Comparison of the effect of fibrinogen concentrate with fresh frozen plasma (FFP) in management of hypofibrinogenemic bleeding after congenital cardiac surgeries: A clinical trial study*

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Original Article

Abstract

BACKGROUND: Hypofibrinogenemia is an independent factor of excessive bleeding after congenital cardiac surgeries. Fresh frozen plasma (FFP) and fibrinogen concentrate are examples of recommended products for management of hypofibrinogenemic bleedings. Unfortunately, there is no study to compare these treatments in pediatric cardiac surgeries. Therefore, this study aimed to compare the effect of fibrinogen concentrate with FFP on postoperative bleeding and clinical outcome after congenital cardiac surgeries in pediatric population.

METHODS: Phis prospective clinical trial study was carried out on 90 consecutive pediatric patients who underwent congenital cardiac surgeries. The eligible pediatrics who met our study criteria, randomly received FFP (10 ml/kg) or fibrinogen concentrate (70 mg/kg) to assess postoperative bleeding and blood-products requirements.

RESULTS: Each of FFP and fibrinogen concentrate significantly reduced total chest tube drainage (CTD) at 3, 6, 12, and 24 postoperative hours (P = 0.04). The analysis of time*intervention revealed that our intervention (fibrinogen group) significantly reduced CTD more (P = 0.01). Moreover, fibrinogen group had a significantly higher plasma fibrinogen level in first 24 hours (P = 0.02).

CONCLUSION: Nowadays, both of fibrinogen concentrate and FFP product are widely used for management of hypofibrinogenic bleedings after cardiac surgeries. According to our results, we concluded that although the both product had a comparable effect on management of hypofibrinogenemic bleeding in pediatrics undergoing congenital cardiac surgeries, choosing better product depended on general condition of patients such as their body fluid status.

Keywords: Congenital Defects, Fibrinogen, Cardiac Surgery, Pediatric Intensive Care Units, Blood Coagulation, Blood Transfusion

Introduction

Hypofibrinogenemia (plasma fibrinogen level of lower than 200 mg/dl) is associated with increasing risk of perioperative bleeding after cardiac surgeries.[1,2] Utilization of cardiopulmonary bypass (CPB) during congenital cardiac surgeries cause a significant drop (by approximately 34-42 percent) in plasma fibrinogen level, which would then result in excessive postoperative bleeding.[2,3] Pediatric patients are more susceptible to CPB-induced coagulopathies and excessive bleeding after congenital cardiac surgeries.[4]

The traditional treatment of hypofibrinogenemic bleeding is transfusion of allogeneic blood products such as fresh frozen plasma (FFP).[1,5] Unfortunately, transfusion of allogeneic blood products are strongly associated with increased mortality, infection, allergic reaction, neurologic complications, renal failure, and poor outcome.[1,6] Hence, hypofibrinogenemic bleeding is a life-threatening condition after congenital cardiac surgeries in pediatric patients, not only because of excessive blood loss, but also because of the additional risks of transfusion-related

complications.[4,7] Therefore, fibrinogen concentrate is currently preferred by many clinical practitioners, because of the lack of risks of transfusion-related complications.[1,5]

Despite the importance of hypofibrinogenemic bleeding in pediatrics, there is no study on comparing the efficacy of fibrinogen concentrate with FFP in hypofibrinogenemic bleeding in pediatric population after congenital cardiac surgeries.[8,9] Therefore, this study was carried out to compare this efficacy. In addition, this study compared the efficacy of fibrinogen concentrate with FFP on correction of plasma fibrinogen level, and blood requirement in pediatric cardiac intensive care unit (PCICU).

Materials and Methods

The study protocol was approved by ethical committee of Isfahan University of Medical Sciences, Isfahan, Iran (with number of 394081). Informed written consent was obtained from patients' parents or legal guardian. This clinical trial study was carried out between March 2014 and February 2015 in a single center. The inclusion criteria was fibrinogen levels of lower than 200 mg/dl in presence of bleeding exceeded 3 ml/kg in first postoperative hour. Exclusion criteria were age older than 2 years, history of cardiothoracic surgery (redo operation), emergency surgery, anemia [preoperative hemoglobin (Hb) level < 10 g/dl], thrombocytopenia [platelet count (Plt) < $100 \times 10^3/\mu l$], coagulopathy [prothrombin time (PT) > 14.8 s], liver disease (alanine aminotransferase or aspartate aminotransferase > 150 IU/l), active infection, using anticoagulant agents during last month, requirement for additional dose of FFP or fibrinogen concentrate, and known hypersensitivity to fibrinogen concentrate. Our study population primarily consisted of 162 patients who were candidate for congenital cardiac surgery in our center (between March 2014 and February 2015). The patients who did not meet our criteria (n = 54) or their parents (or guardians) did not sign informed consent (n = 18) were excluded from study. Finally, we totally recruited 90 eligible pediatric patients in our study.

