Balanced ratio of plasma to packed red blood cells improves outcomes in massive transfusion: A large multicenter study

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Received July 27, 2014; Accepted April 2, 2015

DOI: 10.3892/etm.2015.2461

Abstract. Resuscitation with the early administration of plasma can improve the survival of patients undergoing surgery or trauma patients who require massive transfusion. To ascertain the optimal ratio of fresh frozen plasma (FFP) to packed red blood cells (pRBCs) in massive transfusions, the records of 1,048 patients who received a massive transfusion at 20 hospitals were retrospectively reviewed. The patients were stratified into three groups according to the ratio of FFP to pRBCs. These were the low (<1:2.3), middle (1:2.3-0.75) and high (≥1:0.75) ratio groups. For 24-h treatment, the middle FFP:pRBC ratio led to a lower mortality rate (9.31%) compared with that in the low (11.83%) and high (11.44%) ratio groups (P=0.477). For 72-h treatment, the middle FFP:pRBC ratio also lead to the lowest mortality rate (7.25%), which was significantly lower than the ratios in the low (10.39%) and high (13.65%) ratio groups (P=0.007). The length of hospital stay, ICU stay, and FFP:pRBC ratio in 72 h were found to be significant associated with mortality. The optimal ratio of FFP to pRBCs of 1:2.3-0.75 in 72 h can improve the survival of patients undergoing massive transfusions.

Introduction

Hemorrhagic shock remains a leading cause of potentially preventable morbidity and mortality in severely injured civilians and military personnel (1,2). Although the earlier control of life-threatening hemorrhage can significantly improve patient outcomes, massive transfusion is still required and is a critical lifesaving treatment for hemorrhagic shock (3,4). Massive transfusion is commonly defined as the administration of ≥10 units of packed red blood cells (pRBCs) to an individual patient or the transfusion of more than one blood volume in 24 h (5-9). Alternative definitions that may be more helpful in the acute situation include a 50% blood volume loss within 3 h or a rate of loss of 150 ml/min (5).

Severe trauma is the most common reason for massive transfusion. Massive transfusion is also frequently required as a treatment for severe hemorrhage in patients undergoing complex surgery. (3) The rapid identification of patients who may require massive transfusion is critically important as it may enable the lives of the most severely injured patients to be saved. A rational blood transfusion treatment can improve patient outcomes, but unreasonable transfusion can increase mortality in patients. Therefore, determining the optimal ratio of fresh frozen plasma (FFP) to pRBCs is a major step in delivering optimal care. A number of studies have reported that a high ratio of FFP to pRBCs at an early phase may reduce the mortality rate of trauma patients (10-16).

It is noteworthy that the effects of FFP to pRBCs ratios on patient outcomes in China have not yet been clearly defined. Therefore, the present retrospective study of 20 centers in China was performed. The purpose of the study was to determine the optimal ratio of FFP to pRBCs for severely bleeding patients who received massive transfusions.

Materials and methods

General information. A multicenter, retrospective analysis was performed at 20 tertiary hospitals in China. The study protocol was approved by the institutional review boards at all participating centers.

Massive transfusion. In this study, massive transfusion was defined as the receipt of ≥10 U of pRBCs in the first 24 h of admission to the surgical operation or emergency room or the intensive care unit (ICU).

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Key words: fresh frozen plasma, packed red blood cells, surgical transfusion

Study population. The study population included adults (18 years and older) who presented to 20 tertiary hospitals between January 2009 and December 2010 and received a massive transfusion due to severe trauma or surgery. The severely bleeding patients undergoing surgery consisted of cardiac surgery patients, patients undergoing general surgery (for example, orthopedic, chest, general, urinary or hepatobiliary surgery or neurosurgery) and obstetric patients. Patients were excluded if they had suffered severe hemorrhage due to blood diseases, liver failure or clotting factor defects. To eliminate the bias of the delay in availability of plasma, all trauma patients who succumbed within 30 min of arrival to the emergency room were excluded.

