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Original Article

Combined Use of Rotational Thromboelastometry (Rotem) and Platelet Impedance Aggregometry (Multiplate Analyzer) in Cyanotic and Acyanotic Infants and Children Undergoing Cardiac Surgery With Cardiopulmonary Bypass: Subgroup Analysis of a Randomized Clinical Trial

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Objectives: Few studies have investigated the Multiplate platelet function analyzer in pediatrics. The authors evaluated Multiplate combined with Rotem in terms of guiding platelet transfusion after pediatric cardiac surgery with cardiopulmonary bypass (CPB). The authors further compared coagulation parameters between cyanotic and acyanotic patients.

Design: Subgroup analysis of a randomized clinical trial.

Setting: Tertiary hospital.

Participants: Patients weighing between seven and 15 kg.

Interventions: None.

Measurements and Main Results: Rotem and Multiplate tests were performed (1) after anesthesia induction, (2) upon CPB separation, and (3) upon intensive care unit arrival. Among a total of 59 subjects, 9 patients required platelet transfusion. In multivariate linear regression, analysis EXTEM maximum clot firmness upon CPB separation was associated with the volume of transfused platelets (regression coefficient = −0.348 [95% confidence interval −1.006 to −0.028]; p = 0.039). No such association was found for the Multiplate test. Acyanotic and cyanotic heart disease were present in 32 and 27 children, respectively. There were no significant differences between these two groups in terms of platelet count and function. Postoperative blood loss was significantly higher in the cyanotic group compared with the acyanotic arm (p = 0.015; difference [95% confidence interval −2.40 {−4.20 to −0.60}]). There were no differences between groups regarding transfusion of allogeneic blood products.

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Conclusions: This study showed that Rotem, but not Multiplate results, were associated with platelet transfusion in pediatric cardiac surgery with no intake of platelet inhibitors. The usefulness of combining these tests in platelet transfusion decision-making needs to be evaluated in larger populations.

Key Words: pediatric cardiac surgery; cyanotic heart disease; platelet function; Rotem; Multiplate; cardiopulmonary bypass

DESPITE MODERN surgical and cardiopulmonary bypass (CPB) techniques, infants, and children undergoing cardiac surgery are at high risk of postoperative bleeding and often need transfusion of hemostatic factors.[1] The risk of postoperative bleeding and transfusion of allogeneic blood products has been shown to be higher in patients with cyanotic heart disease compared with those with acyanotic disease.[2,3] The use of whole-blood rotational thromboelastometry, Rotem, demonstrated to be efficacious in reducing postoperative blood loss and transfusion of allogeneic blood products in pediatric cardiac surgery.[4-6] The point-of-care (POC) test Multiplate is a whole-blood platelet function analyzer based on impedance aggregometry. It uses different tests, providing comprehensive information on platelet function and antiplatelet therapy. It is, therefore, routinely used in adults treated with platelet inhibitors.[7] Only few studies in pediatric cardiac surgery have evaluated the Multiplate test alone[8-11] or in combination with the Rotem.[12,13] It is, therefore, not clear if in pediatric cardiac surgery, and, thus, in patients not taking any antiplatelet therapy, the association of Multiplate with the POC test Rotem can be useful in the treatment of bleeding. The authors investigated this in a group of infants and children undergoing surgery with CPB. The authors further analyzed if there were any differences between cyanotic and acyanotic patients regarding POC coagulation parameters, postoperative bleeding, and transfusion of platelet concentrates. The following two specific aims were established: (1) to determine whether the Multiplate test performed after weaning from CPB and performed at the pediatric intensive care unit (PICU) arrival is associated with perioperative transfusion of platelet concentrates taking into account the EXTEM maximum clot firmness (MCF) of Rotem, which a priori provides information regarding the platelet count; and (2) to compare POC hemostatic parameters and, more specifically, platelet count and function between cyanotic and acyanotic children.

Methods

This was a subgroup analysis of a previously published study.[14] All the patients included in the original trial were included for this subgroup analysis. The study was approved by Comité d'Ethique Hospitalo-Facultaire Saint Luc of Université Catholique de Louvain on September 7, 2015 (2015/20AOUT/449). The study was registered before patient enrolment by the Principal Investigator (M.M.) at ClinicalTrials.gov (NCT02567786) on September 29, 2015. Written parental informed consent was obtained for all children. This work has been carried out in accordance with the Declaration of Helsinki.

