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Fibrinogen levels and postoperative chest drain blood loss in low-weight (<10 kg) children undergoing cardiac surgery

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Abstract

Introduction: Low-weight (<10 kg) children undergoing cardiac surgery with cardiopulmonary bypass are prone to dilution and consumption of soluble coagulation factors and fibrinogen. Low levels of fibrinogen may represent a possible cause of severe postoperative chest drain blood loss. The present study investigates the association between post–cardiopulmonary bypass fibrinogen levels and postoperative chest drain blood loss and severe bleeding, aiming to identify possible cut-off values to trigger specific interventions.

Methods: Prospective cohort study on 77 patients weighing <10 kg undergoing cardiac surgery with cardiopulmonary bypass. Haemostasis and coagulation data were collected before surgery (standard tests and thromboelastometry), after protamine (thromboelastometry) and at the arrival in the intensive care unit (standard tests). The primary outcome variable was severe bleeding (chest drain blood loss >30 ml kg^{-1}/24h).

Results: Factors being independently associated with severe bleeding were the international normalized ratio and the fibrinogen levels at the arrival in the intensive care unit. Once corrected for other confounders, fibrinogen levels had an odds ratio of 0.2 (95% confidence interval = 0.011-0.54) per 1 gL^{-1} for severe bleeding. The discrimination power was fair (area under the curve = 0.770). The best cut-off value was identified at a fibrinogen level of 150 mg dL^{-1}, with a sensitivity of 52%, a specificity of 85% and a positive predictive value of 60% for severe bleeding.

Conclusion: Both a prolonged international normalized ratio and low fibrinogen levels were predictive for severe bleeding, underscoring the role of coagulation factors dilution and consumption in this specific patient population.

Keywords
newborn; surgery; cardiac; fibrinogen

Introduction

Paediatric cardiac surgery is associated with bleeding and blood transfusion requirements. The main cause of this risk is the immaturity of the haemostatic system of neonates and small infants.[1] Moreover, cyanosis is associated with polycythaemia, low fibrinogen and clotting factors concentration, low platelet count and increased fibrinolysis.[2]

Nonetheless, the use of cardiopulmonary bypass (CPB) determines variations in temperature, activation of the inflammatory cascade and haemodilution. Despite the use of miniaturized circuits,[3] CPB still has a major impact on perioperative bleeding.

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In low-weight children undergoing cardiac surgery, red blood cells (RBCs) are usually added to the CPB priming volume to prevent haemodilution, with fresh frozen plasma (FFP) or albumin to preserve colloid osmotic pressure.[4–8]

A few studies investigated the superiority of FFP or albumin-based priming solutions in neonates and small infants, and the results were conflicting.[9–13]

Recently, our group investigated the use of FFP in the priming solution (APPEAR study). This was the largest randomized study comparing different timing strategies for FFP administration in children weighing <10 kg. This study showed a lower postoperative chest drain blood loss in patients receiving FFP in the priming solution, raising the hypothesis that this could be due to a more preserved fibrinogen concentration at the end of surgery.[14]

Other groups studied the relationship between fibrinogen levels and postoperative bleeding and transfusions in paediatric cardiac surgery, but in different kind of patients.[15]

The present study, based on a continuation of the APPEAR data collection, aims (1) to verify the hypothesis that in children weighing <10 kg the postoperative fibrinogen levels are associated with chest drain blood loss and (2) to detect possible trigger values for fibrinogen supplementation.

Materials and methods

This study was approved by the Local Ethics Committee (San Raffaele Hospital, protocol number 116/int/2017, approved on 12 October 2017), and parents of all patients provided a written informed consent. The study was registered prior to patient enrolment at clinicaltrials.gov (NCT02738190).