Groups. The massive transfusion patients were stratified into three groups according to their receipt of low, middle and high ratios of FFP:pRBCs in 24 and 72 h, specifically at ratios of <1:2.3, 1:2.3-0.75, and ≥1:0.75. A FFP:pRBC ratio of 1-1.5:1 is reported to be required in massive transfusion (17), and a FFP:pRBC ratio of 1:1-2 is capable of correcting coagulopathy in the massive transfusion (12,17,18). Therefore, a FFP:pRBC ratio of 1:1-2 is considered routine, and is included in the middle ratio group; a FFP:pRBC ratio ≥1:0.75 has a high proportion of plasma and a FFP:pRBC ratio <1:2.3 has a low proportion of plasma.

Data collection. The data were collected prior to transfusion. All measurements of respiration, pulse, systolic blood pressure (SBP), body temperature, red blood cell (RBC) count, hemoglobin (Hb) concentration, platelet (PLT) count, prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), international normalized ratio (INR), and fibrinogen (FIB) concentration were recorded as often as clinically assessed.

A database was created, and detailed information on patient demographic characteristics and clinical features were collected, including age, gender, weight, blood products, the time and date of injury and admission, mechanism of injury, time of admission to the ICU, time of surgery, and time from admission to discharge.

Mortality assessment. Dates of mortality were recorded for those that occurred between study enrollment and on or before day 30 after hospital admission. Mortality was defined as death in hospital within 30 days, prior to discharge.

Statistical analysis. Statistical analysis was conducted using SPSS version 18.0 for Windows (SPSS, Inc., Chicago, IL, USA). EpiData software, version 3.01 (Epidata Association, Odense, Denmark) was used for double data entry and data construction. Demographic characteristics and clinical features are expressed as means with standard deviations or as absolute numbers. Categorical variables were analyzed by χ^2 tests. Continuous variables with normal distribution were analyzed by the Shapiro-Wilk test, Student's t-test or Mann-Whitney U test, as appropriate. To adjust for other risk factors, logistic regression was used. Results from logistic regression models are reported as odds ratios (OR) with 95% confidence intervals (CI). Survival rates between patients receiving different ratios of FFP:pRBCs were estimated by the Kaplan-Meier method and the curves were analyzed using the log-rank test. A two-sided P-value <0.05 was considered statistically significant.

Results

Baseline characteristics of study subjects. Data were obtained from 1,048 patients who received a massive transfusion. There were no differences among all groups in gender, age, causes of massive transfusion, and the majority of the clinical features. The detailed data of baseline characteristics and clinical features of the patients are listed in Tables I and II.

Outcomes. The overall mortality rate was 10.31% (108 patients succumbed, 940 patients survived). Although the mortality rate was the lowest when patients received a 1:2.3-0.75 ratio of FFP:pRBCs in 24 h, there were no significant differences among the groups (Table III). In a 72-h treatment period, a similar trend was observed; however, the mortality rate was significantly lower than that in the other groups when patients received a 1:2.3-0.75 ratio of FFP:pRBCs (Table III).

Kaplan-Meier survival analysis with log-rank testing was performed for calculating the cumulative probability of patient survival with different ratios of FFP:pRBCs in 24 h and 72 h. The results revealed no significant differences among the groups with different ratios of FFP:pRBCs in 24 h (P=0.060; Fig. 1). However, the results highlight the superiority of a 1:2.3-0.75 ratio of FFP:pRBCs in 72 h with the highest probability of patient survival (P=0.003; Fig. 2).

Multivariate analysis for control of confounding variables. A multivariate logistic regression analysis was further performed for control of confounding variables and to determine which variables are independent predictors of in-hospital mortality. Adjustment for the confounding effects of age, gender, surgery time, weight, primary disease, length of stay, ICU stay, FFP:pRBC ratio in 24 h and FFP:pRBC ratio in 72 h was conducted. The results revealed that length of hospital stay (OR=1.113; 95% CI: 1.056-1.172; P<0.001), ICU stay (OR=0.315; 95% CI: 0.137-0.725; P=0.007) and FFP:pRBC ratio in 72 h (OR=0.349, 95% CI: 0.232-0.523; P<0.001) were significantly and independently associated with in-hospital mortality (Table IV).

Discussion

This large multicenter study, to the best of our knowledge, is the first to reveal the associations between the ratio of FFP to pRBCs and mortality in patients receiving massive transfusions in China.