We assigned eligible patients (n = 90) into two equal groups of fibrinogen concentrate and FFP product. The first eligible patient allocated to fibrinogen group by lottery, then, the next recruitments were performed in a 1:1 ratio (one patient in FFP group and one patient in fibrinogen group). The fibrinogen group received 70 mg/kg fibrinogen concentrate (Haemocomplettan® P, CSL Behring GmbH, Marburg, Germany), and the FFP group received 10 ml/kg FFP. Blood loss and plasma fibrinogen level of each group was measured and recorded every hour. Coagulation and hematology tests including Hb, Plt, PT, activated partial thromboplastin time (aPTT), and activated clotting time (ACT) was obtained at the 1st, 12th, and 24th postoperative hours.

Routine cardiorespiratory care was performed for all of the patients. Operations performed under standard general anesthesia. After median sternotomy, cardiopulmonary bypass with aortobicaval cannulation was initiated under mild hypothermia (35 °C). Myocardial protection achieved with single injection of cold-crystalloid cardioplegia. Before initiation of CPB, anticoagulation therapy was established via heparinization of patients. In order to achieve ACT of 480 seconds as a target value, 400 IU/kg heparin was administrated through central venous line. According to our perfusionist's protocol, the priming solution was consisted of 10-20 ml/kg human albumin 20%, 10-20 mEq/l bicarbonate sodium, and 0.5 g/kg mannitol 20%. CPB circuit filled up with 300-1000 ml lactated Ringer's solution as needed. In order to maintain hematocrit (HCT) between 20%-25%, packed red blood cells (RBCs) added to solution during bypass. A centrifugal blood pump (Medtronic, Minneapolis, MN, USA), and a hollow-fiber oxygenator (Dideco, Sorin Group Italia, Mirandola, Italy) was used for CPB. Following completion of surgeries and correction of cardiac anomalies, protamine sulfate was administrated in ratio of 1 mg per 100 IU of the total heparin dose to neutralize anticoagulant effect of heparin. The value of ACT less than 150 second was accepted as target value for adequate reversal of heparin. After medical normalization of coagulation and weaning from CPB, surgical hemostasis was performed by placement of suture and using diathermy. Surgical hemostasis was continued until surgeon ensured that there was no source of active bleeding or obvious blood loss. Hypofibrinogenemic bleeding was managed using fibrinogen concentrate (in fibrinogen group) or FFP (in FFP group). Then, patients were rewarmed to 37°C, and transferred to PCICU.

Following PCICU arrival, any blood products were transfused, if necessary, according to our institutional protocol. The protocol consisted of transfusion of 10 ml/kg RBCs if hemoglobin was below 12 g/dl (to maintain Hb > 12 g/dl), and 20 ml/kg of platelets if Plt count was below $100 \times 10^3/\mu l$ (to maintain Plt count > $100 \times 10^3/\mu l$).

Table 1. The demographic characteristics of the participants (n = 90)

Characteristic	Group	Fibrinogen concentrate (n = 45)	Fresh frozen plasma (n = 45)	P
		Mean ± SD	Mean ± SD	
Age (month)		21.93 ± 12.20	21.15 ± 28.80	0.88[*]
Height (cm)		76.91 ± 16.30	73.95 ± 19.94	0.44[*]
Weight (kg)		8.95 ± 4.17	8.42 ± 4.82	0.57[*]
Body mass index (kg/m^2)		14.31 ± 1.56	14.91 ± 2.66	0.18[*]
CPB time (minute)		125.15 ± 20.14	128.33 ± 28.80	0.82[*]
		n (%)	n (%)	
Gender	Male as boy	27 (60.00)	23 (51.11)	0.52[**]
	Female as girl	18 (40.00)	22 (48.89)	
Diagnosis	PS	2 (4.44)	4 (8.88)	N/A
	AS	0 (0)	3 (6.66)	
	ASD	14 (31.11)	8 (17.77)	
	TR	4 (8.88)	4 (8.88)	
	ASD + PDA	4 (8.88)	0 (0)	
	ASD + PS	2 (4.44)	0 (0)	
	PDA	4 (8.88)	10 (24.40)	
	VSD + ASD	6 (13.33)	2 (4.44)	
	VSD	9 (20.00)	14 (31.11)	
Open Sternum		2 (4.44)	2 (4.44)	> 0.99[**]

SD: Standard deviation; CPB: Cardiopulmonary bypass; PS: Pulmonary stenosis; AS: Aortic stenosis; ASD: Atrial septal defect; TR: Tricuspid regurgitation; PDA: Patent ductus arteriosus; VSD: Ventricular septal defect; N/A: Not available
[*] Continues variables were analyzed using paired-sample t test; [**] Categorical variables were analyzed using chi-square or Fisher's exact tests (as appropriate).

