Original Article

Cryoprecipitate May Reduce the Need for Blood Products During Congenital Heart Surgery

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ABSTRACT

Background: This study assessed the effectiveness of cryoprecipitate — a concentrated product containing coagulation factors from fresh frozen plasma — in managing dilutional coagulopathy during congenital heart surgery.

Methods: This prospective observational study included 10 consecutive patients with complex congenital heart disease, including tetralogy of Fallot, who underwent surgery involving cardiopulmonary bypass during the period from November 2014 to April 2015. The 10 patients received cryoprecipitate and cryoprecipitate-removed plasma in addition to conventional transfusion. Their results were compared with those of 10 consecutive patients with complex congenital heart disease who had undergone heart surgery during the period from January 2014 to October 2014 and received conventional transfusion alone.

Results: Plasma fibrinogen concentration increased from 257 mg/dl to 892 mg/dl during the acquisition of cryoprecipitate from plasma. The average number of transfused units of fresh frozen plasma, including the cryoprecipitate source and amount of platelet concentrate transfused, were lower in patients receiving cryoprecipitate (4.5 ± 2.2 vs 6.3 ± 4.4 units, 56.3 ± 61.6 vs 135 ± 152 ml, respectively; $p < 0.05$).

Conclusions: Use of cryoprecipitate might reduce the amount of transfused blood products needed during complex congenital heart surgery under cardiopulmonary bypass.

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KEYWORDS: congenital heart surgery, blood transfusion, cryoprecipitate

Congenital heart surgery for patients with complex congenital heart disease, particularly procedures during the neonatal or early infant period and multistage surgery involving cardiopulmonary bypass (CPB), is frequently complicated by hemorrhage, which is often aggravated by dilutional coagulopathy with hypofibrinogenemia. Baseline plasma fibrinogen concentrations decrease by 34% to 58% during CPB for adult heart surgery.[1,2] Failure to manage coagulopathy and control microvascular bleeding during cardiac surgery may increase subsequent morbidity and mortality.[3]

The dilutional effect in coagulation factors, including fibrinogen, red blood cells, and platelet concentrate (PC), is more frequent in congenital heart surgery than in adult heart surgery.[4-6] Severe hypofibrinogenemia in dilutional coagulopathy during cardiac surgery involving CPB causes uncontrollable oozing at multiple sites in the operative field. This bleeding requires quick action and a suffi-

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cient supply of coagulation factors, especially fibrinogen. Because fibrinogen is the first coagulation factor to decrease below the critical value during massive bleeding and hemodilution, it is the most important of the coagulation factors to be supplied.[7] In the setting of bleeding control in congenital heart surgery, fresh frozen plasma (FFP) is slowly administered for the small amount of circulating blood. Use of low doses of FFP to correct low fibrinogen values is inefficient, as large doses of FFP are usually required, especially when correcting fibrinogen deficiencies. However, FFP is the only available treatment for acquired hypofibrinogenemia in Japan. Cryoprecipitate is not generally supplied by the Japanese Red Cross Society, and, in Japan, a purified fibrinogen concentrate product derived from pooled human plasma (Fibrinogen HT; Japan Blood Products Organization, Tokyo, Japan) is available only for congenital fibrinogen deficiency. Although an increasing number of Japanese reports have described the limitations of FFP for ongoing severe hypofibrinogenemia in cardiac surgery, these studies only investigated adult cardiovascular surgery.[8]

This study examined the effectiveness of cryoprecipitate and cryoprecipitate-removed plasma (CRP) in reducing transfused blood volume in congenital heart surgery. Plasma concentration of FFP, cryoprecipitate, and CRP were measured. In addition, plasma fibrinogen concentration, platelet count, and hemoglobin concentration were measured at several time points in patients undergoing complex congenital heart surgery. The hypothesis was that rapid recovery from severe hypofibrinogenemia is the most important factor in hemostasis during congenital heart surgery. Thus, the hemostatic effects of fibrinogen concentrate and FFP alone were compared.

Methods

Study protocol

This study was designed as a prospective observational study of patients undergoing complex congenital heart surgery, including tetralogy of Fallot, under CPB. We enrolled two types of patients with complex congenital heart surgery: those with a body weight of <5 kg at surgery during the neonatal or early infant period and those who had undergone prior procedures as part of multistage therapy. All patients received cryoprecipitate and CRP in addition to conventional transfusion therapy. Patients requiring extracorporeal membrane oxygenation and those older than 15 years were excluded. Among patients undergoing congenital heart surgery at Toho University Omori Medical Center from November 2014 to April 2015, 10 consecutive patients were enrolled in this study. As historical controls, data were analyzed from 10 consecutive patients who underwent similar congenital heart surgery between January 2014 and October 2014. A local ethics committee approved the protocol for the study (protocol number 26-161), and informed consent was obtained from all patients or a legal guardian.

