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Evaluation of a Possible Effect of In-House Cryoprecipitate Transfusion on Outcome of Severe Upper Gastrointestinal Bleeding: A Retrospective Cohort Study

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Abstract

Purposes: Hypofibrinogenemia is usually complicated with severe and massive upper gastrointestinal (GI) bleeding, especially in liver cirrhosis. In Japan, neither fibrinogen concentrate nor cryoprecipitate (CRYO) is available for cases of acquired hypofibrinogenemia to recover the hemostatic level of fibrinogen rapidly. We prepared and produced in-house CRYO from fresh frozen plasma, and compared mortality between pre-implementation and post-implementation of CRYO. **Methods:** We performed a retrospective cohort study of patients admitted to our single tertiary medical center with upper GI bleeding from January 2011 to December 2016. The observational control period was from January 2011 to February 2013. From March 2013 to December 2016, we implemented the transfusion of CRYO, which was prepared and produced in our hospital. Clinical outcomes were compared between the patients in the two periods. **Patients:** Eleven patients in the control period and 10 in the intervention period were eligible for analysis. **Results:** In-hospital mortality (55% vs. 20%, $P = 0.238$) and mortality within 24 hour after admission (27% vs. 0%, $P = 0.246$) tended to be lower in the intervention period than in the control period, although the patients had more severe coagulation on admission than those in the control period. The plasma fibrinogen level before the treatment of hemostasis in the intervention period was higher than that in the control period (80 ± 9 mg/dL vs. 127 ± 15 mg/dL, $P < 0.05$). **Conclusion:** Implementation of in-house CRYO transfusion may reduce the rate of mortality due to severe upper GI bleeding.

Keywords

Esophageal Varix, Resuscitation, Mortality, Hypofibrinogenemia

1. Introduction

Fresh frozen plasma (FFP) is commonly used to correct acquired hypofibrinogenemia due to massive hemorrhage as a result of trauma, postpartum hemorrhage, and other conditions, as neither fibrinogen concentrate nor cryoprecipitate (CRYO) is available in Japan. CRYO contains a high concentration of fibrinogen, clotting VIII factor (FVIII), clotting XIII factor (FXIII), von Willebrand factor, fibronectin, and other clotting factors [1] [2]. Compared with FFP, CRYO and fibrinogen concentrate can theoretically recover the normal values of fibrinogen in the patients with acquired hypofibrinogenemia immediately [3]. Accepted indications for the use of CRYO include but are not limited to hypofibrinogenemia, t-plasminogen activator-related life-threatening hemorrhage, and massive transfusion (red blood cell [RBC] solution > 10 U in 24 hours with continued bleeding) [4]. Inappropriate indications are known to be warfarin reversal, surgical hemostasis, and hepatic coagulopathy [4]. Nascimetro *et al.* also reported that CRYO was most commonly used to replace the fibrinogen levels in patients with acquired coagulopathy, such as in the clinical settings with hemorrhage, including trauma, cardiac surgery, liver transplantation, or obstetric hemorrhage [5]. Coagulopathy complicated with massive bleeding such as digestive tract bleeding may indicate poor prognosis [6], and the international normalized ratio > 1.5 is one risk factor according to the AIMS65 bedside score [7]. To date, however, the optimal transfusion strategy to treat acute hypofibrinogenemia after severe upper gastrointestinal (GI) bleeding has only been investigated in a few clinical studies, and guidelines of its kind on CRYO or the fibrinogen concentrate do not exist in Japan.

On the basis of hypofibrinogenemia in severe upper GI bleeding, which is similar to massive bleeding and associated with increased mortality, we therefore hypothesized that the implementation of CRYO transfusion would contribute to preventing the development of hypofibrinogenemia and to reducing mortality in the patients with severe upper GI bleeding. However, CRYO is neither produced nor supplied by the Japanese Red Cross Society. In-house CRYO is produced in our hospital using a method described by the Japan Society of Transfusion Medicine and Cell Therapy [8]. Therefore, we aimed to evaluate the feasibility of our transfusion practice of producing in-house CRYO for the patients with severe upper GI bleeding.

2. Materials and Methods

2.1. Study Setting

This retrospective cohort study was performed at a tertiary medical center lo-

cated in the eastern part of metropolitan Tokyo, Japan. In our practice, we routinely perform blood tests immediately after patient arrival and throughout the treatment for hemostasis. In our 24-bed intensive care unit, patients were managed by full-time physicians, including surgeons and intensivists.