Study Protocol

Detailed description of the study protocol is described elsewhere.[14] The initial study was a parallel arm, double-blinded study including patients weighing between seven and 15 kg randomly assigned to a CPB priming with 15 mL/kg of Plasmalyte or 15 mL/kg of fresh frozen plasma (FFP) in addition to a predefined amount of packed red blood cells in all patients. Nonpulsatile normothermic (core temperature, 36°C) CPB routinely was performed in all children except in few cases which moderate hypothermia (core temperature, 32°C) was performed at surgical request. Postoperative bleeding was defined as blood loss in the first six hours after PICU arrival tracked by chest tubes. Transfusion of allogeneic blood products was recorded in the intraoperative period and up to six hours after PICU arrival. Tranexamic acid was administered in all patients at a total intraoperative dose of 30 mg/kg (15 mg/kg after the induction of anesthesia and 15 mg/kg in the pump prime). The definition of cyanotic heart disease was based on the pathophysiology of the lesion.

Blood Analyses

Routine hematologic and coagulation tests were performed the day before surgery. The whole-blood tests Rotem (TEM International, Germany) and Multiplate (Dynabyte, Germany) were performed via the indwelling arterial catheter, which was inserted after the induction of anesthesia. Blood analyses were performed at three different time points: (1) after the induction of anesthesia but before surgical incision, (2) upon CPB separation, and (3) upon arrival at the PICU. As described in the original manuscript, tissue-factor activated Rotem tests, with and without addition of Cytochalasin D (EXTEM and FIBTEM tests), were used. The Rotem parameters measured included the clotting time, clot formation time, MCF, and maximum of lysis for the EXTEM test, and MCF for the FIBTEM test. The normal values for infants and children were used as a reference range.[15] For the Multiplate test, the following agonists were used: the adenosine diphosphate (ADP test), the arachidonic acid (ASPI test), and the thrombin receptor-activating peptide (TRAP test). The Multiplate analyzer is based on impedance aggregometry, which assumes that platelets expose receptors on their surface when they get activated, allowing them to aggregate. The instrument used to perform

the Multiplate test detects the change in impedance and this impedance change is expressed in aggregation units and plotted against time. A regression analysis, including different variables, was performed to test if the Multiplate test results were associated with perioperative transfusion of platelet concentrates.

All POC tests were analyzed by dedicated personnel at the Blood Bank of the hospital within five-to -15 minutes after blood sampling. The Rotem tests were run for at least 45 minutes. At the moment of weaning from CPB, in addition to Rotem and Multiplate tests, a platelet count was performed. The POC test results were available to the anesthesiologists and to the intensive care unit physicians caring for the patients. An internal algorithm (Fig 1) was used to help physicians in choosing the adequate hemostatic factors, as previously described.[14] Information from the Multiplate test was associated with the Rotem results. In case the EXTEM MCF was <43 mm, the FIBTEM MCF was checked. In the presence of clinical bleeding, whenever the FIBTEM MCF was >6 mm and the Multiplate tests showed abnormalities, platelets were transfused. However, knowing that the platelet aggregation measured with the Multiplate is substantially influenced by platelet count,[16] and in the absence of any reference values in children with congenital heart disease, no specific pediatric cut-off values were used for the Multiplate test in this study. The decision to transfuse children after weaning from CPB and in the postoperative period was a clinical decision and only guided by the POC tests in order to choose the adequate hemostatic factors necessary to stop bleeding. If there were signs of clinical bleeding in the operating room or there was postoperative bleeding of more than 5 mL/kg/h and the POC tests showed abnormalities, the patient was transfused. Whenever the POC tests showed abnormalities but there was no clinical bleeding, the patient was not transfused. In cases of severe clinical bleeding in which the POC tests were within normal range, surgical revision was considered.

