TRANSFUSION MEDICINE AND TRANSFUSION COMPLICATIONS

Original article

Effects of in-house cryoprecipitate on transfusion usage and mortality in patients with multiple trauma with severe traumatic brain injury: a retrospective cohort study

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Background - Hypofibrinogenaemia is a common complication of multiple trauma with severe traumatic brain injury (Abbreviated Injury Scale score of the head ≥4; body ≥3). In Japan, neither fibrinogen concentrate nor cryoprecipitate is permitted to treat acquired hypofibrinogenaemia with the purpose of rapidly restoring a haemostatic level of fibrinogen. The aim of this study was to investigate transfusion usage and mortality in patients with multiple trauma and severe traumatic brain injury who were given a cryoprecipitate prepared in-house, comparing those administered the product early or later.

Material and methods - We prepared and produced cryoprecipitate from fresh-frozen plasma beginning in March 2013. We performed a retrospective cohort study of patients admitted to our single tertiary medical centre with severe multiple trauma with traumatic brain injury from March 2013 to June 2018, sorting them into those given the cryoprecipitate infusion within 90 minutes of admission (Early group) and those given it more than 90 minutes after admission (Late group). Clinical outcomes were compared between the two groups using chi-square or Fisher's exact tests and the Wilcoxon test as appropriate.

Results - There were 26 and 16 patients in the Early and Late groups, respectively. The 24-hour mortality tended to be lower in the Early group than in the Late group (8 *vs* 13%, respectively). The patients were more severely anaemic and thrombocytopenic after haemostatic therapy in the Late group than in the Early group. Transfusion usage in the Early group was lower than that in the Late group (red blood cells: 7±1 units *vs* 17±3 units, p<0.05; fresh-frozen plasma: 9±1 units *vs* 16±3 units, p<0.05; platelet concentrate: 3±1 units *vs* 15±4 units, p<0.05, respectively).

Discussion - Early administration of an in-house cryoprecipitate may reduce transfusion usage in patients with multiple trauma with severe traumatic brain injury.

Keywords: *multiple trauma, resuscitation, mortality, hypofibrinogenaemia.*

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INTRODUCTION

Despite the high usage rate of fresh-frozen plasma (FFP) to correct acquired hypofibrinogenaemia due to massive bleeding in various conditions, including trauma

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and post-partum haemorrhage, neither fibrinogen concentrate nor cryoprecipitate is permitted in Japan. Cryoprecipitate contains a high concentration of fibrinogen, clotting factor VIII (FVIII), clotting factor XIII (FXIII), von Willebrand factor, and fibronectin, among other substances[1,2]. In contrast to FFP, cryoprecipitate and fibrinogen concentrate can, theoretically, immediately restore the normal level of fibrinogen in patients with acquired hypofibrinogenaemia[3]. The accepted indications for the administration of cryoprecipitate include, but are not limited to, hypofibrinogenaemia, t-plasminogen activator-related life-threatening haemorrhage, and massive transfusion (>10 units of red blood cells [RBC] in 24 hours with continued bleeding)[4]. Nascimetro *et al.* also reported that cryoprecipitate is commonly used to restore fibrinogen levels in patients with acquired coagulopathy, such as in those with haemorrhage from trauma, cardiac surgery, liver transplantation, or obstetric conditions[5]. Coagulopathy complicated with massive bleeding may indicate a poor prognosis. Although the optimal transfusion strategy to treat acute hypofibrinogenaemia after severe multiple trauma has been extensively investigated[6-10], no transfusion guidelines for the administration of cryoprecipitate or fibrinogen concentrate have been established in Japan. Moreover, cryoprecipitate is neither produced nor supplied by the Japanese Red Cross Society. We, therefore, produced cryoprecipitate in our hospital using a method described by the Japan Society of Transfusion Medicine and Cell Therapy[11]. In this study, we aimed to evaluate the effects of transfusing our in-house cryoprecipitate in patients with severe multiple trauma. Moreover, given that early administration of fibrinogen concentrates or cryoprecipitate has been reported to be beneficial for patients with severe multiple trauma[12-14], we also aimed to examine the effects of early administration of the in-house cryoprecipitate in patients with multiple trauma with severe traumatic brain injury (TBI).