Patient population

The patient population was represented by neonates and small (<10 kg) children undergoing cardiac surgery with CPB. The initial series (80 patients) was recruited during the APPEAR study.[14] The following series (not randomized, 20 patients) was recruited from September 2017 through January 2018. Inclusion criteria were planned cardiac surgery with CPB and blood priming solution and a weight <10 kg. Exclusion criteria were emergency surgery, known congenital coagulopathy, participation in another study, or refusal to participate. Withdrawal criteria were the following: death within 24 h from surgery, need for extracorporeal membrane oxygenation within the first 24 h from surgery, and fibrinogen concentrate supplementation after the arrival in the intensive care unit (ICU) and within the following 24 h. Patients receiving fibrinogen concentrate in the operating room were excluded from the main analysis but included in a post hoc analysis.

Twenty-three patients met one or more of these conditions and were excluded from the main analysis, leaving a final patient population of 77 subjects; 10 patients received fibrinogen concentrate in the operating room and were admitted to the post hoc analysis, including 87 subjects.

CPB and surgery

Every subject received our standard surgical care and CPB technique. A total intraoperative dose of 30 mg kg^{-1} of tranexamic acid was administered in all patients. CPB was established after a loading dose of 300 IU kg^{-1} of unfractionated heparin plus additional doses (80 IU kg^{-1}) to reach and maintain a target-activated clotting time of >450 s. The CPB circuit included a hollow fibre oxygenator (Sorin KIDS D100 or D101; Livanova, Mirandola, Italy), a roller head pump (Sorin S5 HLM; Livanova), or a centrifugal pump (Bio-Medicus; Medtronic, Minneapolis, MN, USA).

The patients received either an albumin 5% plus RBC priming or an FFP plus RBC priming, with the relative proportions calculated to achieve an 'on pump' hematocrit (HCT) of 30%. The first 80 patients received 5% albumin of FFP prime in a randomized fashion, while the following 20 received FFP-based prime. There were no significant differences in the patients' characteristics between those randomized for FFP and those for 5% albumin.[14] The amount of RBCs used in the priming solution varied according to the patient's baseline HCT and weight and the priming volume.

Ultrafiltration was a standard of care: conventional or modified ultrafiltration were applied respectively according to the surgeon's preferences. A hemoconcentrator (BC 20 Plus; Maquet Getinge Group, Rastatt, Germany) was placed after a dedicated pump, and blood was driven by the arterial side to the patient via the venous line prior to decannulation or during CPB. During ultrafiltration, patients treated with 5% albumin priming had half of the volume replaced with FFP (15 ml kg^{-1}) and an additional dose of 15 ml kg^{-1} of FFP during haemostasis and before transfer to the ICU. Patients treated with FFP in the priming received the same replacement with albumin 5%. The target HCT to achieve after hemofiltration was 35%.

Coagulation-related measurements

Apart from the standard data included in our institutional data base (demographics, type of surgery, Risk Adjusted classification for Congenital Heart Surgery

(RACHS-1), CPB management details), the patients received the following measurements:

1. Baseline: activated partial thromboplastin time (aPTT, seconds), international normalized ratio of the prothrombin time (INR), fibrinogen levels (mg dL^{-1}), platelet count (x1,000 cell μl^{-1}); ROTEM® (TEM International, Munich, Germany) tissue-factor activated (EXTEM) and fibrin-based thromboelastometry tests (FIBTEM), with measure of the clotting time (seconds) at EXTEM and maximum clot firmness (MCF; mm) at the EXTEM and FIBTEM.
2. After protamine administration: ROTEM® analysis.
3. At the arrival in the ICU: standard coagulation tests.
4. After 24 h from the admission in the ICU: standard coagulation tests + ROTEM® analysis.

INR and aPTT were assessed using respectively the STA-NeoPTimal 10 and the STA-Cephascreen 10 (Diagnostica Stago, Asnières sur Seine, France); fibrinogen was measured using the Clauss-based STA-LiquidFib (Diagnostica Stago, Asnières sur Seine, France).

EXTEM and FIBTEM were performed by a dedicated biologist (E.B.) in the operating room. The postoperative results were provided, on request, to the attending anesthesiologist. This is our standard practice in case of signs of excessive bleeding.

