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Original Article

The plasma and platelet are important in reducing the mortality in surgical massive blood transfusion: a large multicenter study in China

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Abstract: Objective: The aim of this study was to learn the current situation of surgical massive transfusion of death and survival groups in China, which could provide the basis for the formulation of guidelines on massive transfusion. Methods: A multicenter retrospective research for the application status of blood constituents during massive blood transfusion was conducted, the differences of fresh frozen plasma and platelet application between death group and survival group were compared, and the transfusion volume and the distribution of other blood constituents were analyses at different periods of time when red blood cells are infused between death group and survival group. Results: The patients with fresh frozen plasma compare the patients with red blood cell was 1:1-2 during massive transfusion, while the dosage of platelet and cryocepitate were transfused very small. Results showed that the average amount of platelet and plasma in death group was significantly lower than those in survival group. Conclusion: During massive transfusion, clinicians in 20 Chinese hospitals paid more attention to the infusion of fresh frozen plasma while making the infusion of red blood cells. However, they paid little attention to the supplement of platelet and cryocepitate. The average quantity of plasma and platelet in survival group were also higher than those in death group.

Keywords: Massive transfusion, blood constituents, plasma, platelet

Introduction

Massive transfusion is generally defined as the administration of ≥ 10 U of packed red blood cells (pRBC) to a patient [1, 2] or the transfusion of more than one blood volume in 24 h [1, 3-5]. Acute clinical situations that warrant the administration of massive transfusion include a 50% blood volume loss within 3 h or a blood loss rate of 150 ml/min [3]. Massive transfusion is generally necessary in severely injured military personnel or patients with multiple injuries. Such patients often require multiple, complex surgical procedures. A rational blood transfusion protocol can improve the outcome of surgery, whereas unreasonably excessive transfusion can increase the mortality, which mainly due to coagulation disorders, acidosis, and hypothermia. Most of the studies published hitherto have been conducted in western countries and on trauma patients [5-10]. No multicenter data are currently available on the influence of massive transfusion on the application of blood constituents during the perioperative period in Chinese patients.

In this study, in order to learn the current situation of surgical massive transfusion in China's Class III general hospitals and provide the basis for the formulation of China's guidelines on massive transfusion (draft for recommendation), we undertook a retrospective investiga-

tion of 1601 cases of surgical inpatients from 20 large-scale, comprehensive hospitals in different regions in China and analyzed the application of blood constituents in death and survival groups transfusion patients.

Methods

This study has been approved by the ethics committee of Shaanxi Provincial People's Hospital. The subjects' informed consent was obtained from each of the participants.

Collecting data

In this study, the massive transfusion is defined as the administration of ≥ 10 U of packed red blood cells (pRBC) in 24 h. We collected data from the medical records of surgical inpatients who received massive transfusion at 20 large-scale hospitals (in the northwest, southwest, central south, north, and northeast parts of China) between January 2009 and December 2010, we distributed 2000 copies of the Massive Transfusion Survey Table (hereafter referred to as "Survey Table") to 20 Participate in the hospital. Members of the National Massive Transfusion Current Status Investigation Coordination Group (hereafter referred to as the "Coordination Group") were responsible for collecting the data from these hospitals using the Survey Table. The data analysis was conducted at Shaanxi Provincial People's Hospital, the Third Affiliated Hospital of the Medical College of Xi'an Jiaotong University. The center is a level-3 grade-A hospital and has 73 clinical departments, 7 research centers, 4500 well-trained staff members, and 2600 beds.

Study population

Patients who received transfusion greater than or equal to 10 U of pRBCs in 24 hours for trauma, cardiac surgery, obstetric conditions, or other common surgeries (e.g., orthopedic, thoracic, general, urinary, hepatobiliary, and neurological surgery) were included in the study as research group. Patients who received transfusions less than 10 U of pRBCs in 24 hours were defined as control group. On the other hand, patients with coagulation disorders and/or hepatic failure due to medical causes were excluded from the analysis. The cases of death in this study refer to fatalities occurring during the period of hospitalization.