Statistical Analysis

No power analysis was performed for the purposes of this subgroup analysis. The study was considered exploratory. The Kolgomorov-Smirnov test was used to check the normality of the data. The categorical data were presented as numbers and percentages. Continuous variables were presented as mean ± standard deviation or medians (25th percentile, 75th percentile) depending on whether they were normally distributed or not. Univariate and multivariate linear regression analyses were used to predict the volume of transfused platelets. As only a few children were transfused with platelet concentrates, the amount of transfused platelets was taken into consideration for the regression analysis. A Pearson χ^2 test or Fisher's exact test was used to compare categorical variables between the cyanotic and acyanotic groups. A Mann-Whitney U test or an independent t test was used to compare continuous variables between the cyanotic and acyanotic groups for nonparametric and parametric data, respectively. Repeated measure analysis of variance, with a between-subjects factor (cyanotic *v* acyanotic patients), was performed to evaluate time-related changes in POC tests that showed a normal distribution. Confidence intervals for median differences were calculated using Hodges-Lehmann estimates. Any p value of <0.05 was considered significant. The statistical analyses were performed using IBM SPSS Statistics version 25, and SAS version 9.4.

Results

In total, 59 patients were included and analyzed for the purposes of this study. Nine (15%) patients were transfused with

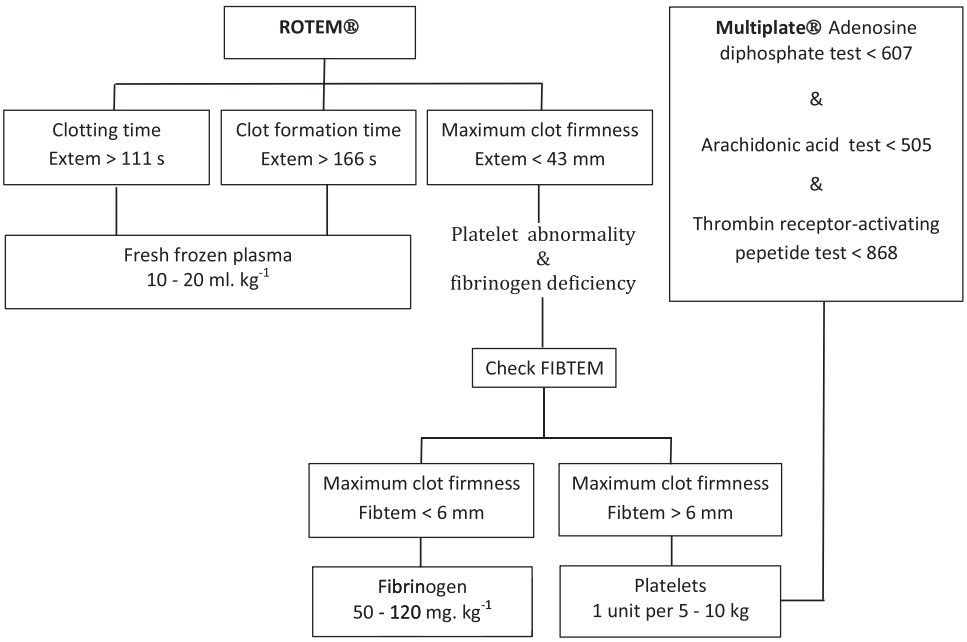

Fig 1. Point-of-care test guided algorithm for transfusion of hemostatic factors in case of clinical bleeding.

platelet concentrates at any moment intraoperatively and/or up to six hours postoperatively. Among these nine children, two showed normal EXTEM MCF values together with a mild platelet dysfunction based on a pathologic ADP test; four children showed low EXTEM MCF values and severe abnormalities of the three Multiplate tests; and three patients had normal EXTEM MCF values but severe platelet dysfunction as demonstrated by the three Multiplate tests. Table 1 illustrates univariate linear regression analysis associating platelet transfusion (mL/kg) for the entire study cohort with specific POC test results (obtained at the end of CPB and at PICU arrival) and other study variables. As shown in Table 1 the EXTEM MCF, the ADP test, the ASPI test, and the TRAP test results performed upon weaning from CPB were significantly associated with the volume of transfused platelets. The EXTEM MCF and the three Multiplate tests performed at PICU arrival showed, paradoxically, a positive standardized regression coefficient when associated with transfusion of platelet concentrates and thus, were not taken into account in the multivariate linear regression analysis. The duration of CPB and the platelet count upon weaning from CPB were, in univariate regression analysis, significantly associated with transfusion of platelet concentrates as well (Table 1). A multivariate linear regression analysis was performed to associate different variables with the volume of transfused platelets. Variables that were statistically significant in the univariate analysis were considered in the multivariate regression analysis. As all the Multiplate tests significantly decreased with reduced platelet count, only one Multiplate test was used at a time in order to avoid any collinearity among the three Multiplate tests. The results of this multivariate linear regression analysis with the TRAP test are presented in Table 2. The model was statistically significant as follows: $F(4, 54) = 8{,}734$; $p < 0.001$. The adjusted R square was 0.348, indicating that 34.8% of the variations in platelet transfusion were explained by the predictors. The Variance Inflating factors were as follows: 1.151 for CPB time, 2.400 for EXTEM MCF, 2.074 for TRAP test, and 2.528 for platelet count upon weaning from CPB. The EXTEM MCF at the end of CPB was significantly associated with the amount of transfused platelets ($p = 0.039$) (Table 2). The platelet count and the TRAP test, upon weaning from CPB, were not associated with the volume of transfused platelets. As shown in Table 2 the duration of CPB instead significantly was associated statistically with the amount of transfused platelets ($p < 0.001$). The results of this multivariate linear regression analysis were similar when the ASPI test or the ADP test was analyzed. Table 3 shows the POC test results at the moment of CPB separation between patients who were transfused with platelets and those who did not receive any platelet transfusion. Most of the EXTEM results were abnormal in children who had required platelet transfusion. The Multiplate test results were significantly lower in children who received platelet transfusion.