Bleeding management and related measures

Apart from the pre-defined amount of FFP received by the patients in the priming volume or at the end of CPB, in the presence of ongoing microvascular bleeding intra- or postoperatively, transfusions and anaemia control were guaranteed by our standard protocol that includes correction of residual heparin, use of fibrinogen concentrate, RBCs, platelets and FFP transfusions. All interventions were driven by viscoelastic tests (protamine administration based on differences in clotting times with or without heparinase, FFP supplementation based on clotting time with heparinase) and standard coagulation tests (platelet concentrate administration based on platelet count). Prothrombin complex concentrate is not considered by our protocol, whereas fibrinogen concentrate is considered in case of active bleeding and a value of MCF <7 mm at FIBTEM test. However, for the purpose of the present study, patients receiving fibrinogen concentrate after the arrival in the ICU were excluded from the analysis, and those receiving fibrinogen concentrate during surgery were excluded from the main analysis but included in a post hoc analysis. Of notice, a FIBTEM <7 mm without signs of excessive bleeding was not an indication to fibrinogen-concentrate administration. Our routine practice is to perform point-of-care tests only in bleeding patients (according to clinical judgement).

Postoperative chest drain blood loss was measured from chest closure through 24 h from the arrival in the ICU, and transfusions were assessed separately for RBCs, FFP, platelets during the first 24 h. To take into account weight differences, bleeding and transfusions were normalized for the body weight (ml kg^{-1}). Definition for severe bleeding (SB) in children undergoing cardiac surgery is not universally accepted. For this reason we opted for >30 mL kg^{-1} which, analysing our historical data, corresponds to the upper tertile of the distribution.[14]

Study endpoints and sample size

The primary endpoint was the association between postoperative fibrinogen levels and SB. For SB, the primary endpoint included the identification of adequate cut-off values of fibrinogen levels. Secondary endpoints were the association between postoperative fibrinogen levels and 24-h chest drain blood loss, and the outcome in patients with low fibrinogen levels. The sample size was based on the assumption that about 33% of the patient population would experience an SB, therefore providing about 33 events. This allows the inclusion of three independent variables in a multivariable logistic regression model for SB (including fibrinogen levels) avoiding an overfitting and based on the general rule of admitting one independent variable per 10 events. This was considered acceptable for a clinical model of SB prediction, allowing the inclusion of other possible confounders.

Statistics

Data are presented as number and percentage for dichotomous variables, mean and standard deviation for continuous normally distributed variables and as median and interquartile range for continuous, non-normally distributed variables. Normality of the distribution was checked with the Kolmogorov-Smirnov test.

The association between coagulation tests and chest drain blood loss was tested with linear and polynomial regression analyses, selecting the best-fit equation based on the correlation coefficient, and presented with 95% confidence interval. The association between coagulation tests and SB was tested with logistic regression analyses (univariate and multivariable stepwise forward). For variables being associated with SB, a

Table 1. Baseline demographic characteristics, clinical and surgical details (N = 77).

Variable	Value
Age (months)	6 (2–6.0)
Neonates	15 (19.5)
Weight (kg)	4.8 (3.8–6.6)
Hematocrit (%)	36.7 (5.9)
RACHS-1	3 (2–4)
Type of surgery	
Repair of ventricular septal defect	20 (26)
Repair of tetralogy of Fallot	4 (5.2)
Repair of atrioventricular canal	8 (10.4)
Cavopulmonary connection	3 (3.9)
Arterial switch	15 (19.5)
Repair of truncus arteriosus	4 (5.2)
Others	23 (29.8)
Type of pump	
Centrifugal	40 (52)
Roller	37 (48)
Priming volume (mL)	280 (280–360)
Priming nature	
Albumin 5% + RBC	31 (40.3)
FFP + RBC	46 (59.7)
Cardiopulmonary bypass time, min	119 (72–150)
Aortic cross-clamp time (min)	60 (40–86)
Lowest hematocrit on CPB (%)	30 (3.0)
Lowest temperature on CPB (°C)	30.6 (28–32)
Total heparin dose (IU kg^{-1} min^{-1})	4 (2.4-5.9)

Data are number (percentage) or median (interquartile range).
RACHS-1: Risk Adjusted classification for Congenital Heart Surgery; FFP: fresh frozen plasma; RBC: red blood cells.

multivariable analysis (logistic regression) was applied to identify the independent predictors. A predictive analysis on postoperative coagulation tests was conducted using a receiver operating characteristics (ROC) analysis producing the area under the curve (AUC); different cut-off values were tested for sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV). The best cut-off value was selected based on the combination of sensitivity and specificity (Youden's index). Differences between continuous variables were tested with parametric (Student's t test) or non-parametric (Mann–Whitney U test) methods as appropriate. Differences in proportions were tested with a Fisher exact test.