We reviewed a prospectively maintained database of all transfused patients who were admitted to our institution from January 2011 to December 2016. This study was divided into two periods. During the first period (January 2011 to February 2013), which was an observational control period, CRYO transfusion was not implemented. During the second interventional period (March 2013 to December 2016), we implemented CRYO transfusion that enabled us to transfuse CRYO to patients who were diagnosed as having severe upper GI bleeding (AIMS65 score ≥ 2) to immediately correct acute hypofibrinogenemia. Severe upper GI bleeding with an AIMS65 score ≥ 2 indicated high mortality [9].

Transfusion of the blood component was performed based on reference guidelines described by the Ministry of Health, Labour, and Welfare in Japan [10], and transfusion for massive bleeding was performed using a reference guideline on trauma [11] [12] [13]. In the interventional period, three packs of CRYO were transfused in principle for adult patients with hypofibrinogenemia or for those receiving massive blood transfusion (RBC solution ≥ 10 units), although the decision was ultimately left to the attending physician's discretion.

2.2. Subjects Studied

We included all patients who were diagnosed as having severe upper GI bleeding (AIMS65 score ≥ 2) in the first period (control group). They were compared with the patients who were diagnosed as having severe upper GI bleeding (AIMS65 score ≥ 2) and received CRYO transfusion in the second period (CRYO group). No patients were excluded during this research period.

2.3. Data Collection

The variables under consideration were patients' medical history, age, sex, underlying diseases causing the upper GI bleeding, systolic blood pressure on admission, shock index on admission, laboratory values obtained on admission, transfused units administered for 24 hours and during hospitalization, and outcome. Risk for upper GI bleeding was evaluated by the Glasgow-Blatchford score and AIMS65 score [7].

2.4. In-House CRYO and Blood Products

Blood products, such as an RBC solution, FFP, and platelet concentrate (PC) were supplied by the Japan Red Cross Society (Tokyo, Japan). Although the RBC solution (one unit: 140 mL, two units: 280 mL) and FFP (one unit: 120 mL, two units: 240 mL) are produced from donated whole blood, the PC and 480-mL FFP are obtained by apheresis from donors.

Since CRYO is not supplied by the Japan Red Cross Society, CRYO was pre-

pared and produced by staff of our Department of Transfusion Medicine, using a modified method as previously described [8]. Briefly, one pack of CRYO 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. CRYO can be stored for up to 1 year at −20˚C or colder. At least 20 packs of CRYO were always ready for use in our hospital. A pack of CRYO can be thawed within 9 minutes using a recirculating water bath thawing system at 37˚C (FF-40, Kawasumi Laboratories Incorporated, Oita, Japan). A pack of 240-mL FFP could be thawed within 13 minutes [14]. Methods of manufacturing may vary in different facilities, although the feature of the products is largely common [1].

Clotting test results including the activated partial thromboplastin time, % prothrombin time, fibrinogen, and various clotting factors in the expired in-house CRYO packs (N = 6) were measured by Biomedical Laboratories Company (Tokyo, Japan).

2.5. 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). We tested for differences in baseline characteristics between patients of the first period (control group) and those of the second period (CRYO group) using the chi-square or Fisher exact test for categorical data and the Wilcoxon test for continuous data. A P-value < 0.05 was considered significant.

2.6. Ethical Approval

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

3. Results

3.1. Clotting Tests and Various Clotting Factors Containing In-House CRYO

As shown in Table 1, in-house CRYO contained the concentrated FVIII, FXIII, von Willebrand factor, and fibrinogen. Clotting factors except those aforementioned did not increase in the CRYO. Inhibitory factors of fibrinolysis such as anti-plasmin and plasminogen activator inhibitor-1 also did not increase. Protein S activity decreased in in-house CRYO, but protein C and anti-thrombin III activities did not change. The volume of in-house CRYO was 37 ± 4 mL (N = 6).

3.2. Clinical Features of Patients with Severe Upper GI Bleeding

From January 2011 to December 2016, 21 patients met the inclusion criteria. Eleven patients in the first period (control group) and 10 in the second period (CRYO group) were eligible for analyses. In the second period, we identified 10

Table 1. Clotting activities in the in-house cryoprecipitatetype styles.