MATERIALS AND METHODS

Study setting

This retrospective cohort study was performed in a tertiary medical centre located in the eastern part of metropolitan Tokyo, Japan. In our 24-bed Intensive Care Unit, patients are managed by full-time physicians, including surgeons and intensivists.

We reviewed a retrospectively maintained database of all transfused patients with multiple trauma with severe TBI, defined as having an Abbreviated Injury Scale (AIS) score of the head ≥4 and body ≥3, who were admitted to our institution from March 2013 to June 2018. Patients who were younger than 10 years old, had cardio-pulmonary arrest at admission, or were transferred from other hospitals were excluded.

In our tertiary emergency medical centre, we routinely perform blood tests immediately after a patient's arrival and throughout the treatment of haemostasis in patients with severe trauma. Computed tomography (CT) of the whole body was performed as soon as possible during stabilisation of the respiratory and circulatory systems. Based on the circulatory state, Glasgow Coma Scale, and CT findings, senior emergency physicians determined the haemostatic and transfusion strategies.

Blood components were transfused based on reference guidelines issued by the Ministry of Health, Labour, and Welfare in Japan[15], and transfusion for massive bleeding was performed based on the guidelines on trauma[16-18]. In principle, three packs of cryoprecipitate were transfused for adult patients with hypofibrinogenaemia or for those receiving massive blood transfusions (≥10 units of RBC), although the decision was ultimately left to the attending physician's discretion.

Data collection

The following data were collected: medical history; age; sex; vital signs on admission, such as systolic blood pressure, heart rate, and body temperature, Glasgow Coma Scale score, Injury Severity Score, and probability of survival based on the trauma and injury severity score (TRISS); laboratory values obtained on admission and after treatment (in principle, after early haemostatic treatment); units transfused in 24 hours and during hospitalisation; and outcome. The duration of hospitalisation, time spent in the Intensive Care Unit, duration of ventilation, modified Rankin scale score, and 24-hour mortality were the parameters used to assess outcomes.

To evaluate the effectiveness of early transfusion of in-house cryoprecipitate, we divided the eligible patients into two groups: those given the in-house cryoprecipitate

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within 90 minutes of admission (Early group) and those given the transfusion more than 90 minutes after admission (Late group). We set the threshold of 90 minutes on the basis of a report by Curry *et al*.[13]. The typical treatment course of each group was as follows: the Early group was administered cryoprecipitate immediately after prompt resuscitation and CT evaluation, while the Late group was administered the product after surgical intervention, massive fluid infusion, and RBC/FFP transfusion.

In-house cryoprecipitate and blood products

Blood products, such as RBC solutions, FFP, and platelet concentrates, were supplied by the Japan Red Cross Society (Tokyo, Japan). The RBC solutions (one unit: 140 mL; two units: 280 mL) and FFP (one unit: 120 mL, two units: 240 mL) were produced from donated whole blood, while the platelet concentrates and 480-mL FFP were obtained *via* apheresis from donors.

Because cryoprecipitate is not supplied by the Japan Red Cross Society, it was prepared and produced by the staff of our Department of Transfusion Medicine using a modified method, as previously described[11]. Briefly, one pack of cryoprecipitate was prepared from type AB RhD-positive FFP (480 mL) by collecting the precipitate formed during controlled thawing at 4 °C for 24 hours and re-suspending it in 30-50 mL of plasma. Cryoprecipitate can be stored for up to 1 year at a temperature of –20 °C or below. At least 20 packs of cryoprecipitate are always ready for use in our hospital. A pack of cryoprecipitate can be thawed within 9 minutes using a recirculating water-bath thawing system at 37 °C (FF-40; Kawasumi Laboratories Inc., Oita, Japan). A pack of 240-mL FFP can be thawed within 13 minutes[19]. Although production methods may vary in different facilities, the products have relatively similar features[1]. The fibrinogen level in the in-house cryoprecipitate (n=6) was 1,992±515 mg/dL.