The data showed that, in a total of 1,048 massive transfusion patients, 108 patients succumbed and 940 patients survived, corresponding to a mortality rate of 10.31%, which is lower than that reported by other studies 30-70% (19), 19-45% (11) and 39% (20). One reason may be that the subjects of the present study included a relatively small proportion of trauma patients.

Numerous studies have demonstrated a potential survival benefit from higher ratios of FFP to PRBCs in patients with trauma-induced coagulopathy requiring massive transfu-

Table I. Demographic characteristics and clinical features based on FFP:pRBC ratio in 24 h.

Variable	Ratio			P-value
	<1:2.3	1: 0.75-2.3	≥1:0.75	
Number of patients	186	591	271	
Demographics				
Age, years	45.8±17.2	45.4±16.4	43.2±17	0.160[a]
Male gender, n (%)	123 (19.0)	364 (56.3)	159 (24.6)	0.273[b]
Weight, kg	59.4±11.5	58.6±11.4	57.7±11.3	0.365[a]
Causes of massive transfusion				
Trauma, n	31	111	45	0.657[b]
Cardiac surgery, n	40	144	83	0.056[b]
General surgery, n	107	304	130	0.130[b]
Obstetric delivery, n	8	32	13	0.798[b]
Investigations before transfusion				
Respiration, n/min	20.4±3.5	20.5±3.5	20.4±3.9	0.898[a]
Pulse, n/min	98.7±90	91.7±49.5	89.9±21.1	0.336[a]
SBP, mmHg	119.7±31.5	111.9±29.1	110±31.2	0.014[a]
Temperature, ˚C	36.6±0.9	36.6±0.5	36.4±0.9	0.053[a]
RBC, $x10^{12}$/l	3.9±1	3.8±1	3.9±1.2	0.674[a]
Hb, g/l	117.8±33.2	116.8±43.5	115±34	0.660[a]
PLT, $x10^{9}$/l	175.1±91.5	180.3±95.7	171.1±99.9	0.304[a]
PT, sec	13.4±4.2	14.1±6.5	14.3±6.6	0.327[a]
APTT, sec	34.2±20.1	35.6±21.6	35.3±18.7	0.793[a]
TT, sec	16.4±5.3	17.5±11.1	17.6±8.1	0.463[a]
INR	1.2±0.5	1.3±1.8	1.2±1	0.423[a]
FIB (g/l)	16.1±65.5	9.5±39.6	11.7±46.1	0.356[a]
Management				
Length of hospital stay, days	27.8±19.2	31.3±26.3	27.7±21.1	0.063[a]
Length of ICU stay, days	7.8±14	7.7±11	11.5±42.1	0.478[a]
Surgery time, h	3.48±3.7	3.85±3.05	3.45±3.45	0.313[a]
pRBC in 24 h, U	16	19	20	0.107[b]
FFP in 24 h, U	14	12	15	0.139[b]
PLT in 24 h, U	7	10	4	0.803[b]
pRBC in 72 h, U	16	18	21	0.006[b]
FFP in 72 h, U	14	12	14	0.256[b]
PLT in 72 h, U	10	10	3	0.734[b]

Values are mean ± standard deviation, unless otherwise indicated. FFP, fresh frozen plasma; pRBC, packed red blood cell; SBP, systolic blood pressure; RBC, red blood cell count; Hb, hemoglobin concentration; PLT, platelet count; PT, prothrombin time; APTT, activated partial thromboplastin time; TT, thrombin time; INR, international normalized ratio; FIB, fibrinogen concentration; ICU, intensive care unit. [a]Determined using analysis of variance. [b]Determined using Kruskall-Wallis test.

sions (7,21-26). Borgman *et al* (13) reported that the ratio of blood products transfused affects mortality in patients receiving massive transfusions following a retrospective chart review of 246 massive transfusion patients. In the review, it was found that overall mortality rates in the low (1:8), medium (1:2.5), and high (1:1.4) plasma to RBC ratio groups were 65, 34 and 19%, respectively. Upon logistic regression, a high 1:1.4 plasma to RBC ratio was found to be independently associated with improved survival. The authors suggested that massive transfusion protocols should utilize a 1:1 ratio of FFP to pRBCs for all patients who are hypocoagulable with traumatic injuries. Murad *et al* (16) performed a meta-analysis and confirmed that a ratio of FFP to pRBCs of >1:3 was associated with reduced mortality in massive transfusion patients.