All the analyses were performed with computerized packages (SPSS 20.0 (IBM, Chicago, IL, USA) and MedCalc (MedCalc Software, Ostend, Belgium)). A p value <0.05 was considered significant.

Results

Table 1 reports the general characteristics of the patient population. Overall, 23 (30%) patients met the criteria for SB, confirming our assumption that the value of chest drain blood loss >30 ml kg^{-1} roughly corresponds to the upper tertile of distribution.

Table 2. Univariate association between coagulation parameters, 24-h chest drain blood loss and severe bleeding.

Postoperative 24-hr chest drain blood loss (ml kg^{-1})		
Variable	Correlation coefficient	p
Baseline		
aPTT (s)	0.052	0.656
International normalized ratio	0.054	0.642
Platelet count (x1,000 cells µL)	−0.036	0.756
Fibrinogen (mg dL^{-1})	−0.098	0.459
EXTEM CT (s)	−0.133	0.250
EXTEM MCF (mm)	0.142	0.217
FIBTEM MCF (mm)	0.031	0.787
Post-protamine		
EXTEM CT (s)	0.001	0.999
EXTEM MCF (mm)	**−0.288**	**0.011**
FIBTEM MCF (mm)	−0.154	0.281
Arrival in the intensive care unit		
aPTT (s)	**0.370**	**0.001**
International normalized ratio	**0.453**	**0.001**
Platelet count (x1,000 cells $µL^{-1}$)	−0.206	0.071
Fibrinogen (mg dL^{-1})	**−0.409**	**0.001**
Severe bleeding (>30 ml $24h^{-1}$)		
Variable	Regression coefficient	p
Baseline		
aPTT (s)	0.062	0.147
International normalized ratio	0.798	0.646
Platelet count (x1,000 cells µL)	0.001	0.838
Fibrinogen (mg dL^{-1})	−0.005	0.235
EXTEM CT (s)	−0.011	0.333
EXTEM MCF (mm)	0.057	0.235
FIBTEM MCF (mm)	0.007	0.841
Post-protamine		
EXTEM CT (s)	0.001	0.875
EXTEM MCF (mm)	**−0.092**	**0.033**
FIBTEM MCF (mm)	−0.144	0.081
Arrival in the intensive care unit		
aPTT (s)	**0.179**	**0.006**
International normalized ratio	**9.896**	**0.001**
Platelet count (x1,000 cells µL)	−0.001	0.051
Fibrinogen (mg dL^{-1})	**−0.031**	**0.001**

aPTT: activated partial thromboplastin time; CT: clotting time; MCF: maximum clot firmness.
Note. Boldfaced values in the table highlights statistically significant associations.

The association between coagulation parameters and chest drain blood loss and SB is shown in Table 2. No preoperative parameter was associated with postoperative chest drain blood loss nor SB. After protamine,

there was a negative association between MCF at EXTEM and chest drain blood loss and SB. At the arrival in the ICU, aPTT, INR, and fibrinogen levels were associated with chest drain blood loss and SB.

The association between fibrinogen levels at the arrival in the ICU and postoperative chest drain blood loss is defined by a cubic spline function ($R^2 = 0.207$, $p = 0.001$) reported in Figure 1. The coagulation test and general characteristics of the patients with or without SB are reported in Table 3. The values of fibrinogen were significantly lower in SB patients at the arrival in the ICU.