	Reference value	Cryoprecipitate N = 6
Clotting test results		
aPTT (sec)	26 - 38	32.3 (2.2)
% PT (%)	80 - 120	72.1 (3.4)
Fibrinogen level (mg/dL)	170 - 410	1992 (515)
Clotting factor activity		
Factor II (%)	66 - 118	115 (6)
Factor V (%)	73 - 122	74 (5)
Factor VII (%)	54 - 162	114 (10)
Factor VIII (%)	78 - 165	545 (65)
von Willebrand factor (%)	50 - 150	1117 (158)
Factor IX (%)	67 - 152	92 (7)
Factor X (%)	58 - 200	94 (4)
Factor XI (%)	75 - 137	111 (7)
Factor XII (%)	36 - 152	75 (17)
Factor XIII antigen (%)	70 - 140	238 (42)
Fibrinolysis test results		
Anti-plasmin activity (%)	80 - 130	109 (3)
Plasminogen activity (%)	80 - 130	161 (14)
PAI-1 (ng/mL)	<50	36.5 (4)
Anticoagulant factor activity		
Anti-thrombin III (%)	80 - 130	101 (3)
Protein C (%)	70 - 140	119 (9)
Protein S (%)	63 - 149	33 (5)

Data represent the means with standard errors in parentheses. The reference value represents the value in healthy Japanese subjects, as measured by Biomedical Laboratories Company. aPTT, activated partial thromboplastin time; % PT, % prothrombin time; PAI-1, plasminogen activator inhibitor-1.

patients who were transfused with CRYO. The demographic characteristics and clinical features of these two groups are summarized in Table 2. There was no significant difference in demographic characteristics, clinical features, and severity between the CRYO group and control group. While endoscopic hemostasis was performed for all patients (N = 21), angiographic treatment was implemented for three patients with arterial rupture in the cryoprecipitate group. Sub-gastrectomy was undertaken for perforated gastric ulcer (N = 1) in the cryoprecipitate group.

3.3. Laboratory Findings at Admission, Details of Transfusion, and Outcome

Laboratory findings at admission, details of transfusion, and outcome are summarized in Table 3. There was no significant difference in hematology and clotting test results at admission between the two groups. The fibrinogen level before treatment of hemostasis was performed (endoscopically, angiographically, or surgically) was significantly lower in the control group than in the CRYO group (80 ± 9 mg/dL vs. 127 ± 15 mg/dL, $P < 0.05$).

The number of transfused units administered for 24 hours was not different in terms of RBC, FFP transfusion, and albumin infusion between the two groups.

Table 2. Clinical features of patients with severe upper gastrointestinal bleeding.

	Cryoprecipitate group N = 10	Control group N = 11
Age (years)	66 (6)	61 (6)
Sex (M/F)	7/3	11/0
Vital signs at admission		
Systolic blood pressure (mmHg)	80 (8)	86 (7)
Pulse (beats/minute)	129 (8)	122 (7)
Shock index	1.6 (0.2)	1.4 (0.1)
Shock index < 0.7 (n, %)	1, 10%	0, 0%
Cardiac arrest (n, %)	3, 30%	1, 9%
Previous diseases		
Liver disease (n, %)	6, 60%	8, 73%
Heart disease (n, %)	2, 20%	2, 18%
Medication		
Anticoagulant (n, %)	2, 20%	0, 0%
Anti-platelet drug (n, %)	1, 10%	1, 9%
Risk stratification		
Glasgow-Blatchford score	14 (1)	14 (1)
AIMS65 score	3.6 (0.3)	3.1 (0.3)
Underlying diseases		
Esophageal or gastric varix (n, %)	5, 50%	8, 73%
Arterial aneurysm (n, %)	3, 30%	0, 0%
Gastric ulcer (n, %)	1, 10%	2, 18%
Duodenal ulcer (n, %)	1, 10%	1, 9%

Data represent the means with standard errors in parentheses. F, female; M, male.

However, the number of PC units given for 24 hours and during hospitalization was significantly higher in the CRYO group than in the control group. The number of transfused RBC units and FFP administered during hospitalization tended to be higher in the CRYO group than in the control group.

Although it did not reach statistical significance, in-hospital mortality (55% vs. 20%, $P = 0.238$) and mortality within 24 hours after admission (27% vs. 0%, $P = 0.246$) tended to be lower in the CRYO group than in the control group.

4. Discussion

In this study, we found that the patients who were treated with CRYO transfusion experienced less frequent hypofibrinogenemia development and lower 24-hour, in-hospital mortality, as shown in Table 2 and Table 3. To the best of our knowledge, our study is the first to report the feasibility of an intervention for acute hypofibrinogenemia after severe upper GI bleeding using in-house CRYO. The in-house CRYO we produced contained concentrated fibrinogen, as shown in Table 1. Three packs of in-house CRYO might be capable of supplying approximately 2 g of fibrinogen. Massive bleeding has been reported to induce acute acquired hypofibrinogenemia, as a result of resuscitation by massive transfusion and fluid infusion [15]. In addition, dysfibrinogenemia and hypofibrinogenemia in patients with liver cirrhosis have already been reported [16]. In the

Table 3. Laboratory findings, details of transfusion, and mortality in the patients with severe upper gastrointestinal bleeding.