In the current study, a retrospective analysis was performed of 1,048 patients who received ≥10 U of pRBCs in the first 24 h of admission. The patients were divided into three groups according to their ratio of FFP to pRBCs, namely the low (<1:2.3), medium (1:2.3-0.75), and high (≥1:0.75) ratio groups. It was found that the mortality rate when a ratio of 1:2.3-0.75

Table II. Demographic characteristics and clinical features based on FFP:pRBC ratio in 72 h.

Variable	Ratio			P-value
	<1:2.3	1:0.75-2.3	≥1:0.75	
Number of patients	154	469	425	
Demographics				
Age, years	46.1±16.4	44.4±16.6	45±17.0	0.576[a]
Male gender, n (%)	100 (15.5)	269 (41.6)	277 (42.9)	0.038[b]
Weight, kg	60.2±10.9	59.1±10.8	57.4±12.0	0.030[a]
Causes of massive transfusion				
Trauma, n	28	89	70	0.621[b]
Cardiac surgery, n	31	98	138	<0.001[b]
General surgery, n	89	251	201	0.046[b]
Obstetric delivery, n	6	31	16	0.122[b]
Investigations before transfusion				
Respiration, n/min	20.3±2.5	20.6±3.9	20.4±3.6	0.668[a]
Pulse, n/min	95.6±67.8	90.7±43.6	93.4±59.9	0.660[a]
SBP, mmHg	122.6±32	112.5±27	108.8±32.3	<0.001[a]
Temperature, ˚C	36.6±0.9	36.6±0.5	36.5±0.8	0.210[a]
RBC, $x10^{12}$/l	3.9±1.0	3.8±1.0	3.9±1.2	0.233[a]
Hb, g/l	3.8±1.1	120.1±34	117.4±50.2	0.698[a]
PLT, $x10^{9}$/l	179.2±96.1	180.9±98.7	167.1±100.2	0.169[a]
PT, sec	13.7±5	14.3±5.5	14.1±6.5	0.653[a]
APTT, sec	35.6±23.4	35.9±15.3	37.2±33.1	0.801[a]
TT, sec	17±5.8	17.3±6.0	18.1±8.8	0.312[a]
INR	1.2±0.6	1.3±1.4	1.2±0.4	0.323[a]
FIB (g/l)	12.6±27.1	7.4±29.9	15.3±67.9	0.163[a]
Management				
Length of hospital stay, days	29.6±25.9	31.1±27.2	28.3±18.6	0.222[a]
Length of ICU stay, days	9.2±14.6	7.5±11.7	10.2±35.7	0.649[a]
Surgery time, h	3.7±3.9	3.8±4.0	3.5±4.0	0.508[a]
pRBC in 24 h, U	16	19	20	0.055[b]
FFP in 24 h, U	14	12	15	0.567[b]
PLT in 24 h, U	8	10	4	0.737[b]
pRBC in 72 h, U	16	18	21	0.006[b]
FFP in 72 h, U	14	12	14	0.256[b]
PLT in 72 h, U	10	10	5	0.734[b]

Values are mean ± standard deviation, unless otherwise indicated. FFP, fresh frozen plasma; pRBC, packed red blood cell; ; SBP, systolic blood pressure; RBC, red blood cell count; Hb, hemoglobin concentration; PLT, platelet count; PT, prothrombin time; APTT, activated partial thromboplastin time; TT, thrombin time; INR, international normalized ratio; FIB, fibrinogen concentration; ICU, intensive care unit. [a]Determined using analysis of variance. [b]Determined using Kruskall-Wallis test.

was used was the lowest (9.3%). Above and below this ratio, the mortality rate was higher, but the difference between groups did not reach statistical significance.