After FFP was melted at 4℃ over a period of 20 hours, the centrifuged and collected blood product was defined as cryoprecipitate, which was then prepared according to patient body weight. The volume of cryoprecipitate prepared was 20 ml from 2 units of FFP for patients weighing less than 5 kg, 40 ml from 4 units for those weighing 5 − 10 kg, and 60 ml from 6 units for those weighing more than 10 kg. Then, the plasma fibrinogen concentration in cryoprecipitate-removed plasma, cryoprecipitate, and CRP was determined.

Patients received the prescribed dose of cryoprecipitate after they were weaned from CPB. Fifty milliliters of CRP was used as a filling fluid for CPB, and additional CRP was administered as an infusion solution during surgery and in the intensive care unit (ICU) after surgery. Plasma fibrinogen concentration, platelet count, hemoglobin concentration, and hemostatic markers (prothrombin time/international normalized ratio and activated partial thromboplastin time) were measured at four time points (preoperatively, before cryoprecipitate administration, immediately after entering ICU, and on postoperative day 1 [POD 1]).

Surgery, CPB, and perioperative management

All patients underwent median sternotomy as part of our standard surgical treatment and normothermic or moderate hypothermic CPB. CPB was established after a loading dose of 300 IU/kg of unfractionated heparin plus additional doses to reach and maintain a target activated clotting time of 400 seconds or longer. Anesthetic management was done in a like manner by an experienced anesthesiologist.

Statistical analysis

The data were analyzed with the IBM SPSS 20 software package (International Business Machines [IBM] Corp., Armonk, NY, USA). For continuous variables, descriptive statistics were calculated and reported as mean ± standard deviation. Categorical variables are described using frequency distributions and are presented as frequency (%).

The Mann-Whitney *U* test was used for comparisons of continuous variables, and the Fisher exact test was used for comparisons of frequencies between groups. Statistical significance was defined as a p value of <0.05.

Results

Patient enrollment

Ten patients were enrolled initially. The mean body weight of these patients was 7.5 ± 4.2 kg, and mean body surface area was 0.36 ± 0.16 m^2. Ten patients who had undergone congenital heart surgery between January 2014 and October 2014 were selected as the historical control group. The baseline characteristics of these groups are shown in Table 1. Hemoglobin concentration and some hemostatic markers before surgery, and operative time and CPB time during surgery, did not significantly differ between the groups (Table 2).

Fibrinogen concentration of FFP, cryoprecipitate, and CRP

The mean fibrinogen concentrations in FFP as the cryoprecipitate source, cryoprecipitate, and CRP were 257 ± 40.6 mg/dl (range, 174 − 325), 892 ± 338 mg/dl (range, 436 − 1323), and 172 ± 19.9 mg/dl (range, 138 − 216), respectively. The condensed fibrinogen concentration of cryoprecipitate was 3.4 times that of FFP. Although the refinement of blood products was done by the same technician, fibrinogen concentration varied widely, particularly in cryoprecipitate.

Perioperative change in fibrinogen concentration and platelet count

The mean fibrinogen concentration at four time points (preoperatively, before cryoprecipitate administration, in the ICU, and on POD1) in both groups is shown in Fig. 1 (a, b), but there were no data on concentrations before administration of cryoprecipitate in the controls. In the study group, plasma fibrinogen concentration decreased from