Statistical analysis

Data are expressed as group means ± standard errors of the mean. All statistical calculations were performed using JMP version 8.0 software (SAS Institute Inc., Cary, NC, USA). We tested for differences in baseline characteristics between patients in the Early and Late groups using the chi-square or Fisher's exact test for categorical data and the Wilcoxon test for continuous data. A p-value <0.05 was considered statistically significant.

Ethical approval

This study was approved by the institutional review board of the Tokyo Metropolitan Bokutoh Hospital. Informed consent for blood product transfusion, including cryoprecipitate, was obtained from the patients.

RESULTS

Clinical features and outcomes of patients with multiple trauma with severe traumatic brain injury.

From March 2013 to June 2018, 42 patients met the inclusion criteria. The mean time from the trauma scene to arrival at hospital was 33 minutes, and all patients were transferred without fluid infusion. The Early and Late groups comprised 26 and 16 patients, respectively. In the Early group, cryoprecipitate was administered subsequently to early resuscitation and CT evaluation, and as one of the first components of massive transfusion. In contrast, in the Late group, cryoprecipitate was administered during the course of massive transfusions and often during surgical interventions. The demographic characteristics, clinical features and outcomes of these two groups are summarised in **Table I**. There were no significant differences

Table I - *Clinical characteristics and outcomes of the study population*

	Early cryoprecipitate group (N=26)	Late cryoprecipitate group (N=16)
Age	58 (5)	61 (4)
Sex (male/female, % of males)	17/9 (65%)	12/4 (75%)
Vital signs and scores on admission		
Systolic blood pressure (mmHg)	135 (11)	115 (9)
Heart rate (beats/minute)	102 (5)	103 (6)
Temperature (°C)	35.8 (0.2)	36.1 (0.2)
Glasgow Coma Scale score	7.4 (0.8)	7.8 (1.1)
Injury Severity Score	38 (2)	40 (2)
AIS score of the head	4.5 (0.1)	4.6 (0.1)
Probability of survival	0.46 (0.06)	0.43 (0.08)
Interventions		
Surgery (n, %)	15, 58%	13, 81%
Angiography (n, %)	9, 35%	2, 13%
None (n, %)	2, 8%	1, 6%

Data are presented as the mean with standard errors in parentheses.
AIS: abbreviated injury scale.

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Table II - *Laboratories values of the study population*

	On admission		After treatment	
	Early cryoprecipitate group (N=26)	Late cryoprecipitate group (N=16)	Early cryoprecipitate group (N=24#)	Late cryoprecipitate group (N=15#)
Haematology				
Haemoglobin (g/dL)	11.7 (0.4)	12.9 (0.5)	10.1 (0.3)*	8.7 (1.7)
Platelet count (×10⁴/µL)	21.3 (1.4)	19.8 (1.5)	13.4 (1.2)*	7.3 (0.9)
Clotting activity				
% prothrombin time (%)	80 (5)	75 (6)	69 (5)	59 (5)
aPTT (sec)	32.0 (2.0)	32.7 (3.8)	37.0 (4.1)	42.0 (6.2)
fibrinogen (mg/dL)	233 (20)	189 (25)	211 (16)	179 (25)
FDP (µg/dL)	422 (124)	509 (158)	240 (54)	157 (36)

Data are presented as the mean with standard errors in parentheses. #with missing values due to death. *p<0.05 *vs* values in the Late cryoprecipitate group. aPTT: activated partial thromboplastin time; FDP: fibrinogen degradation products.

in demographic characteristics, clinical features, or injury severity between the two groups. Moreover, there was no significant difference in haemostatic treatments; however, the number of angiographic interventions in the Early group tended to be higher than that in the Late group (35 *vs* 13%; respectively) (**Table I**).

Laboratory findings on admission and after treatment

Laboratory findings on admission and after treatment are shown in **Table II**. The results of haematological and clotting tests on admission were not significantly different between the two groups. Haemoglobin levels and platelet counts after angiographic or surgical treatment for haemostasis were significantly higher in the Early group than in the Late group (**Table II**).

Transfusion volume and clinical outcome

The volume of transfused units of RBC, FFP, platelet concentrate, and albumin administered during the first 24 hours was significantly lower in the Early group than in the Late group (**Table III**). Moreover, the volume of transfused RBC units and FFP during hospitalisation was significantly lower in the Early group than in the Late group.