Table 1
Univariate Linear Regression Analysis Associating Point-of-Care Tests and Other Study Variables With Volume of Transfused Platelets

	Transfused Platelets (mL/kg)	
	Standard Regression Coefficient	p Value
Preoperative platelet count	0.024	0.858
Preoperative fibrinogen	−0.299	0.046
Groupe allocation CPB priming (FFP *v* crystalloids)	0.196	0.138
CPB time	0.563	<0.001
Platelet count upon weaning CPB	−0.270	0.038
FIBTEM MCF upon weaning CPB	−0.161	0.223
EXTEM MCF upon weaning CPB	−0.425	0.001
Multiplate ADP test upon weaning CPB	−0.269	0.039
Multiplate ASPI test upon weaning CPB	−0.348	0.007
Multiplate TRAP test upon weaning CPB	−0.314	0.016
Platelet count PICU arrival	0.227	0.084
FIBTEM MCF PICU arrival	0.127	0.352
EXTEM MCF PICU arrival	0.382	0.004
Multiplate ADP test PICU arrival	0.342	0.009
Multiplate ASPI test PICU arrival	0.331	0.012
Multiplate TRAP test PICU arrival	0.451	< 0.001

Abbreviations: ADP, adenosine diphosphate; ASPI, arachidonic acid; CPB, cardiopulmonary bypass; FFP, fresh frozen plasma; MCF, maximum clot firmness; PICU, pediatric intensive care unit; TRAP, thrombin receptor-activating peptide.

There were 32 and 27 children in the acyanotic and cyanotic groups, respectively. The characteristics and perioperative data of both groups are represented in Table 4. Fourteen (52%) patients in the cyanotic group and six (19%) patients in the acyanotic group underwent a repeat surgery ($p = 0.007$). Fourteen (52%) patients in the cyanotic arm and 16 (50%) subjects in the acyanotic group were allocated to a priming strategy based on FFP ($p = 0.887$), as was planned for the initial trial. Fifteen (56%) cyanotic patients were on chronic aspirin therapy that was discontinued at least seven days before surgery. The duration of CPB was significantly longer in children with cyanotic heart disease (162 ± 68 *v* 123 ± 66; $p = 0.026$). Otherwise, the median time between the end of CPB and chest closure was 62 minutes (47, 74) in cyanotic patients versus 46 minutes (39, 52) in acyanotic children ($p = 0.008$), indirectly indicating that intraoperative bleeding was more important in the cyanotic group.