None of antifibrinolytic agents were routinely administrate in our institute. As mentioned before, requirement for additional doses of FFP/fibrinogen considered as an exclusion criterion in our study.

Statistical analysis was performed using SPSS software (version 20, IBM Corporation, Armonk, NY, USA). Continuous variables of the study were presented as mean ± standard deviation (SD). Normal distribution of sample data was determined by normality tests. Therefore, parametric tests including paired-sample independent t test and repeated measures ANOVA (as appropriate) were used to find statistically significant differences between continuous variables of patient's characteristics and outcome. Homogeneity of variance (assumption of sphericity) determined by Mauchly test. Categorical variables were shown as frequency (percent), and were analyzed using chi-square or Fisher's exact tests (as appropriate).

P-value of less than 0.05 was considered as significant level for all of the tests.

Results

Demographic Data: There was no significant difference in demographic and baseline characteristics of patients in fibrinogen and FFP groups. The mean age of participants was 21.93 ± 12.20 and 21.15 ± 28.80 month in fibrinogen and FFP groups, respectively. The mean CPB time was 125.15 ± 20.14 minute and 128.33 ± 28.80 in fibrinogen and FFP groups, respectively (Table 1).

Postoperative Bleeding: Postoperative chest tube drainage (CTD) in the groups are summarized in table 2. As the table shows, CTD was significantly reduced in the two group over the time (P = 0.04), but our intervention significantly decreases the amount of bleeding more in fibrinogen group (P=0.01).

Table 2. Postoperative chest tube drainage (CTD) in studied groups (n = 90)

Time duration	Chest tube drainage (ml/kg/hour)		P			
	Fibrinogen concentrate group (n = 45)	Fresh frozen plasma group (n = 45)				
First 3 hours	4.77 ± 2.05	6.94 ± 6.05	0.02[*]	0.02[**]	0.04[£]	0.01[§]
First 6 hours	4.13 ± 1.84	6.31 ± 6.22	0.02[*]			
First 12 hours	3.40 ±1.29	4.52 ± 4.37	0.04[*]			
First 24 hours	1.93 ± 6.63	2.64 ± 2.18	0.04[*]			

[*] Analysis was performed using paired-sample t-test; [**] Analysis of the effect of intervention, performed using repeated measures ANOVA; [£] Analysis of the effect of time, performed using repeated measures ANOVA; [§] Analysis of the effect of time*intervention, performed using repeated measures ANOVA.

Table 3. Postoperative outcomes in studied groups (n = 90)

Characteristic	Fibrinogen concentrate (n = 45) Mean ± SD	Fresh frozen plasma (n = 45) Mean ± SD	P
Length of, (hour)			
Mechanical ventilation support	14.00 ± 4.00	12.53 ± 4.24	0.08[*]
ICU stay	3.04 ± 1.79	3.66±1.80	0.89[*]
Inotrope requirement	29.71 ± 18.77	26.40 ± 17.16	0.38[*]
	n (%)	n (%)	
Total allogeneic blood transfusion			
Platelet (Plt)	0 (0)	2 (4.44)	0.38[*]
Red blood cells (RBCs)	5 (11.11)	9 (20.00)	0.49[*]
Complication			
Renal failure	0 (0)	1 (2.22)	> 0.99[**]
Respiratory failure	0 (0)	1 (2.22)	> 0.99[**]
Neurologic (Stroke, CVA)	0 (0)	0 (0)	-
Hemodynamic instability	4 (8.88)	1 (2.22)	0.36[**]
Reoperation due to surgical bleeding	0 (0)	1 (2.22)	> 0.99[**]

SD: Standard deviation; ICU: Intensive care unit; CVA: Cerebrovascular accident
[*] Continues variables were analyzed using paired-sample t test; [**] Categorical variables were analyzed using chi-square or Fisher's exact tests (as appropriate).

Allogeneic Blood Transfusions: As is shown in table 3, there were no requirement for Plt transfusion in fibrinogen group whereas 2 patients received Plt in FFP group. Moreover, 5 patients in fibrinogen group and 9 patients in FFP group received RBCs; however, but the difference was not significant. None of the patients received antifibrinolytic agents.