Design survey table

The directors of the transfusion departments of the 20 participating hospitals discussed the topic, consulted experts, and designed the Survey Table with reference to several international and domestic sources, in accordance with the principle of voluntary participation in this project. A meeting of the Coordination Group was then held (06-05-2010, Xi'an), where 35 experts of clinical transfusion, surgery, anesthesia, gynecology and obstetrics, hematology, and medical statistics discussed the study protocol and mode of data collection and also perfected and added supplements to the Survey Table. Suitable training was then offered to the investigating staff.

Components of the survey table

The survey table comprised 4 sections: 1. Clinical and demographic characteristics of the patient: including name, gender, age, body weight, blood type, ethnicity, admission number, admission department, primary diagnosis, secondary diagnosis, pathologic diagnosis, nature of surgery, and vital signs on admission; 2. Details regarding the perioperative complications, clinical condition within 24 h and after 24 h of the transfusion, and the total amount of blood transfused; 3. The results of the following blood tests performed before, within 24 h, and after 24 h of transfusion: routine blood test, coagulation tests, liver function test, kidney function test, and arterial blood gas analysis; 4. Adverse events due to massive transfusion.

Quality control

The Survey Table was first subjected to a small-scale preliminary test at Shaanxi Provincial People's Hospital so that revisions could be made on the basis of the results and comments by experts to further improve the table. The protocol for massive transfusion, as per the Chinese standards, was as follows: one unit of pRBC derived from 200 ml of whole blood and with a volume of 140-172 ml; one unit of fresh frozen plasma (FFP) derived from 200 ml of whole blood and a volume of 100 ml; one bag of apheresis platelet of 10 U and a volume of 150-250 ml; and one unit of platelet concentrate derived from 200 ml of whole blood and with a volume of 20-30 ml. One bag of apheresis platelet is 10 U of platelet concentrate. The

Table 1. Baseline data of 1601 patients receiving massive transfusion

	< 10 U§ (n = 553)	≥ 10 U (n = 1048)	P
Demographics			
Age (years, median)	46	46	0.085**
Males, n (%)	253 (45.8)	646 (61.6)	0.000‡
Weight (kg, median)	60	60	0.785**
Trauma, n, (%)	81 (30.2)	187 (69.8)	0.008‡
Cardiac surgery, n, (%)	116 (30.3)	267 (69.7)	
General surgery, n, (%)	335 (38.2)	541 (61.8)	
Obstetric, n, (%)	21 (28.4)	53 (71.6)	
Trauma deaths, n, (%)	7 (8.6)	27 (14.4)	0.000†
Cardiac surgery deaths, n, (%)	4 (3.4)	49 (18.4)	
General surgery death, n, (%)	13 (3.9)	29 (5.4)	
Obstetric death, n, (%)	0 (0)	3 (5.7)	
Clinical data (before transfusion)			
Respiration (n/min, mean ± SD)	20.3 ± 3.5	20.5 ± 3.6	0.043*
Pulse (n/min, mean ± SD)	94.1 ± 69.8	92.5 ± 54.3	0.452*
SBP (mmHg, mean ± SD)	113.5 ± 24.7	112.8 ± 30.2	0.020*
Temperature (°C, mean ± SD)	36.6 ± 1.0	36.5 ± 0.7	0.319*
RBC (× 10^{12}/L, mean ± SD)	3.8 ± 1.0	3.8 ± 1.1	0.323*
Hb (g/L, mean ± SD)	114.3 ± 30.2	117.4 ± 43.2	0.213*
Hct as (%, mean ± SD)	21.2 ± 17.7	16.6 ± 17.6	0.834*
PLT (× 10^9/L, mean ± SD)	179.5 ± 91.5	175.6 ± 98.9	0.324*
PT (s, mean ± SD)	13.7 ± 6.0	14.1 ± 5.8	0.173*
APTT (s, mean ± SD)	33.6 ± 11.7	36.3 ± 24.2	0.006*
TT (s, mean ± SD)	17.1 ± 12.8	17.5 ± 7.1	0.529*
INR (mean ± SD)	1.3 ± 2.1	1.2 ± 1.1	0.041*
FIB (g/L, mean ± SD)	11.3 ± 44.4	11.0 ± 46.6	0.801*
Clinical data (after transfusion)			
Length of hospital stay (d, mean ± SD)	24.9 ± 14.3	29.8 ± 23.9	0.000*
Length of ICU stay (d, mean ± SD)	3.8 ± 3.5	8.7 ± 23.4	0.006*
Operation time (h, mean ± SD)	2.5 ± 3.2	3.7 ± 3.9	0.000*
pRBC in 24 h (U, medians)	9	25	0.000**
FFP in 24 h (U, medians)	8	20	0.000**
PLT in 24 h (U, medians)	10	6	0.009**
pRBC in 72 h (U, medians)	20	18	0.202**
FFP in 72 h (U, medians)	14	13	0.499**
PLT in 72 h (U, medians)	8	8	0.873**