	Cryoprecipitate group N = 10	Control group N = 11
Hematology results		
Hb level (g/dL)	5.6 (0.7)	6.6 (1.0)
Platelet count $\times 10^4/\mu L$	13 (4)	13 (3)
Clotting test results		
% PT (%)	37 (5)	56 (8)
aPTT (sec)	67 (13)	34 (2)
FDP (μg/mL)	18 (7)	34 (23)
D dimer (μg/mL)	8 (4)	3 (1)
Fibrinogen level (mg/dL)		
At admission	146 (32)	156 (32)
Before treatment	127 (15)*	80 (9)
After treatment	172 (13)	189 (40)
Transfusion volume		
24-hour transfusion		
RBC solution (U)	18 (3)	17 (3)
FFP (U)	13 (3)	11 (3)
PC (U)	15 (2)*	6 (3)
PC (n, %)	9, 90%	4, 36%
Albumin (bottle)	2 (1)	2 (1)
Albumin (n, %)	6, 60%	6, 55%
Total transfusion volume		
RBC solution (U)	28 (5)	20 (3)
FFP (U)	19 (4)	13 (4)
PC (U)	42 (15)*	8 (3)
Outcome		
24-hour mortality (n, %)	0, 0%	3, 27%
Mortality at discharge (n, %)	2, 20%	6, 55%

Data represent the means with standard errors in parentheses. *: $P < 0.05$ vs. the control group. Hb, hemoglobin; aPTT, activated partial thromboplastin time; % PT, % prothrombin time; FDP, fibrinogen degradation product; RBC, red blood cell; FFP, fresh frozen plasma; PC, platelet concentrate.

control group of the present study, hypofibrinogenemia was significantly complicated with severe and massive upper GI bleeding, as compared with the CRYO group (Table 2). Therefore, we considered that CRYO might correct the hypofibrinogenemia in the patients with severe upper GI bleeding. As a result, in-house CRYO might improve mortality. In Japan, both fibrinogen concentrate and CRYO are unavailable for acquired hypofibrinogenemia to recover the hemostatic level of fibrinogen rapidly. However, we are the first to report the possibility that in-house CRYO might correct the hypofibrinogenemia in patients with severe upper GI bleeding. The fibrinogen concentrate is also beneficial for treating hypofibrinogenemia after massive bleeding [17]. In the case of acute massive variceal bleeding, the recommended transfusion protocol includes 2 g of fibrinogen [18].

As shown in Table 1, in-house CRYO included the FXIII, FVIII, von Willebrand factor, and fibrinogen. The binding of FXIII with endogenous anti-plasmin reveals the anti-fibrinolytic action and fibrin polymerization [19]. In liver cirr-

hosis, reduced FXIII activity induces hemorrhagic complication [16] [20]. Therefore, it was a possibility that CRYO might correct the decreased FXIII level in the hemorrhagic setting. Activities of FVIII and von Willebrand factor have been known to increase to compensate for deficient vitamin K-dependent factors in patients with liver cirrhosis [20]. We speculated that concentrated FVIII and von Willebrand factor in CRYO might not be involved in improving the outcome of patients with severe upper GI bleeding.

The reason why the volume of transfusion was higher in the CRYO group than in the control group might be due to the survivor effect. Compared with patients in the control group (55%), those in the CRYO group could receive massive transfusion more frequently with less mortality (20%).

Inappropriate indications for CRYO are warfarin reversal, surgical hemostasis, and hepatic coagulopathy [4]. However, we considered that CRYO use for hepatic coagulopathy with severe upper GI bleeding or massive upper GI bleeding might be an appropriate indication. Accepted indications for the use of CRYO are acquired hypofibrinogenemia, massive transfusion (RBC solution ≥ 10 U) within 24 hours with continued bleeding, and the like [4]. Therefore, we expect that the Japan Red Cross will supply CRYO to Japanese hospitals and blood centers in the United States and Europe.

Limitations

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

5. Conclusion

This study's results suggest that the implementation of our in-house CRYO transfusion may reduce the rate of 24-hour mortality after trauma and in-hospital mortality in patients with severe upper GI bleeding, with improvement of hypofibrinogenemia.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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