Factors being associated with SB were tested in a univariate and multivariable analysis (logistic regression) to identify the independent predictors (Table 3). Factors admitted to this analysis were the post-CPB EXTEM MCF and the INR, aPTT and fibrinogen levels at the arrival in the ICU. In addition, clinical factors being different between SB and non-SB at a p value <0.05 were included as potential confounders. Factors being independently associated with SB were a low weight ($p = 0.035$), a high INR ($p = 0.009$) and a low fibrinogen level ($p = 0.021$). Fibrinogen levels had an odds ratio of 0.961 (95% confidence interval = 0.929-0.994) for SB once corrected for the weight and the INR. This corresponds to an 80% reduction in the risk of SB per each gL^{-1} of fibrinogen levels.

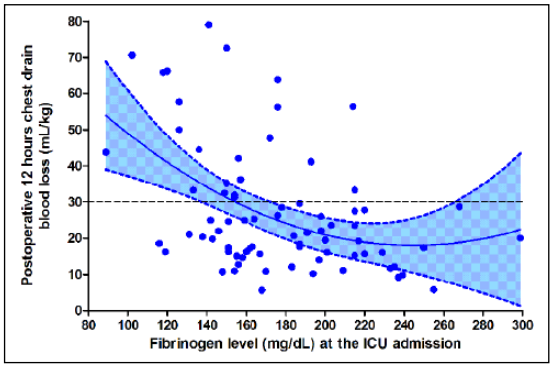

Figure 1. Association between fibrinogen levels at the arrival in the intensive care unit (ICU) and postoperative chest drain blood loss.

To investigate the predictive properties of INR and fibrinogen levels at the arrival in the ICU, ROC analyses were performed. The INR had an AUC of 0.826 (95% confidence interval = 0.721-0.904); a cut-off value at an INR of 1.47 had a sensitivity of 50% and a specificity of 91% for SB, with a NPV of 81% and a PPV of 69%.

The fibrinogen levels had an AUC of 0.770 (95% confidence interval = 0.660-0.858); the (best) cut-off value was identified at a fibrinogen level of 150 mg dL^{-1}, with a sensitivity of 52%, a specificity of 85%, an NPV of 81% (Youden's index = 0.37) and a PPV of 60% for SB. The PPV is lower (45%) for fibrinogen levels <175 mg dL^{-1} and higher (92%) for fibrinogen levels <100 mg dL^{-1}.

In an additional analysis, we created a logistic regression model inclusive of fibrinogen and INR for prediction of SB. When tested for discrimination, this combined model yielded an AUC of 0.867 at a ROC analysis, significantly ($p = 0.027$) higher than fibrinogen alone (Figure 2).

Eighteen (23.4%) patients had a fibrinogen level at the arrival in the ICU <150 mg dL^{-1}. Factors being associated with this condition were a low weight ($p = 0.019$),

Table 3. Univariate and multivariable analysis of factors associated with severe bleeding.

Item	SB (N = 23)	No SB (N = 54)	p	Odds ratio (95% CI)	p
Age (months)	5 (1–11)	8 (4.8–12)	0.054	N/A	N/A
Weight (kg)	3.9 (3.2–4.8)	5.7 (4–7.1)	0.001	0.431 (0.198–0.941)	0.035
RACHS–1	3 (3–4)	3 (2–3)	0.012	2.859 (0.791–10.4)	0.109
Cyanosis	14 (61)	23 (42)	0.142	N/A	N/A
Hematocrit (%)	40 (34–42)	36 (32–40)	0.090	N/A	N/A
Priming volume (ml)	280 (280–300)	280 (280–360)	0.170	N/A	N/A
CPB time (min)	139(102–171)	104 (67–137)	0.002	1.016 (0.987–1.044)	0.283
Lowest hematocrit on CPB (%)	29 (28–31)	30 (28–32)	0.466	N/A	N/A
Lowest temperature on CPB (°C)	28 (28–31)	31 (29–32)	0.009	1.729 (0.913–3.275)	0.093
Hematocrit arrival ICU (%)	39 (33–45)	36 (31–38)	0.007	1.203 (0.093–1.458)	0.058
EXTEM CT (s)	94 (90–117)	100 (88–118)	0.859	N/A	N/A
EXTEM MCF (mm)	45 (41–50)	49 (45–53)	0.036	1.095 (0.919–1.305)	0.311
FIBTEM MCF (mm)	9 (6–11)	10 (6–12)	0.080	N/A	N/A
International normalized ratio	1.5 (1.4–1.6)	1.3 (1.2–1.4)	0.001	$43 \cdot 10^3$ ($15 - 1 \cdot 10^8$)	0.009
aPTT (s)	37 (35–39)	32 (31–37)	0.001	1.141 (0.925–1.408)	0.219
Platelet count (x1,000 Cells μl^{-1})	104 (80–122)	120 (92–150)	0.057	N/A	N/A
Fibrinogen (mg dL^{-1})	150 (126–172)	186 (156–215)	0.001	0.961 (0.929–0.994)	0.021