Table 5 shows the Rotem test results for cyanotic and acyanotic children. Cyanotic patients showed, in general, statistically significantly disturbed Rotem test results, but this difference was not consistent over time. The EXTEM maximum lysis (%) test was significantly lower in the cyanotic group compared with acyanotic patients at both weaning from CPB (3 [1, 7] *v* 7 [5, 11]; $p = 0.007$) and at PICU arrival (3 [2, 6] *v* 8 [3, 11]; $p = 0.007$). In total, 40 children did not receive any allogeneic blood products (CPB priming not included)

Table 2
Multivariate Linear Regression Analysis Predicting the Administered Volume of Platelets

Variables	Standardized Coefficient B	t	p	95% CI (Lower, Upper)
Constant		1.478	0.145	−5.485 to 36.254
CPB time	0.482	4.235	< 0.001	0.043-0.121
Platelet count upon weaning CPB	0.076	0.451	0.654	−0.044 to 0.070
EXTEM MCF upon weaning CPB	−0.348	−2.119	0.039	−1.006 to −0.028
Multiplate TRAP test upon weaning CPB	0.020	0.128	0.899	−0.006 to 0.007

Abbreviations: CPB, cardiopulmonary bypass; MCF, maximum clot firmness; TRAP, thrombin receptor-activating peptide.

Table 3
Point-Of-Care Test Results Obtained at Cardiopulmonary Bypass Separation in Patients Having Required or Not Any Platelet Transfusion

Variables	Patients Not Transfused With Platelets (N = 50)	Patients Transfused With Platelets (N = 9)	p
EXTEM clotting time (s)	82 (77, 94)	90 (87, 104)	0.187
EXTEM clot formation time (s)	157 (122, 206)	217 (168, 326)	0.008
EXTEM maximum clot firmness (mm)	50 (46, 57)	43 (37, 50)	0.009
EXTEM maximum lysis (%)	7 (3, 10)	1 (1, 2)	0.003
FIBTEM maximum clot firmness (mm)	9 (7, 12)	7 (5, 8)	0.067
Multiplate ADP test (AU)	340 (168, 456)	110 (70, 263)	0.009
Multiplate ASPI test (AU)	804 (508, 1,290)	185 (96, 541)	0.001
Multiplate TRAP test (AU)	893 (518, 1,283)	412 (214, 520)	0.018

NOTE. All continuous variables are expressed as median (25th percentile, 75th percentile).
Abbreviations: AU, aggregation Units; ADP, adenosine diphosphate; ASPI, arachidonic acid; TRAP, thrombin receptor-activating peptide.

despite the fact that all patients showed various degrees of abnormality in their POC test results.

Table 6 shows the results of the repeated measure analysis of variance for POC tests evaluating platelet count and platelet function. As expected, platelet count and function showed significant deterioration after CPB. No statistically significant differences could be found for any of these tests between the cyanotic and acyanotic children at different time points.

Median postoperative blood loss was 8.1 (5.7-9.7) mL/kg in the cyanotic group and 5.6 (3.1-8.4) mL/kg in the acyanotic patients (p = 0.015; difference 95% confidence interval [CI] −2.40 [−4.20 to −0.60]) (Table 7). Seven (26%) patients in the cyanotic arm received platelets at any moment in the intraoperative or postoperative period compared with two (6%) in the acyanotic group (odds ratio [95% CI]: 5.25 [0.99-27.90]; p = 0.036). There were no statistically significant differences between the cyanotic and acyanotic patients regarding the transfusion of platelet concentrates, red blood cells, and FFP.

Discussion

The results of this study showed that when coming off CPB, the EXTEM MCF of Rotem was significantly associated with perioperative platelet transfusion in pediatric cardiac surgery. No such association could be found between the Multiplate test results and platelet transfusion. Indeed, the combination of Rotem and Multiplate in patients without platelet function inhibitor is questionable. Different studies in pediatric cardiac surgery have assessed the Multiplate platelet function analyzer.[8-13] However, this study was the first to investigate whether the Multiplate should be added to the Rotem test, as in all the other studies either the Multiplate test was not analyzed together with Rotem [8-11] or its use was not associated with any clinical outcome.[10,12,13] The authors results were in line with observations made by others.[8,11] Romlin et al. showed that prevalence of any transfusion was higher in case the three Multiplate tests were ≤30 U. However, they did not specifically separately evaluate transfusion of platelets.[10] In any case, despite the authors' observed postoperative platelet dysfunction and thrombocytopenia, only nine (15%) children received perioperative platelet transfusion and the POC test results of these nine patients showed variable abnormalities. This is an important point to consider in future studies showing the usefulness of the Multiplate analyzer in children not taking any platelet inhibitors.

The authors' findings need to be interpreted taking into account that these POC tests were used to guide transfusion. The authors, indeed, used an algorithm based on Rotem and Multiplate to transfuse platelets, but platelets only were administered in case there was clinical bleeding associated with POC test abnormalities.