An analysis of the effect on survival of the ratio of FFP to pRBCs in massive transfusion patients in the first 72 h of admission was also performed. The results indicated that the mortality rate with a 1:2.3-0.75 FFP:pRBC ratio was the lowest (7.25%); above and below this ratio, the mortality rates were higher (13.65 and 10.39%, respectively). The mortality rate with a high FFP level was particularly high. Therefore, a suitable ratio of FFP to pRBCs (1:2.3-0.75) can improve the survival rate of patients with massive transfusion in the first 72 h; however, transfusion with a high FFP content increased mortality. The findings of the present study were in contrast to those of previous studies (13,16,27), which suggested that transfusion with a high FFP transfusion can improve survival. The factors leading to the divergence require further study.

Whether the results were influenced by confounding factors was also investigated. The results of multivariate analysis demonstrated that length of stay, ICU stay and FFP:pRBC

Table III. Mortality rates according to the FFP:pRBC ratio in 24 and 72 h.

Patient outcome	Ratio				P-value[a]
	Total	<1:2.3	1:0.75-2.3	≥1:0.75	
At 24 h, n (%)					
Mortality	108 (10.31)	22 (11.83)	55 (9.31)	31 (11.44)	0.477
Survival	940 (89.69)	164 (88.17)	536 (90.69)	240 (88.56)	
Total	1,048 (100)	186 (100)	591 (100)	271 (100)	
At 72 h, n (%)					
Mortality	108 (10.31)	16 (10.39)	34 (7.25)	58 (13.65)	0.007
Survival	940 (89.69)	138 (89.61)	435 (92.75)	367 (86.35)	
Total	1,048 (100)	154 (100)	469 (100)	425 (100)	

[a]In the first 24 and 72 h of admission, comparison of mortality between different ratios of FFP to PRBCs. FFP, fresh frozen plasma; pRBC, packed red blood cell.

Table IV. Multivariate analysis for control of confounding variables.

Variable[a]	β	SE	P-value	Odds ratio	95% CI
Length of hospital stay	0.107	0.027	0.000	1.113	1.056-1.172
ICU stay	-1.155	0.425	0.007	0.315	0.137-0.725
72-h ratio of FFP:pRBC	-1.054	0.207	0.000	0.349	0.232-0.523
Constant	3.518	0.75	0.000	33.734	1

[a]The following variables were considered as confounding effects: age, gender, duration of surgery, weight, primary disease, length of hospital stay, ICU stay, FFP:pRBC ratio in 24 h and FFP:pRBC ratio in 72 h. ICU, intensive care unit; FFP, fresh frozen plasma; pRBC, packed red blood cell; SE, standard error; CI, confidence interval.

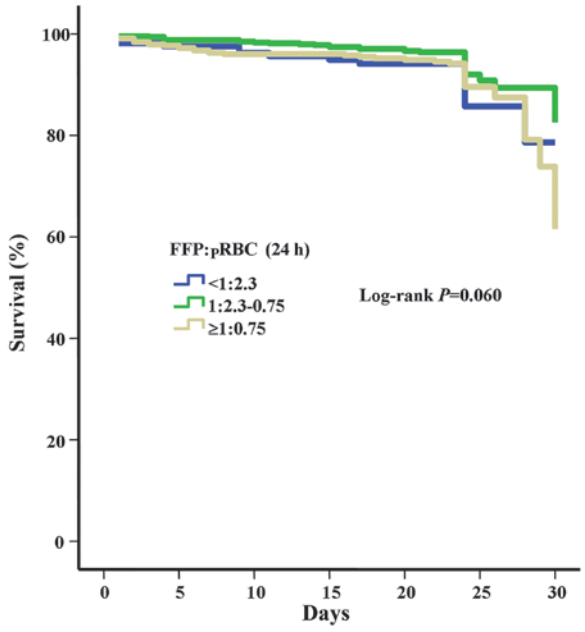

Figure 1. Mortality rates grouped by different FFP:pRBC ratios in 24 h are presented as a Kaplan-Meier survival plot. There were no significant differences in mortality among the three groups (P=0.060). However, for the middle FFP:pRBC (1:2.3-0.75) and high FFP:pRBC (≥1:0.75) ratio groups, the mortality rates were the lowest and highest, respectively. FFP, fresh frozen plasma; pRBC, packed red blood cell.