Although there was not a significant difference in clinical outcomes between the Early and Late groups (**Table III**), the 24-hour mortality (8 *vs* 13%, respectively) and the number of patients with a modified Rankin scale <4 (31 *vs* 13%, respectively) tended to be better in the Early group than in the Late group. Mortality at discharge was not different between the two groups (31 *vs* 25%, respectively); however, it was better than the estimated probability of survival of each group (**Table I**).

Table III - *Transfusion usage and clinical outcome in the study population*

	Early cryoprecipitate group (N=26)	Late cryoprecipitate group (N=16)
24-hour transfusion, or infusion		
Red blood cells (U)	7 (1)*	17 (3)
Fresh-frozen plasma (U)	9 (1)*	16 (3)
Platelet concentrates (U)	3 (1)*	15 (4)
Platelet concentrates (n, %)	7, 27%	10, 63%
Cryoprecipitate (pack)	3.6 (0.2)	3.1 (0.2)
5% albumin product (bottles)	0.2 (0.1)*	1.4 (0.7)
5% albumin product (n, %)	3, 12%	7, 44%
Tranexamic acid (n, %)	25, 96%	12, 75%
Total transfusions		
Red blood cells (U)	9 (1)*	23 (5)
Fresh-frozen plasma (U)	9 (1)*	17 (4)
Clinical outcome		
ICU stay (days)	12 (2)	12 (2)
Duration of ventilation (days)	9 (2)	7 (2)
Duration of hospitalisation (days)	41 (6)	46 (8)
24-hour mortality (%)	2/26 (8%)	2/16 (13%
Mortality at discharge (%)	8/26 (31%)	4/16 (25%)
Modified Rankin scale <4 n, %	8, 31%	2, 13%

Data are presented as the mean with standard errors in parentheses. *p<0.05 *vs* values in the Late cryoprecipitate group. ICU: Intensive Care Unit.

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DISCUSSION

To our knowledge, this is the first paper reporting that in-house cryoprecipitate may be beneficial for treating patients with multiple trauma with severe TBI.

We previously reported that in-house cryoprecipitate significantly reduced post-partum haemorrhage and transfusion usage as compared to standard treatment without in-house cryoprecipitate in a Japanese study[20]. However, in the early analysis of severe trauma patients, there was no difference in the number of blood transfusions or better prognoses resulting from the administration of in-house cryoprecipitate. Then, as a control group of patients for the cryoprecipitate treatment, we reviewed the data of patients who were admitted to our institution from January 2011 to February 2013, and extracted the data regarding patients with multiple trauma with severe TBI (AIS of head ≥4; body ≥3) who were treated with more than 2 units of FFP within 24 hours after arrival in hospital (historical FFP group). Twenty patients were eligible, and their 24-hour and discharge mortality rates were 35% (7/20 died) and 55% (11/20 died), respectively. Both mortalities rates were higher than those in the current study (**Table I**). We speculated that FFP transfusions alone did not correct the coagulopathy in patients with severe multiple trauma, resulting in the observed higher mortality. Similarly, Kahn *et al*. reported that FFP alone did not improve trauma-induced coagulopathy[21]. Meanwhile, we have not yet reported on the difference in transfusion usage between the historical FFP group (24-hour RBC: 10±2 units, 24-hour FFP: 12±2 units) and the in-house cryoprecipitate groups (**Table III**). Although the apparent lack of effectiveness on transfusion usage might be a result of survivorship bias, we also speculated that the timing of the administration of cryoprecipitate would be an important factor. We, therefore, examined the effects of the timing of in-house administration of cryoprecipitate on transfusion usage and mortality in this study. We found that blood transfusion usage was lower in the patients treated early with cryoprecipitate transfusion. In this study, we evaluated patients with multiple trauma with severe TBI, who were at very high risk of developing severe coagulopathy. By excluding mildly to moderately injured patients and those with isolated TBI, we were able to analyse the data of patients who needed massive blood transfusions by standard treatment methods. Although the haematological parameters of patients on arrival at the hospital did not appear to be seriously deranged in spite of the high Injury Severity Score, these parameters were evaluated before the patients had received fluid infusions. Previous studies have reported worse coagulopathy data on admission, because pre-hospital fluid strategies vary between countries and hospital systems[22,23].