SB: severe bleeding; RACHS-1: Risk Adjusted classification for Congenital Heart Surgery; CPB: cardiopulmonary bypass; ICU: intensive care unit; CT: clotting time; MCF: maximum clot firmness; N/A: not applicable; aPTT: activated partial thromboplastin time.
Data are number (percentage) or median (interquartile range).

low preoperative fibrinogen levels (p = 0.001) and a lower HCT on CPB (p = 0.032). In Table 4 their transfusion needs and general outcome are reported. Patients with a fibrinogen level <150 mg dL^{-1} at the arrival in ICU required significantly more FFP and total allogeneic blood products in the following 24 h. Moreover, they had higher peak values of serum bilirubin. The differences in general outcome are negligible or in favour of the group with fibrinogen levels ⩾150 mg dL^{-1}, without reaching statistical significance.

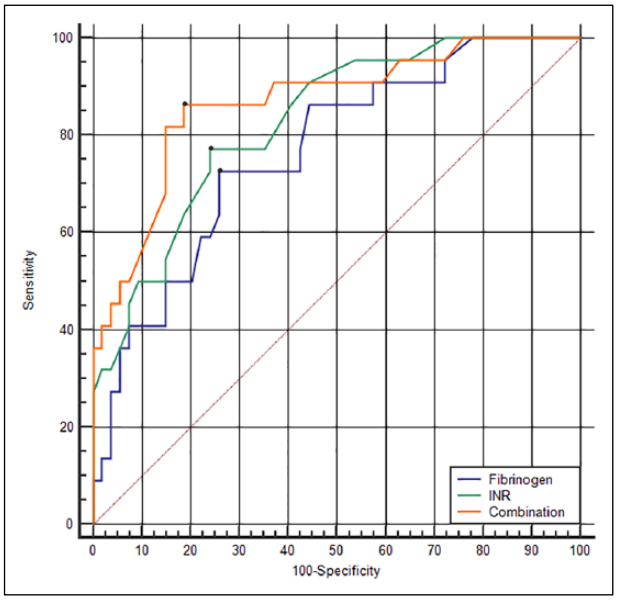

Figure 2. Receiver operating characteristics analysis for severe bleeding prediction based on postoperative fibrinogen levels, international normalized ratio (INR) and the combination of the two.

Post hoc analysis

This analysis includes patients receiving fibrinogen concentrate before arriving in the ICU (10 subjects), for a total sample size of 87 patients. The median dose was 35 mg kg^{-1} (interquartile range = 30-64 mg kg^{-1}). When including these patients, the fibrinogen levels at the arrival in the ICU were 176 mg dL^{-1} (interquartile range = 151-209 mg dL^{-1}), the 24-h chest drain blood loss was 22 ml kg^{-1} (interquartile range = 16-36 ml kg^{-1}) and the SB events were 28 (32.2%). The AUC for SB at the ROC analysis was 0.725, and the best cut-off value was identified at a fibrinogen level of 143 mg dL^{-1}, with an NPV of 73.6% and a PPV of 60%.