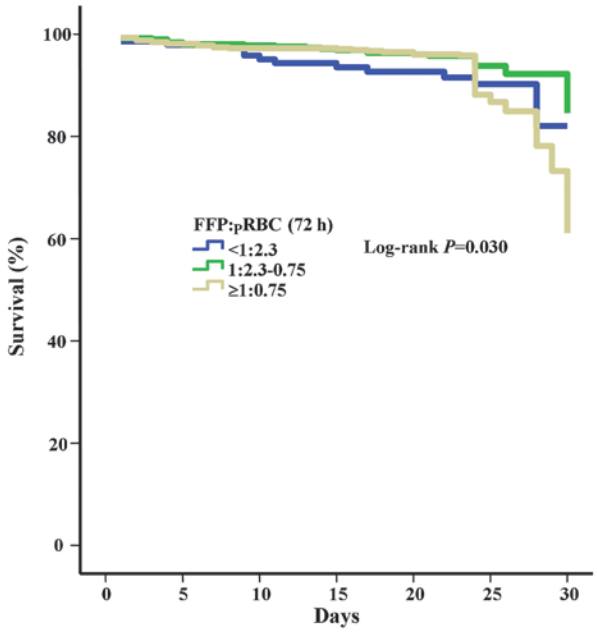

Figure 2. Mortality rates grouped by different FFP:pRBC ratios in 72 h are presented as a Kaplan-Meier survival plot. There were significant differences in mortality among the three groups (P=0.003). The middle ratio group (FFP:pRBC ratio, 1:2.3-0.75) had the lowest mortality rate and the high ratio group (FFP:pRBC ratio, ≥1:0.75) had the highest mortality rate. FFP, fresh frozen plasma; pRBC, packed red blood cell.

ratio in 72 h were significantly and independently associated with in-hospital mortality. By contrast, Scalea *et al* (28) found that the ratio of FFP to pRBCs was not an independent risk factors for in-hospital mortality.

In conclusion, to the best of our knowledge, this study is the first retrospective analysis of the effect of the ratio of FFP to pRBCs on survival in a large multicenter population. The data demonstrated that the optimal ratio of FFP to pRBCs was 1:2.3-0.75 in massive transfusion patients in the first 72 h of admission. The optimal ratio of FFP to pRBCs was also found to be 1:2.3-0.75 in massive transfusion patients in the first 24 h of admission, but this was not statistically significant. Transfusion with a high ratio of FFP to pRBCs in 72 h is an independent risk factor for in-hospital mortality.

Acknowledgements

The authors thank collaborators from the other 19 centers participating in this study: Shi-Jie Mu, Ai-Jun Xia and Xian-Qin Zhang from Xijing Hospital, the Fourth Military Medical University (Xi'an, China); Dai-Yu Li from Affiliated Hospital of Luzhou Medical College (Luzhou, China); Shu-Min Zhao from Xinang Southwest Hospital, the Third Military Medical University (Chongqing, China); Wei Jiao from the People's Hospital of Zhuang Autonomous Region (Nanning, China); Li Tong from First Affiliated Hospital of Kunming Medical University (Kunming, China); Qing-Bao Meng from Shenzhen People's Hospital (Shenzhen, China); Jie Li from the Fourth Clinical Medical College of Hebei Medical University (Shijiazhuang, China); Shi-Ming Yang from Tangdu Hospital, the Fourth Military Medical University (Xi'an, China); Suo-Liang Yao from Xi'an Hong Hui Hospital (Xi'an, China); Bi-Juan Li from Xiangya Hospital Center of South University (Changsha, China); Qiu-Shi Wang from Shengjing Hospital of China Medical University (Chenyang, China); Cui-Ying Li from General Hospital of Chengdu Military Region (Chengdu, China); Mei-Ning Han from the Second Affiliated Hospital of Medical College of Xi'an Jiaotong University (Xi'an, China); Zhi-Xi Hu from Yan'an University Affiliated Hospital (Yan'an, China); Jin-Shan Jiao from the First Affiliated Hospital of Shanxi Medical University (Taiyuan, China); Xian-Ping Lv from the First Affiliated Hospital of Zhengzhou University (Zhengzhou, China); Yan-Li Bai from Xi'an Central Hospital (Xi'an, China); Xiao-Xia Shi from Xianyang 215 Hospital (Xianyang, China); and Fang-Xiang Chen from Daping Hospital, the Third Military Medical University (Chongqing, China).

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