Table 1 Baseline characteristics of participants

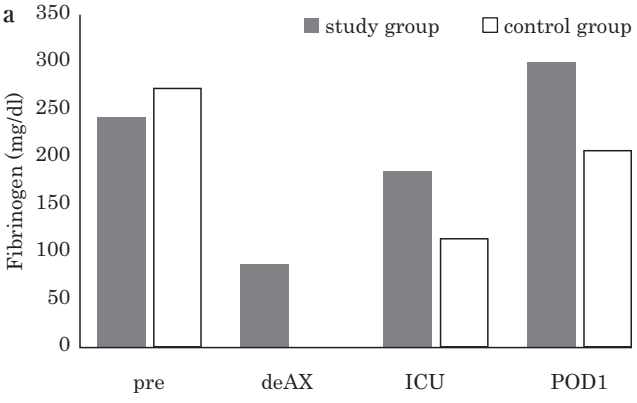
Number	Group	Indication	Age	Weight (kg)	Diagnosis	Procedure	Prior procedures
1	control	staged	1y	7.5	cAVSD	ICR	PAB
2	control	staged	2y	14.8	DORV/PS, RVOTS	RVOTR	ICR for DORV
3	control	small	4m	4.9	TOF	ICR	-
4	control	staged	1y	9.7	SV, DORV	TCPC	PAB, BDG
5	control	staged	1y	9.9	PPA	ICR	BTS
6	control	small	10d	2.1	Ebstein anomaly	Stanes	-
7	control	staged/small	1m	3.2	IAA, SAS, MS	Norwood	bilPAB
8	control	small	0d	2.8	TAPVC	ICR	-
9	control	staged/small	1m	2.8	IAA, SAS, DORV	Norwood	bil PAB
10	control	small	15d	2.6	TGA	ASO	-
11	study	small	17d	2.5	CoA complex	ICR	-
12	study	staged	2y	10.6	HLHS	TCPC	Norwood, BDG
13	study	small	2m	4.8	TOF	ICR	-
14	study	staged	2y	14.4	SV, DILV	TCPC	PAB, ASD creation, BDG
15	study	staged	1y	8.1	MA, hypoLV, DORV	BDG	PAB, ASD creation
16	study	small	1m	3.5	Heterotaxy, PA/VSD	BTS	-
17	study	staged	6m	5.4	IAA, SAS, DORV	BDG	bilPAB, Norwood
18	study	small	1m	2.9	TOF, hypoPA	BTS	-
19	study	staged	2y	10.8	DORV, VSD	TCPC	PAB, BDG
20	study	staged	2y	11.8	Multiple VSDs	ICR	PAB

y: year, m: month, d: day, cAVSD: complete atrioventricular septal defect, DORV: double outlet right ventricle, PPA: pure pulmonary atresia, PS: pulmonary stenosis, RVOTS: right ventricular outflow tract stenosis, TOF: tetralogy of Fallot, SV: single ventricle, IAA: interrupted aortic arch, SAS: subaortic stenosis, MS: mitral stenosis, TAPVC: total anomalous pulmonary venous connection, TGA: transposition of the great arteries, CoA: coarctation of the aorta, HLHS: hypoplastic left heart syndrome, DILV: double inlet left ventricle, MA: mitral atresia, hypoLV: hypoplastic left ventricle, PA: pulmonary atresia, VSD: ventricle septal defect, ICR: intracardiac repair, RVOTR: right ventricular outflow tract reconstruction, TCPC: total cavopulmonary connection, ASO: arterial switch operation, BDG: bidirectional Glenn, BTS: Blalock-Taussig shunt, PAB: pulmonary artery banding, ASD: atrial septal defect

Table 2 Preoperative characteristics of patient subgroups

	Study group (n = 10)	Control group (n = 10)	*P*-values
Preoperative			
Body weight (kg)	7.5 ± 4.2	6.1 ± 4.3	0.77
Body surface area (m^2)	0.36 ± 0.16	0.30 ± 0.15	0.68
Number of prior procedures	6	6	
Fibrinogen (mg/dl)	254 ± 35	261 ± 99	0.30
Plt ($\times 10^4/\mu l$)	38.9 ± 12.2	31.2 ± 18.3	0.28
Hb ($\times 10^4/\mu l$)	13.4 ± 2.3	13.2 ± 2.5	0.82
Intraoperative			
Operative time (min)	417 ± 102	449 ± 122	0.25
CPB time (min)	152 ± 41	193 ± 85	0.20

＊continuous data presented as mean ± standard deviation
Plt: platelet, Hb: hemoglobin, CPB: cardiopulmonary bypass



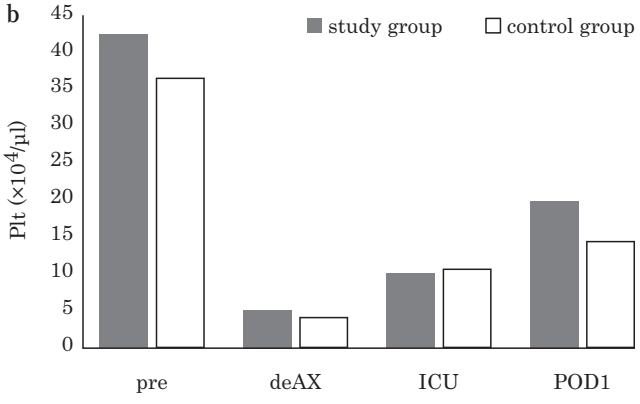


Fig. 1
a: Perioperative change in fibrinogen concentration during complex congenital heart surgery.
b: Perioperative change in platelet (Plt) count during complex congenital heart surgery.
pre: preoperative, deAX: de-clamping of aortic cross, ICU: intensive care unit, POD1: on postoperative day 1