APTT, activated partial thromboplastin time; FIB, fibrinogen concentration; Hb, hemoglobin concentration; ICU, intensive care unit; INR, international normalized ratio; PLT, platelet count; PT, prothrombin time; RBC, red blood cell count; SBP, systolic blood pressure; TT, thrombin time; pRBC, Packed Red Blood Cells; FFP, Fresh Frozen Plasma. The superscripts a, b, c, d indicate patients who had trauma, cardiac surgery, general surgery, and obstetric complications, respectively. §Patients who received transfusion of ≥ 10 U of pRBC in 24 h were defined as research group. Patients who received transfusions of < 10 U pRBC in 24 h were defined as the control group. †Fisher's Exact Test. ‡Chi-square test. *Analysis of variance was used. **Kruskall-Wallis test was used.

pRBC were stored at 2°C to 6°C. FFP was stored at ≤ -18°C and thawed in a 37°C water bath, for about 10 to 15 minutes. Platelets were stored at 20°C to 24°C in a platelet shaker.

The main test devices and reagents used were as follows: Sysmex XE-2100/XT-1800i hematology analyzer, Sysmex Corporation, Kobe, Japan; Beckman Coulter LH780 Coulter Hematology Analyzer, Beckman Coulter, CA, USA; Hitachi 7170A/7180 Biochemical Analyzer, Hitachi, Japan; Roche Modular DP Automatic Biochemical Analyzer, Roche, USA; Olympus AU640 Biochemical Analyzer, Olympus Corporation, Japan; Radiometer ABL-77 Blood Gas Analyzer, Radiometer, Copenhagen, Denmark; Roche Cobas-B123 Blood Gas Analyzer, Roche, US; Sysmex CA1500/CA7-000 Automatic Blood Coagulation Analyzer, Japan. All test reagents used were device-supporting reagents.

Data on the blood tests performed were collected from the laboratory records: blood routine, coagulation tests, liver function test, kidney function, and blood gas analysis. The data were collected for the blood tests performed before transfusion and at 16 different time points during the 24-h transfusion (2 U, 4 U, 6 U, 40 U) and subjected to statistical analysis. The tests were conducted at the laboratory of each participating hospital,

Table 2. The blood use for patients in the death group and survival group

	Survived patients (n = 1469)	Dead patients (n = 132)	*P*
Red blood cells (U, medians)	14	23	0.000**
Plasma (U, medians)	14	23	0.000**
Platelet (U, medians)	3	2.5	0.636**
Cryoprecipitate (U, medians)	2	2	0.303**

**Kruskall-Wallis test was used.

which undergoes internal quality control and an external quality assessment conducted by the National Center for Clinical Laboratories.