In this study, the authors further investigated the POC hemostatic parameters and, more specifically, the platelet count and function in a specific group of cyanotic and acyanotic infants and children. The authors' results did not show any statistically significant differences in platelet function and number between cyanotic and acyanotic children. These observations held true before CPB, as well as after surgery, and were in line with other studies evaluating the platelet function with the Multiplate analyzer.[11,12] However, studies analyzing platelet number and function in cyanotic versus acyanotic children[8,11,12] and in cyanotic adults[17] still report conflicting

Table 4
Patients' Characteristics and Perioperative Data

Variables	Cyanotic (N = 27)	Acyanotic (N = 32)	p
Age, mo	23 (13, 37)	17 (12, 33)	0.642
Weight, kg	10.9 ± 2.7	10.1 ± 2.4	0.233
Male/Female, No (%)	19 (70)/8 (30)	16 (50)/16 (50)	0.113
Preoperative hemoglobin (g/dL)	16.0 (14.0, 16.7)	11.9 (11.2, 12.5)	<0.001
Preoperative fibrinogen (mg/dL)	330 ± 79	339 ± 75	0.704
Preoperative activated partial thromboplastin time (s)	31.4 ± 3.7	32.5 ± 5.0	0.331
Preoperative prothrombin time (s)	12.5 ± 0.9	12.3 ± 1.1	0.357
Preoperative international normalized ratio	1.10 ± 0.08	1.08 ± 0.09	0.413
Risk adjustment for congenital heart surgery - 1 category			
No (%)			
1	0	3	0.243
2	13	17	0.703
3	12	11	0.429
4	1	1	>0.999
5	0	0	>0.999
6	1	0	0.458
Type of surgery			
Ventricular septal defect repair	0	4	
Atrial septal defect repair	0	3	
Ventricular septal defect + aortic valve repair	0	2	
Atrial septal defect + other	0	3	
Ventricular septal defect + atrial septal defect	0	1	
Atrioventricular septal defect repair	0	6	
Bidirectional cavopulmonary anastomosis	4	0	
Fontan procedure	8	0	
Subaortic membrane resection	0	3	
Tetralogy of Fallot repair	8	1	
Pulmonary homograft + other	2	1	
Pulmonary venous stenosis repair	0	1	
Mitral valve repair	0	1	
Aortic valve repair	0	3	
Pulmonary atresia repair	1	0	
Damus-Kaye-Stansel procedure	1	0	
Double switch procedure	0	1	
Kawashima procedure	1	0	
''Réparation à l'étage ventriculaire'' procedure	1	0	
Tetralogy of Fallot + total anomalous pulmonary venous return	1	0	
Cor triatriatum repair	0	1	
Aortic valve repair + aortoplasty	0	1	
Redo surgery, No (%)	14 (52)	6 (19)	0.007
Priming CPB with FFP	14 (52)	16 (50)	0.887
CPB time, min	162 ± 68	123 ± 66	0.026
Hypothermic CPB, No (%)	5 (19)	3 (9)	0.307
Time between end of CPB and chest closure, min	62 (47, 74)	46 (39, 52)	0.008
PICU stay (d)	4 (4, 5)	3 (2, 4)	0.010
Hospital stay (d)	14 (11, 20)	12 (10, 13)	0.176
Thromboembolic events, No (%)	0	3 (9)	0.243

NOTE. All continuous variables are expressed as numbers (percentage), median (25th percentile, 75th percentile) or mean ± SD.
Abbreviations: CPB, cardiopulmonary bypass; FFP, fresh frozen plasma; PICU, pediatric intensive care unit; SD, standard deviation.

