = 8).

At the end of the observation period, the animals were sacrificed by exsanguination, and the lungs were quickly removed. The right lung was excised for the wet to dry weight ratio. The left lung was washed with cold saline, snap frozen in liquid nitrogen, and stored in liquid nitrogen for further processing.

2.4. Hemodynamic and blood gas analysis

Hemodynamic parameters, such as MAP, heart rate, and rectal temperature, were recorded using a multiple-channel recorder (MP150 Research System; Biopac System Inc, Montreal, Canada). Blood gas analysis was performed at baseline (base), after blood withdrawal (shock) and 4 hours after resuscitation using 0.15 mL of arterial blood with a blood gas analyzer (ABL90 FLEX; Radiometer, Copenhagen, Denmark).

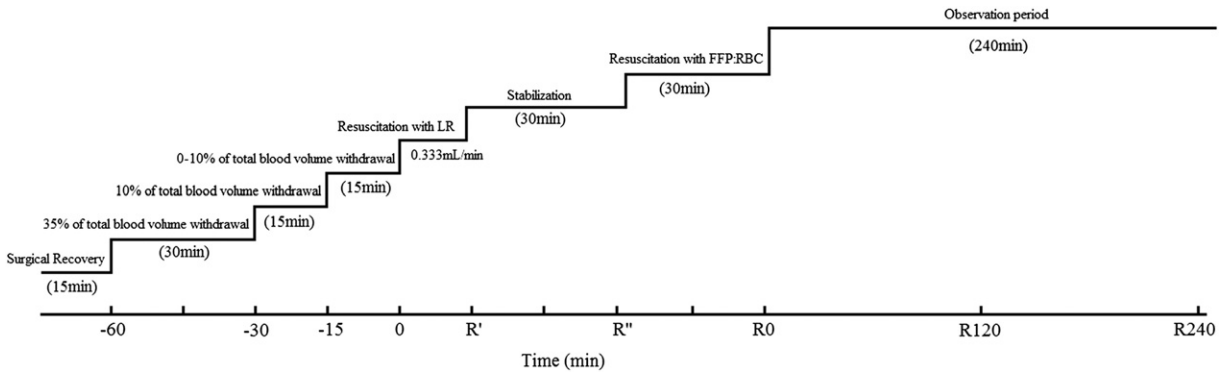

Fig. 1. Study design.