Statistical analysis

Statistical analysis was conducted using SPSS software (SPSS Inc. Released 2009. PASW Statistics for Windows, Version 18.0. Chicago, IL: SPSS Inc.). Epidata (version 3.01; Epidata Association) was used for double data entry verification and database construction. The data on the demographic characteristics and clinical features were expressed as means with standard deviations or as absolute numbers. Categorical variables were analyzed by chi-square test (χ^2), while continuous variables with normal distribution were analyzed by the Shapiro-Wilk test, analysis of Variance, or the Kruskall-Wallis test, as appropriate. A two-sided *P*-value of < 0.05 was considered statistically significant.

Results

Patient characteristics

We were able to retrieve 1753 of the 2000 copies of the Survey Table from the 20 hospitals, at a recovery rate of 87.65%. After excluding tables with missing information, 1601 copies (91.33%; 889, male patients; 702, female patients) were used for the analysis. The age of the enrolled patients was 16-91 years (median: 46 years) and weight was 46-105 kg (median: 60 kg). The data regarding age and weight were tested by the Shapiro-Wilk test (P < 0.01) and showed abnormal distribution; therefore, they were described by median values. Among the 1601 patients who received blood transfusion, 1048 patients received ≥ 10 U of pRBC within 24 h (108 patients died, 940 patients survived; death rate: 10.31%), whereas 553 patients received < 10 U of pRBC within 24 U (24 patients died, 529 patients survived; death rate: 4.34%). The reasons for transfusion in the 1601 patients enrolled cases were as follows: trauma in 268 patients (34 patients died, 234 patients survived; death rate: 12.69%), cardiac surgery in 383 patients (53 patients died, 330 patients survived; death rate: 13.84%), general surgery in 876 patients (42 patients died, 834 patients survived; death rate: 4.79%), and obstetric complications in 74 patients (3 patients died, 71 patients survived; death rate: 4.05%). When the receipt of greater than or equal to 10 U of RBCs in the first 24 hours, the death rate of the four departments as the following order: cardiac surgery (18.4%) > trauma (14.4%) > obstetrics (5.7%) > general surgery (5.4%); When the receipt of less than 10 U of RBCs in the first 24 hours, the death rate of the four departments as the following order: trauma (8.6%) > general surgery (3.9%) > cardiac surgery (3.4%) > obstetrics (0%). The details of the patient characteristics are provided in **Table 1**.

The blood use for patients in the death group and survival group

It can be drawn from **Table 2** that red blood cell suspension used by patients in the death group within 24 hours was 23 U on average, which was far greater than 14 U used by the survival group. The plasma volume was also greater than that used in the survival group, while the dosage of platelet and cryocepitate was very little and basically identical.

The application of red blood cells and plasma in the death group and survival group

When the administration of pRBC within 10 U in 24 h, the ratio of the number of the patients with pRBC transfusion compare with the patients with plasma transfusion was 5~1.5:1, while the administration of pRBC ≥ 10 U in 24 h, the ratio was 1.5:1, when the administration of pRBC between 6-12 U and 28-30 U in 24 h, the ratio in death group was higher than survival group (*P* < 0.05) (**Figure 1A**). When the administration of pRBC between 26 U and 30 U in 24 h, the average of plasma in the death group was significant lower than in survival group (P < 0.05). There were no significant dif-