Postoperative Outcome: In contrast with the FFP group, the fibrinogen group non-significantly had a longer time of mechanical ventilation (14.00 ± 4.00 vs. 12.53 ± 4.24 hours) and inotrope support (29.71 ± 18.77 vs. 26.40 ± 17.16 hours). In contrary, the FFP group non-significantly had a higher intensive care unit (ICU) stay than the fibrinogen group (3.66 ± 1.80 vs. 3.04 ± 1.79 days). No differences were observed between the two groups in incidence of postoperative complications (Table 3).

Discussion

Hypofibrinogenemic bleeding is a common complication of on-pump congenital cardiac surgeries, as a result of hemodilution and consumption of coagulation factors during CPB.[10,11] Currently, allogeneic blood products (i.e., FFP) and fibrinogen concentrate are highly used for management of hypofibrinogenemic bleeding after congenital cardiac surgeries.[12] Unfortunately, there is only a few studies comparing the efficacy and safety of fibrinogen concentrate with FFP in management of postoperative bleeding in pediatric patients undergoing cardiac surgeries.[3,13-15]

Clinical efficacy of fibrinogen concentrate comparing with traditional management of postoperative bleeding in pediatrics with severe cardiac disease was assessed by Cui et al.[4] To their results, fibrinogen concentrate (in combination with Plt) reduced postoperative blood loss of the first postoperative hour (3.5 ± 1.6 vs. 2.9 ± 2.0 ml/kg/h, P = 0.43). The magnitude of the effect of fibrinogen therapy in next 6 hours was not as high as the first hour (1.5 ± 0.6 vs. 1.3 ± 0.1 ml/kg/h, P = 0.41). Moreover, Galas et al. study[5] indicated that 48-hour blood loss of patients reduced after administration of fibrinogen concentrate compared with cryoprecipitate (320 vs. 410 ml, P = 0.67). However, these findings were not statistically significant. Our results are supported by other studies that compared the efficacy of fibrinogen concentrate with traditional management of postoperative bleeding in adult populations.[12,16-18] A retrospective cohort study of patients with ruptured abdominal aortic aneurysm demonstrated that preoperative hypofibrinogenemia was significantly associated with increased risk of perioperative bleeding.[19] The authors noted that plasma fibrinogen level of less than 150 mg/dl resulted in a 10-fold increase in perioperative blood loss as much as 2000 ml. Two prospective randomized trials that studied high-risk aortic surgeries, reported that early fibrinogen concentrate management after removal of CPB significantly reduced postoperative blood loss and transfusion of allogeneic blood products.[3,17] Similarly, three cohort and one review studies endorsed the use of fibrinogen concentrate as an effective management for hypofibrinogenemic bleeding after adult cardiac surgeries.[12,18,20,21] However,

generalization of this results to complex congenital cardiac surgeries in pediatric patients is limited.

Transfusion of RBCs occurs in more than 50% pediatric patients in PCIUCs. Transfusion of RBCs in the pediatrics is independently associated with increased mortality, infection, allergic reaction, prolonged mechanical ventilation, inotrope requirement, neurologic complications, renal failure, and poor outcome.[1,6] Our study showed that our patients who received fibrinogen concentrate, although non-significantly but, received lesser RBCs products. The current evidences from adult cardiac surgeries proposed a beneficial effect for fibrinogen concentrate compared with FFP in reduction of postoperative blood loss and requirement for transfusions.[14] However, the effect of fibrinogen concentrate on reduction of postoperative blood loss is unclear and debated.[5,14,22] Several reasons such as multifactorial nature of blood loss after congenital surgeries, dose and timing of management, and design of studies can explain these controversies.

Conclusion

There is a large body of evidences which proposing that the FFP product has not adequate quantity of fibrinogen concentrate to manage severe hypofibrinogenemia.[12] Transfusion of large volumes of FFP increase the risk of hypercoagulability, hemodilution, volume overload, pulmonary edema, and congestive heart failure.[13,22] In contrast, the fibrinogen concentrate is a small-volume fluid (after dissolution) that does not require a long time for thawing and preparing.[1,8] Moreover, hypercoagulability and thromboembolism do not increase by administration of even high doses of fibrinogen concentrate (up to 600 mg/kg).[21] Considering the differences in volumes of FFP and fibrinogen concentrate, administration of fibrinogen concentrate may be valuable in pediatric patients that need volume restriction such as cases of congestive heart failure, renal disease, volume overload, or any other restricted fluid intake conditions. In contrast, FFP is a high-volume allogeneic product which contains lower fibrinogen concentration, and may be a better choice in management of patients with hypofibrinogenemia requiring volume replacement or with multiple coagulation factor deficiencies. However, cryoprecipitate is an alternative product for FFP which is preferred by many clinicians to avoid issues with volume loading.[5]

Conflict of Interests

Authors have no conflict of interests.

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