253 ± 34.7 mg/dl to 109 ± 35.1 mg/dl during CPB. After transfusion of cryoprecipitate and CRP, plasma fibrinogen concentration increased to 199 ± 35.6 mg/dl in the ICU and to 301 ± 34.8 mg/dl on POD 1. In the control group, plasma fibrinogen concentration changed from 261 ± 99.7 mg/dl preoperatively, to 156 ± 66.5 mg/dl in the ICU, and to 270 ± 88.7 mg/dl on POD1. There was no significant difference between groups at any time point. All patients in both groups received PC transfusion after removal from CPB. The mean platelet counts in both groups at the four time points are shown in Fig. 1. In study group, platelet count decreased from 38.9 ± 12.2 ($\times 10^3/\mu l$) to 4.57 ± 3.31 ($\times 10^3/\mu l$) during CPB. After PC transfusion, platelet count increased to 11.2 ± 4.8 ($\times 10^3/\mu l$) in the ICU and to 21.2 ± 8.3 ($\times 10^3/\mu l$) on POD 1. In the control group, platelet count was 31.2 ± 18.3 ($\times 10^3/\mu l$) preoperatively, 4.80 ± 3.50 ($\times 10^3/\mu l$) after removal from CPB, 10.2 ± 4.6 ($\times 10^3/\mu l$) in the ICU, and 12.1 ± 6.8 ($\times 10^3/\mu l$) on POD 1. There were no significant differences between groups.

Blood transfusion during surgery

Transfusion volume during complex congenital heart surgery was compared between groups. The number of FFP units, including the source of cryoprecipitate, was significantly lower in cases than in controls (4.5 ± 2.2 vs 6.3 ± 4.4 units, respectively; p=0.025) (Fig. 2-a). Similarly, PC volume was significantly lower in cases than in controls (56.3 ± 61.6 vs 135.4 ± 152.1 ml, respectively; p=0.046) (Fig. 2-b). However, there was no significant difference in red blood cell units required (3.2 ± 2.4 vs 2.9 ± 2.1 units, respectively; p=0.554). Thus, timely administration of fibrinogen concentrate after CPB significantly reduced transfused volumes

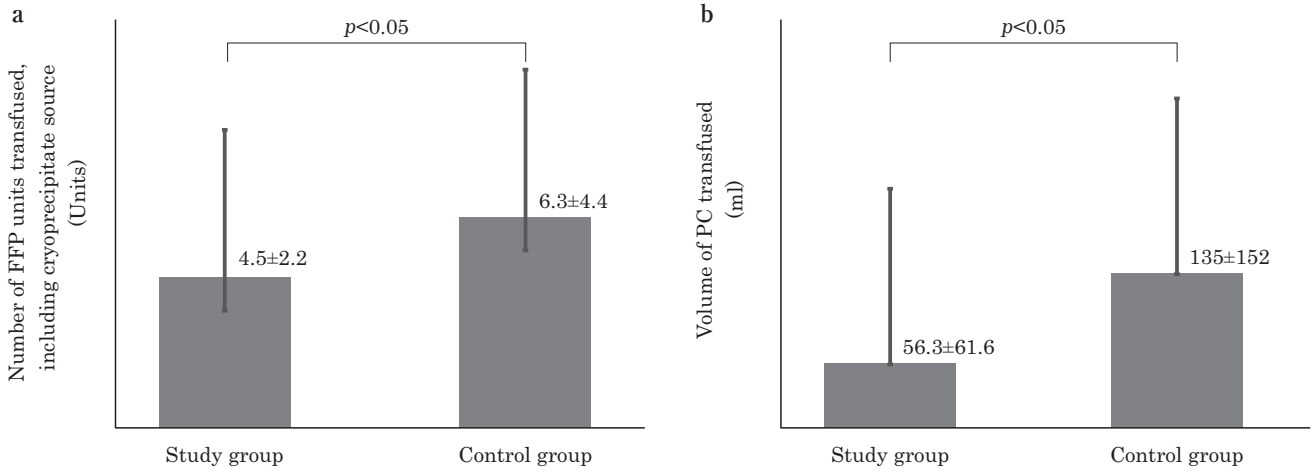


Fig. 2
a: Number of FFP units transfused, including the cryoprecipitate source, during complex congenital heart surgery.
b: Volume of PC transfused during complex congenital heart surgery.
FFP: fresh frozen plasma, PC: platelet concentrate

of FFP and PC during surgical treatment for congenital heart disease.