Discussion

The main findings of our study are (1) fibrinogen levels after cardiac surgery in children weighing <10 kg are associated with postoperative chest drain blood loss and SB, after correction for the INR and other confounders; (2) a postoperative fibrinogen level <150 mg dL^{-1} is predictive of SB with a PPV of 60% and (3) patients with fibrinogen levels below this value at the arrival in the ICU showed a greater need for FFP transfusions. They actually showed a higher peak serum bilirubin value, probably as a consequence of the larger volumes of RBCs administered.

According to our knowledge, this is the only prospective study describing the association between fibrinogen levels and postoperative bleeding after cardiac surgery performed on children <10 kg. Vida et al.[16] found an inverse linear association between preoperative MCF FIBTEM and postoperative fibrinogen administration

Table 4. Transfusion needs and general outcome of patients reaching the ICU with fibrinogen levels <150 mg dL^{-1} or ⩾150 mg dL^{-1}.

Outcome variable	Fibrinogen levels		p
	<150 mg dL^{-1} (N = 18)	⩾150 mg dL^{-1} (N = 59)	
Blood loss (ml 24h^{-1})	33 (20–60)	19.5 (15–29)	0.001
Transfusions			
RBC (ml kg^{-1})	15.1 (9.8–22.3)	11.5 (0–18.5)	0.073
FFP (ml kg-1)	**7.1 (0–18.6)**	**0 (0–5.7)**	**0.028**
PC (ml kg^{-1})	0 (0–0)	0 (0–0)	0.735
Total (ml kg^{-1})	**22.4 (12.4–37.7)**	**14.3 (6.9–23.4)**	**0.021**
Mechanical ventilation (h)	52 (19–86)	37 (17–91)	0.599
ICU stay (days)	5.5 (3.5–8.5)	4.0 (2–8.2)	0.243
Peak serum creatinine (mg dL^{-1})	0.57 (0.23)	0.58 (0.37)	0.907
Peak serum bilirubin (mg dL^{-1})	**1.62 (1.95)**	**0.86 (0.50)**	**0.009**
Low cardiac output	10 (55.6)	31 (53.4)	0.875
Bloodstream infection	1 (5.6)	1 (1.7)	0.420
In-hospital mortality	1 (5.6)	0 (0)	0.237

ICU: intensive care unit; RBC: red blood Cells; FFP: fresh frozen plasma; PC: platelet concentrate.
Data are mean (standard deviation), median (interquartile range) and number (proportion).
Note. Boldfaced values in the table highlights statistically significant associations.

on patients aged <16 years. MCF FIBTEM ≤9 mm after protamine administration was associated with an increased postoperative blood loss during the first 24 h. Faraoni et al.[15] retrospectively analysed a cohort of 191 consecutive children aged <45 months undergoing cardiac surgery with CPB. A statistically significant difference between bleeders and non-bleeders was found for INR, aPTT, PT and plasma fibrinogen concentration 10 min after protamine and on admission to ICU. A cut-off value of 150 mg $dL^{-1}$for plasma fibrinogen concentration and a 3 mm MCF on FIBTEM predicted a significant postoperative bleeding. These results are consistent with our findings.

In general, our results confirm the multifactorial nature of postoperative bleeding in cardiac surgery. At a univariate approach, many factors (patient-related, procedure-related, and hemostasis-related) are associated with SB. However, many of these factors are clearly inter-correlated (i.e. age and weight, RACHS-1 and CPB duration) but, when analyzed, only weight, and postoperative INR and fibrinogen levels appear independent predictors of SB.

Our study was focused on postoperative fibrinogen levels, and fibrinogen concentration at the arrival in ICU was independently correlated with postoperative bleeding and SB.