Table 5
Perioperative Rotem Test Results

Variables	Cyanotic (N = 27)	Acyanotic (N = 32)	p
EXTEM clotting time (s)			
- Postanesthesia induction	70 ± 10	65 ± 7	0.041
- Upon weaning CPB	89 ± 17	84 ± 14	0.203
- Upon PICU arrival	78 ± 10	71 ± 11	0.024
EXTEM clot formation time (s)			
- Postanesthesia induction	97 ± 34	81 ± 26	0.039
- Upon weaning CPB	180 (146, 215)	156 (101, 215)	0.155
- Upon PICU arrival	180 (136, 231)	138 (99, 180)	0.015
EXTEM maximum lysis (%)			
- Postanesthesia induction	10 (8, 13)	12 (9, 14)	0.079
- Upon weaning CPB	3 (1, 7)	7 (5, 11)	0.007
- Upon PICU arrival	3 (2, 6)	8 (3, 11)	0.007
FIBTEM maximum clot firmness (mm)			
- Postanesthesia induction	12 (10, 14)	15 (11, 18)	0.046
- Upon weaning CPB	8 (7, 10)	9 (7, 13)	0.291
- Upon PICU arrival	7 (6, 10)	9 (8, 13)	0.002

NOTE. All continuous variables are expressed as median (25th percentile, 75th percentile) or mean ± SD.
Abbreviations: CPB, cardiopulmonary bypass; PICU, pediatric intensive care unit; SD, standard deviation.

Table 6
Repeated Measure Analysis of Variance for Platelet Count and for Biologic Parameters Evaluating Platelet Function

Variable	Postinduction (Time 1)	Weaning CPB (Time 2)	PICU Arrival (Time 3)	P Group	P Time and Group	P Time 1 *v* 2	P Time 1 *v* 3	P Time 2 *v* 3
Platelet count (cells x 100 μl^{-1})								
Cyanotic	331 ± 93≠	145 ± 44	163 ± 56	0.210	0.545	<0.001	<0.001	0.025
Acyanotic	345 ± 121≠	170 ± 84	192 ± 77					
EXTEM MCF (mm)								
Cyanotic	60 ± 5	49 ± 7	49 ± 7	0.069	0.335	<0.001	<0.001	0.999
Acyanotic	63 ± 6	51 ± 9	53 ± 7					
Multiplate ADP test (AU)								
Cyanotic	734 ± 177	286 ± 186	331 ± 173	0.074	0.540	<0.001	<0.001	0.999
Acyanotic	768 ± 258	379 ± 291	413 ± 239					
Multiplate ASPI test (AU)								
Cyanotic	960 ± 240	732 ± 460	677 ± 314	0.082	0.539	0.048	< 0.001	0.999
Acyanotic	1,037 ± 299	907 ± 614	831 ± 473					
Multiplate TRAP test (AU)								
Cyanotic	998 ± 224	798 ± 446	647 ± 313	0.169	0.623	0.059	<0.001	0.027
Acyanotic	1,087 ± 265	951 ± 576	695 ± 388					

NOTE. All continuous variables are expressed as mean ± SD.
Abbreviations: ADP, adenosine diphosphate; ASPI, arachidonic acid; AU, aggregation units; CPB, cardiopulmonary bypass; MCF, maximum clot firmness; PICU, pediatric intensive care unit; SD, standard deviation; TRAP, thrombin receptor-activating peptide; ≠, values obtained at baseline on the day before surgery.

Table 7
Transfusion of Allogeneic Blood Products and Postoperative Blood Loss Data

Variables	Cyanotic (N = 27)	Acyanotic (N = 32)	p	Difference (95% CI)
Postoperative blood loss (mL/kg)	8.1 (5.7, 9.7)	5.6 (3.1, 8.4)	0.015	−2.40 (−4.20 to −0.60)
Patients transfused with platelets intra- and postoperatively, No (%)	7 (26)	2 (6)	0.036	5.25* (0.99-27.90)
Volume platelets transfused intra- and postoperatively (mL/kg)	N = 7	N = 2	0.056	
Min-Max	14 (13, 16) 12-22	57 (37, 76) 37-76		
Patients transfused with FFP intra- and postoperatively, No (%)†	7 (26)	4 (13)	0.187	2.45* (0.63-9.51)
Volume FFP transfused intra- and postoperatively (mL/kg)†	N = 7	N = 4	0.527	
Min-Max	22 (8, 28) 14-43	34 (17, 52) 7-62		
Patients transfused with RBC intra- and postoperatively, No (%)†	8 (30)	9 (28)	0.899	1.08* (0.35-3.33)
Volume RBC transfused intra- and postoperatively (mL/kg)†	N = 8	N = 9	0.888	
Min-Max	33 (22, 45) 21-61	33 (21, 44) 13-96		

NOTE. All continuous variables are expressed as numbers (percentage) and median (25th percentile, 75th percentile).
Abbreviations: FFP, fresh frozen plasma; RBC, red blood cell.
* Odds ratio.
† Priming cardiopulmonary bypass not included.