Discussion

Cardiovascular surgery using CPB decreases plasma concentrations of coagulation factors and blood cell components, primarily by hemodilution from CPB priming and intravenous fluids.[2] In the present study, plasma fibrinogen concentration decreased to below 100 mg/dl in patients undergoing complex congenital heart surgery. The CPB-associated reduction in fibrinogen concentration depends on consumptive coagulopathy induced by CPB by activation of the coagulation pathway, primarily due to retransfusion of blood aspirated from the surgical field.[9, 10] Fibrin clots that develop when plasma fibrinogen concentration is low are easily lysed by the fibrinolytic system, which is frequently activated by CPB.[11] Thus, severe hypofibrinogenemia during CPB weaning can lead to oozing at multiple sites in the surgical field after completion of surgical hemostasis, which may result in massive hemorrhage. Because fibrinogen seems to be the coagulation factor that first reaches a critically low concentration during massive hemorrhage, even before thrombocytopenia development, treatment in this setting should focus on rapid and sufficient fibrinogen supplementation.[12]

The highly concentrated fibrinogen products used in this study were prepared in our institute, after receiving approval from a local ethics committee. The mean fibrinogen concentration of cryoprecipitate was 892 mg/dl, and the condensed fibrinogen concentration in cryoprecipitate was 3.4 times that in FFP. For a 3-kg neonate undergoing surgery, the estimated circulating blood volume is 250 ml (85 ml/kg) and the total amount of fibrinogen is 250 mg (100 mg/dl) when the patient is weaned from CPB. After administration of 20 ml cryoprecipitate, the additional amount of fibrinogen is estimated to be 180 mg, and the total amount of fibrinogen is thus 430 mg. The fibrinogen concentration in the absence of surgical bleeding is estimated to be 160 mg/dl. This rapid recovery of fibrinogen concentration might decrease the risk of consumptive coagulopathy resulting from CPB-induced activation of the coagulation pathway. When fibrinogen is replaced slowly by administration of FFP, the change in fibrinogen concentration is irreversible. In addition, the amount of fibrinogen and the cryoprecipitate administration schedule may be important in hemostasis.

A simultaneous rapid depletion of platelet count during CPB was observed in this series. Because this possibility was anticipated, abundant PC (5 − 10 units) was made available before surgery. However, the amount of PC required depends on hemostasis in the operative field. The significant decrease in PC seen in this study confirmed that cryoprecipitate resulted in adequate hemostasis and eliminated extra transfusion of PC. In fact, the interval between administration of protamine sulfate and the end of surgery tended to be shorter than that before the intro-

duction of cryoprecipitate (83 ± 29 vs 138 ± 48 min, p= 0.15). Although production of cryoprecipitate and CRP are subject to human error, this shorter interval improves patient outcomes.

In 1991, Naik and colleagues developed a technique for modified ultrafiltration, as an alternative method for reducing the adverse effects of CPB in pediatric patients.[13] Bando et al reported that modified ultrafiltration decreased the need for blood transfusion in neonates and patients requiring prolonged CPB.[14] In the 2000s, aprotinin and tranexamic acid therapy were introduced to reduce intraoperative transfusion,[15–17] and fresh whole blood was found to be effective for congenital heart surgery.[18, 19] However, cryoprecipitate was used for conventional blood transfusion therapy in those series. Timely administration of fibrinogen concentrate after CPB termination, regardless of whether cryoprecipitate or purified fibrinogen concentrate is derived from pooled human plasma, may be indispensable for hemostasis in complex congenital heart surgery, even if fibrinogen concentrate is not yet a standard component of many transfusion protocols in Japan.

This study had several limitations. The number of participants was small, treatment allocation was not randomized, and the study was conducted at a single center. In addition, the author used a historical control group. Although there were no significant differences in patient background characteristics, bias related to surgical skill and the preferences of anesthesiologists, who decide the amount of blood products used in transfusions, is a concern. Another limitation was the effects of CRP, which were not thoroughly investigated in this study. Therefore, the present conclusions should be interpreted with caution, and a larger prospective randomized study is needed in order to determine the efficacy of cryoprecipitate after CPB.

In conclusion, cryoprecipitate was effective for hemostasis in congenital heart surgery involving CPB and therefore might reduce the amount of transfused blood products needed for patients with complex congenital heart disease.

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Conflicts of interest: The author has no conflicts of interest to disclose.

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