In this study, the patients were classified into two groups according to a threshold time of 90 minutes from admission to administration of cryoprecipitate, in accordance with the report by Curry *et al*.[13]. These authors reported that the administration of cryoprecipitate within 90 minutes of arriving in hospital was feasible. Although the appropriateness of this threshold remains unclear, almost all patients in the Early group of our study were administered cryoprecipitate prior to surgical intervention and in the early stages of haemostatic resuscitation. The present study showed that this approach may correct haemostatic conditions early, stop bleeding promptly, and lead to a reduction in transfusion requirements. Moreover, it might improve the outcomes of patients with severe trauma[13,24]. The mortality rate of patients with concomitant TBI and haemorrhagic shock has been reported to be 51.6%[25]. In our study, the discharge mortality rate was 29% (12/42 patients died), indicating that in-house cryoprecipitate might be effective for treating patients with multiple trauma with severe TBI. Early haemostasis and haemodynamic stabilisation may prevent secondary brain injuries in patients with concomitant traumatic brain and torso injury. The 24-hour mortality rate in the Early group tended to be lower than that in the Late group. However, the reason for the discrepancy between mortality rates and transfusion usage remains unclear. Early use of in-house cryoprecipitate might lessen coagulopathy in its acute phase, resulting in reduced transfusion usage and acute-phase mortality. On the other hand, we expected improvements in neurological and performance status at discharge, as well as improved mortality. According to our data, the percentage of patients with a modified Rankin scale <4 tended to be higher in the Early group than in the Late group (31 *vs* 13%, respectively). Given that 15% of the patients (3/20

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patients) in the historical FFP group had a modified Rankin scale score <4, late transfusion of an in-house cryoprecipitate did not improve the rate of transfusion usage or neurological outcomes.

While fibrinogen concentrate is known to be beneficial for treating hypofibrinogenaemia after massive bleeding[26], it does not reduce transfusion usage in patients with severe trauma[8,14]. Three packs of in-house cryoprecipitate might be capable of supplying approximately 2 g of fibrinogen, since each pack contains 1,992±515 mg/dL of fibrinogen. Because of factors other than fibrinogen, more than 3 g of fibrinogen (three vials of fibrinogen concentrate) may be necessary to stop bleeding. Cryoprecipitate contains FXIII, FVIII, von Willebrand factor, and fibrinogen. Binding of FXIII with endogenous anti-plasmin reveals the anti-fibrinolytic action and fibrin polymerisation of cryoprecipitate[27]. Severe isolated TBI has been reported to reveal hyperfibrinolysis[28]. Moreover, reductions in the activity of FXIII, FII, and FX have been reported in patients with severe multiple trauma with hyperfibrinolysis[29]. Cryoprecipitate might, therefore, correct the decreased level of FXIII in haemorrhagic circumstances. We also speculated that concentrated FVIII and von Willebrand factor in cryoprecipitate might be involved in improving the outcome of patients with severe multiple trauma. Reductions in FV and FVIII activity have been reported to be associated with mortality following trauma[29]. Furthermore, it was recently found that blood type O was associated with high mortality in severe trauma patients[30], with results also indicating that von Willebrand factor might be involved in the outcome of trauma patients.

Given these benefits, the Japanese Red Cross is expected to supply cryoprecipitate to Japanese hospitals, similarly to that provided by blood centres in the United States and Europe.

We acknowledge several limitations of this study. First, this was a retrospective cohort study and was, therefore, prone to the biases associated with this research design. Second, the sample size was small, and the statistical power was low. Differences in some analyses did not reach statistical significance. Further research with a larger sample size is, therefore, warranted.

CONCLUSIONS

The early transfusion of our in-house cryoprecipitate might reduce blood transfusion usage in patients with multiple trauma with severe TBI.

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AUTHORSHIP CONTRIBUTIONS

KS designed the research study. HF performed the study and wrote the paper. SN analysed the data.

The Authors declare no conflicts of interest.

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