results. Thrombocytopenia is a late event, occurring in the presence of severe hypoxemia and erythrocytosis.[18] It is explained by a decreased formation of megakaryocytes from stem cells due to an increased production of erythroblasts. Otherwise, a right-to-left shunt can result in a decreased production of megakaryocytes because platelets also are formed in the pulmonary circulation.[19] Chronic cyanosis has otherwise been associated with an enhanced aggregation. In an elegant study comparing 16 cyanotic children with 16 healthy children, the ratio of the urinary excretion of a thromboxane A_2 metabolite (a vasoconstrictor and promoter of platelet aggregation) to a prostacyclin metabolite (a vasodilator and inhibitor of platelet aggregation) was significantly higher in cyanotic patients compared with controls.[20] Factors, such as the severity and the duration of hypoxemia, and also chronic intake of any antiaggregation therapy, may, therefore, explain the conflicting results in the literature.

Although it has been suggested that cyanotic patients have significantly disturbed coagulation parameters compared with acyanotic patients,[2] this often has been performed with

conventional coagulation tests. In this study, cyanotic children showed significantly more disturbed Rotem parameters at different time points, but this significant difference was not constant over time. In a retrospective study, the EXTEM and FIBTEM results of cyanotic and acyanotic patients categorized to three-to-12 months showed similar differences as in the authors' trial.[21] The lower FIBTEM MCF in the authors' cyanotic arm compared with acyanotic children (12 [10, 14] *v* 15 [11, 18]; p = 0.046) was not associated with decreased baseline fibrinogen concentrations. The preoperative fibrinogen concentration was 330 ± 79 mg/dL in the authors' cyanotic children and 339 ± 75 mg/dL in the acyanotic group (p = 0.704). This observation of impaired fibrinogen function, despite its normal concentration, previously has been reported in a cohort of cyanotic patients.[22] Otherwise, a statistically significant difference was observed in maximum lysis between cyanotic and acyanotic children. However, this difference was small from a clinical point of view.

A higher number of cyanotic patients required platelet transfusion, seven (26%) versus two (6%) in acyanotic children. However, this difference was not statistically significant, as the 95% CI of the odds ratio contained the value one (odds ratio [95% CI]: 5.25 [0.99-27.90]). The administration of other allogeneic blood products was not statistically significantly higher in the cyanotic group compared with the acyanotic group. Cyanotic patients in this study more often underwent repeat surgery. Indeed, these patients more often presented a single-ventricle physiology and, therefore, underwent different stages of palliation.

This study had strengths and limitations. The authors studied a group of infants and children of similar age and weight. Postoperative blood loss and transfusion of allogeneic blood products were meticulously analyzed, as this was a subgroup analysis of a prospective trial evaluating two different CPB priming strategies. Moreover, the authors did not use hydroxyethylstarch solutions that have been shown to impair hemostatic test results.[23]

However, the results of Rotem and Multiplate were available to physicians in charge of the patients. These results were used in the decision-making algorithm when administering platelets and other hemostatic factors and may have substantially biased the authors' observations. Only a few children were transfused with platelet concentrates. Thus, larger trials need to evaluate the usefulness of the Multiplate analyzer in pediatric cardiac surgery. The authors did not calculate a power analysis for the purposes of this analysis. Differences between the cyanotic and acyanotic children therefore might have been statistically significant if a larger number of patients were included in each group, but, on the other hand, significant differences that were found could have become nonsignificant in case more patients were included. Moreover, the duration of CPB and the number of repeat surgeries were significantly higher in cyanotic children, which may have resulted in higher postoperative blood loss in cyanotic children.

In summary, this single-center study showed that the results obtained by Rotem, but not by Multiplate analyzer, were associated with platelet transfusion in pediatric cardiac surgery with no intake of platelet inhibitors. Indeed, the predictive value of platelet function monitors for postoperative bleeding or the need for platelet transfusion in patients without platelet inhibitors still is questionable.[24] Platelet function and platelet number, analyzed by Rotem and the Multiplate analyzer, were not significantly different between cyanotic and acyanotic children. Future trials including a larger population thus need to evaluate the usefulness of combining these two tests in platelet transfusion decision-making.

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Conflict of Interest

None.

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