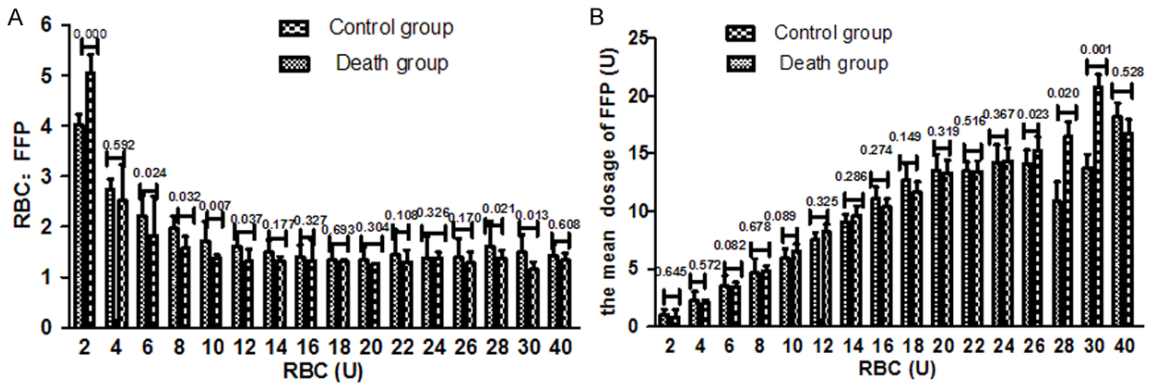

Figure 1. The plasma transfusion in the death group and survival group under different dosage of RBC. A. The ratio of the patients with pRBC transfusion compare with the patients with plasma transfusion in the death group and survival group. B. The mean dosage of plasma in the death group and survival group. The mean dosage of plasma = the amount of plasma/the number of the patients with plasma infusion.

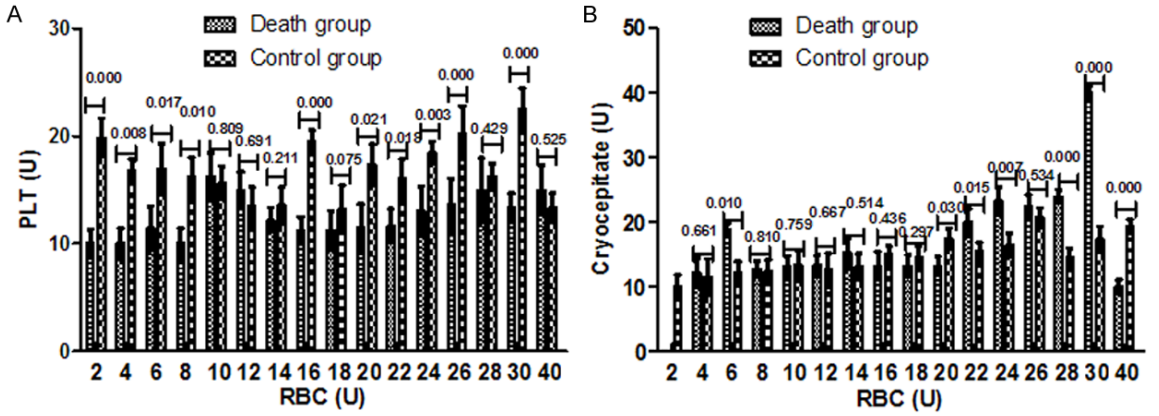

Figure 2. plasma transfusion in the death group and survival group under different dosage of RBC. A. The mean dosage of platelets infusion in the death group and survival group. The mean dosage of platelets = the amount of platelets/the number of the patients with platelets infusion. B. The mean dosage of cryoprecipitate infusion in in the death group and survival group. The mean dosage of cryoprecipitate = the amount of cryoprecipitate/the number of the patients with cryoprecipitate infusion.

ferences between those two groups in other amount of pRBC transfusion (P > 0.05) (**Figure 1B**). Meanwhile, our results also showed that the ratio of average of plasma compare with red blood cell was 1:1~2.

The platelets and cryoprecipitate infusion in the death group and survival group

When the administration of pRBC between 2-8 U, 28-30 U and 30 U in 24 h, the mean platelet infusion in death group were lower than in survival group (P < 0.05) (**Figure 2A**). When the administration of pRBC with 6U, between 22-24 U and 28-30 U, the amount of cryoprecipitate infusion in death group were higher than in survival group (*P* < 0.05), and When the administration of pRBC ≤ 30 U, the amount of cryoprecipitate infusion between 10 U and 20 U (**Figure 2B**).