Factors associated with low (<150 mg dL^{-1}) levels of fibrinogen at the arrival in the ICU were patient-related (low weight and low preoperative fibrinogen levels) and CPB-related (low values of haematocrit on CPB). It is reasonable to hypothesize that the main determinant of hypofibrinogenemia at the arrival in the ICU is a larger hemodilution (in low weight patients, with lower values of haematocrit on CPB), especially in those who reached the operating theatre with low levels of fibrinogen. Together with fibrinogen, the INR at the arrival in ICU is associated with augmented chest drain blood loss and SB. A combined model, inclusive of both fibrinogen levels and INR, increased the discrimination for SB up to an AUC of 0.867. Therefore, both these parameters should be clinically considered when assessing the risk of SB. The discrimination power of a model inclusive of fibrinogen levels and INR was significantly higher than for fibrinogen alone. A prolonged INR after CPB is considered a marker of soluble coagulation factors consumption and dilution. Low fibrinogen levels are generally attributed to the same mechanism.

Platelet count is not associated with postoperative bleeding in our series; however, platelets transfusions were often intraoperatively (post-protamine) administered, and therefore low platelet count at the arrival in the ICU was relatively rare. The overall scenario appears suggestive for a coagulopathy characterized by intraoperative dilution (of both fibrinogen and soluble coagulation factors) and consumption (mainly of soluble coagulation factors) due to the extensive amount of thrombin that, despite heparin, is formed during CPB. Overall, the analysis of the squared correlation coefficients again confirms the multifactorial nature of bleeding, with fibrinogen levels responsible for 21% only of the chest drain blood loss variations, with the remaining 79% that depends on other factors.

This finding generates the hypothesis that small children may benefit from fibrinogen and/or prothrombin complex concentrate supplementation after CPB. For fibrinogen supplementation after CPB, this may be considered especially in patients having low preoperative fibrinogen levels (i.e. <200 mg dL^{-1}), who are the most susceptible to reach the ICU with values <150 mg dL^{-1}. In our series, prothrombin complex concentrate was never used, and exploring this option is outside the purposes of the present study.

Fibrinogen supplementation was addressed by previous studies but not limited to low-weight children. Galas et al.[17] compared fibrinogen concentrate with cryoprecipitate as first-line therapy for post-bypass bleeding. They demonstrated that fibrinogen concentrate administered intraoperatively is as safe and effective as cryoprecipitate in the management of bleeding in this group of patients. Our study suggests that fibrinogen supplementation should be addressed when a severe deficiency of fibrinogen is detected. Trigger points for fibrinogen supplementation can be discussed, and further studies would probably implement a more evidence-based approach. According to our data, a fibrinogen <150 mg dL^{-1} gives a 60% PPV for SB, whereas a value <100 mg dL^{-1}carries a 92% PPV for SB and should prompt fibrinogen supplementation.

Due to the relatively small sample size, we could not see statistically significant differences in the general outcome of patients with fibrinogen levels below or above the identified cut-off value of 150 mg dL^{-1}. However, the significant higher rate of FFP transfusions is representative of the clinical need for controlling bleeding and intravascular volume. There was only a trend towards a larger use of RBCs in patients with low fibrinogen levels; this probably justifies the higher serum bilirubin levels.

There are limitations in our study. We excluded from our analysis patients receiving the fibrinogen concentrate within the first 24 h after the arrival in ICU. These patients certainly presented low fibrinogen levels and might have better described the association between bleeding and fibrinogen levels for lower concentrations but the fact the they received fibrinogen and a consequent correction of their deficiency would have given a strong confounding effect. In addition, we cannot exclude that other non-measured factors may have contributed to the multifactorial nature of bleeding.

As for all the studies taking account of the postoperative drain loss, we are aware that this data might be confounded

by the presence of a quote of non-hematic fluid in the chest drain reservoir. Finally, our results are based on the application of an institutional point-of-care based algorithm for the treatment of postoperative bleeding. Therefore, the results may not be generalizable to other institutions.

In conclusion, we demonstrated a correlation between postoperative fibrinogen concentration and postoperative bleeding. This result generates the hypothesis that fibrinogen levels might represent a central target for replacement therapy. However, given the multifactorial nature of bleeding, a policy based on fibrinogen supplementation alone is not likely to be successful. At the same time, we recognize that there are patients with low fibrinogen levels who actually did not excessively bleed. Further randomized controlled trials should explore the supplementation of either fibrinogen concentrate, FFP or cryoprecipitate when fibrinogen is reduced.

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