Discussion

Blood transfusion plays an important role in the process of rescuing severe patients in emergency and danger. Timely and sufficient blood infusion plays a key role in the rescue of patients loosing massive blood. However recent studies found that mortality was still high for trauma patients who had received massive blood transfusion. The mortality was 19%-70% [11-13]. In this study comprising 1048 cases of massive transfusion (administration of ≥ 10 U of pRBC within 24 h), the death

rate was 10.31%, which is lower than that reported previously [11-13]. This discrepancy may be attributed to a few characteristic features of this study. The 20 participating medical institutions in this study are large-scale general hospitals and well-equipped for life-saving procedures. Among the cases enrolled, only a few were of trauma; most of them were of general surgery with good preoperative preparation of the patient. The transfusion protocol adopted was immediate administration of FFP at a high concentration along with pRBC transfusion to correct the coagulation status at the initial stage. Further research is necessary to determine whether the administration of FFP may have contributed to the reduced death rate in this study.

Our study shown that average dose of red blood cell suspension by patients in the death group (n = 132) within 24 h was 23 U, which was far more than 14 U ($P < 0.001$) used by the survival group (n = 1469), and the same applies to fresh frozen plasma, while the dosage of platelet and cryoprecipitate between two groups was very little change (2 U-3 U) and basically identical. This data analysis also come to that the number of people using red blood cells is 2.8 to 5 times than that of plasma before 4 U RBC administration, that is to say, when 2.8 to 5 persons transfusion the red blood cells, only one chooses the plasma. In blood infusion for general surgery, there is no need for plasma administration after infusing 4 U blood cell suspension within 24 hours. However, when 8 U red blood cell is transfused, the usage of red blood cell is 1.2 to 1.5 times than that of plasma, which provides the basis for the formulation of guidelines on massive blood transfusion, that is, the timing choice for plasma transfusion in massive blood transfusion. In order to reduce the death rate of patients, FFP should be used at the ratio of 1:1~2 to the red blood suspension after 4 U red blood suspension was transfused (**Figure 1A**); for severe traumatic patients, FFP should be used as soon as possible while the transfusion of red blood suspension is more than 3 to 5 U.

This research showed that Chinese clinicians paid more attention to the infusion of fresh frozen plasma while overlooking the infusion of platelet and cryoprecipitate (**Table 2**). Whether due to supply of preparation or to the idea of infusion needs further investigation. The average dosage of plasma in death group was less than that of survival group ($P < 0.05$) when the administration of pRBC between 26 U and 30 U in 24 h, but there were no significant differences between those two groups in other amount of pRBC transfusion ($P > 0.05$) (**Figure 1B**). Overall, the ratio of plasma and red blood cell was between 1 and 2 within 24 hours, which is accord with guidelines of massive transfusion.

Previous studies [14, 15] have shown that coagulation deficiency due to massive transfusion is caused by the platelet dilution-reduction. Our study displays that less attention had been paid to platelet application in china (**Table 2**). In our other findings [16], only 2.46% patients apply platelet transfusion among that of the red blood cell administration within 24 hours in massive transfusion. Our study indicated when the administration of pRBC between 2-8 U, 28-30 U and 30 U in 24 h, the mean platelet infusion in death group were lower than in survival group ($P < 0.05$) (**Figure 2A**), illustrating the significance in reducing the death rate of equal platelet transfusion at the meantime of the red blood cell administration during massive transfusion. In this investigation, three cases of postpartum hemorrhage were saved due to the emphasis on platelet infusion at early period of massive transfusion, which further confirmed the significance of earlier high dosage of platelet transfusion.

Moreover, this study shown that Chinese clinicians neglected cryoprecipitate in massive transfusion (**Table 2**). In our other findings [16], the number of cryoprecipitate application was 3.11% of that of the red blood cell administration in massive transfusion. However, our study indicated when the administration of pRBC with 6U, between 22-24 U and 28-30 U, the amount of cryoprecipitate infusion in death group were higher than in survival group ($P < 0.05$). The reason may be was that the patients transfused with cryoprecipitate were small.

In Conclusion, this study shown that, early high dosage of plasma and platelet administration in massive transfusion played significant role in reducing the death rate, and clinicians should pay more attention to the application of platelet at the time of massive red blood cell transfusion.

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Disclosure of conflict of interest

None.

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