Res Cardiovasc Med. 2017 May; 6(3):e43766. doi: 10.5812/cardiovascmed.43766.

Published online 2016 December 19. **Research Article**

# Risk Factors for the Development of Significant Postoperative Bleeding After Pediatric Cardiac Surgery with Cardiopulmonary Bypass: A Nested Case-Control Study

Isabel Znaya Ramírez-Flores,[1] Maribel Ibarra-Sarlat,[2] Vivian Neme-Bechara,[3] Alejandro Herrera-Landero,[4] Nora Patricia Victorio-Garcia,[5] and Juan Carlos Núñez-Enríquez[6,*]

[1]Department of Pediatric Intensive Care, Pediatrics Hospital, National Medical Center (The Siglo XXI), Mexican Institute of Social Security, Avenida Cuauhtémoc 330, Col. Doctores, Delegación Cuauhtémoc, 06720, Mexico City, Mexico Mexico City, Mexico
[2]Division Chief, Department of Pediatric Intensive Care, Pediatrics Hospital, National Medical Center (The Siglo XXI), Mexican Institute of Social Security, Avenida Cuauhtémoc 330, Col. Doctores, Delegación Cuauhtémoc, 06720, Mexico City, Mexico
[3]National Autonomous University of Mexico, Avenida Universidad 3000, Ciudad Universitaria, Coyoacán, 04510, Mexico City, Mexico
[4]Masters in Sciences, Traumatology and Orthopedics Hospital "Lomas Verdes" Mexican Institute of Social Security, Avenida Lomas Verdes 52, Santa Cruz Acatlán, 53150, Naucalpan de Juárez, Mexico, Mexico
[5]Faculty of Medicine of Tampico "Dr. Alberto Romo Caballero", Autonomous University of Tamaulipas, Circuito Universitario Sn, Congregación Hidalgo, 89000 Tampico, Tamaulipas, México
[6]Research Unit in Clinical Epidemiology, Pediatrics Hospital, National Medical Center (The Siglo XXI), Mexican Institute of Social Security, Avenida Cuauhtémoc 330, Col. Doctores, Delegación Cuauhtémoc, 06720, Mexico City, Mexico

[*]*Corresponding author*: Juan Carlos Núñez-Enríquez, Research Unit in Clinical Epidemiology, Pediatrics Hospital, National Medical Center (The Siglo XXI), Mexican Institute of Social Security, Avenida Cuauhtémoc 330, Col. Doctores, Delegación Cuauhtémoc, 06720, Mexico City, Mexico. Tel: + 52-5556276900, E-mail: jcarlos_nu@hotmail.com

**Received** 2016 November 16; **Accepted** 2016 December 09.

## Abstract

**Background:** Postoperative bleeding of more than 10% of circulating blood volume (CBV) within the first six hours after a cardiac surgery with cardiopulmonary bypass (CBS) is one of the most frequent complications associated with postoperative morbidity and mortality in children.
**Objectives:** This study aimed to identify specific risk factors for the development of this complication in a subpopulation of Mexican pediatric patients.
**Methods:** A nested case-control study was conducted at a tertiary level pediatric intensive care unit (PICU) of Mexico City. Cases were those children who developed bleeding of more than 10% of circulating blood volume (CBV) within the first six hours after the surgery and controls were all those children who did not presented this complication. Bivariate and logistic regression analyses were performed. A P-value less than 0.05 was considered as statistically significant.
**Results:** Results showed that 33% (n = 21) of included children developed significant bleeding in the first six hours after the cardiac surgery. The main risk factors for developing this complication were the cyanotic congenital heart disease ($P < 0.01$), bypass time exceeding 90 minutes ($P < 0.01$), aortic clamping time > 60 minutes ($P = 0.01$), intraoperative bleeding volume ($P = 0.04$), and an initial activated clotting time > 140 seconds ($P < 0.01$).
**Conclusions:** An important proportion of patients developed postoperative significant bleeding. Risk factors identified in the present study could help to identify and close monitor a subgroup of children at high risk for the development of this complication.

*Keywords:* Cardiovascular Surgery, Children, Critical Care, Hemorrhage, Risk Factors

## 1. Background

In last decades, successful achievements in surgical treatment of congenital heart diseases have been mainly due to the use of cardiopulmonary bypass (CBS). Unfortunately, the CBS is associated with postoperative bleeding in 10% of the patients which can increase rates of postoperative morbidity and mortality in these patients (1, 2).

The definition of significant postoperative blood loss is based on a calculation involving the circulating blood volume (CBV). It has been considered as clinically significant when it is observed a loss of 10% to 20% of the CBV within the first six hours after the surgery because its correlation with the need for transfusion of blood products in children and with the need of surgical re-intervention if it is not stopped (3, 4).

Postoperative blood loss can have two origins: surgical and nonsurgical. The surgical origin is related to the complexity of the intervention, surgeries performed under profound hypothermia, prolonged CBS time, young age of patients undergoing surgery, iterative surgeries and treatment of cyanotic heart disease. Also, the nonsurgical is related to 1) preexisting factors in children: diminished values of clotting factors; 2) factors in children with congenital heart disease: thrombocytopenia or problems in platelet aggregation; 3) secondary to the CBS factors: hemodilution, use of heparin and fibrinolysis (5-9).

Based on the above, children undergoing cardiac surgery with CBS are highly susceptible to develop a complex postoperative coagulopathy (7-10). Early detection would allow an opportune application of the hemostatic therapy, thus can prevent postoperative bleeding, and reduce morbidity, mortality and costs.

## 2. Objectives

In this study, we aimed to investigate the risk factors for significant postoperative bleeding after the cardiac surgery with CBS in a subpopulation of Mexican pediatric patients.

## 3. Methods

A nested case-control study was conducted in children who underwent cardiac surgery with cardiopulmonary bypass (CBS) and postoperatively attended at pediatric intensive care unit (PICU) of the pediatrics hospital at the national medical center (The Siglo XXI), Mexican Institute of Social Security, a tertiary referral hospital of Mexico City, from January 2014 to December 2014 (1-year).

### *3.1. Definitions of Cases and Controls*

- Cases: Patients undergoing cardiac surgery with CBS who had bleeding of more than 10% of the circulating blood volume during the first 6 hours after surgery.

- Controls: Patients undergoing cardiac surgery with CBS who did not have bleeding of more than 10% of the circulating blood volume during the first 6 hours after surgery.

### *3.2. Selection Criteria*

#### *3.2.1. Inclusion Criteria*

- Patients undergoing cardiac surgery with cardiopulmonary bypass (CBS);

- Any age;

- Any sex;

- Admitted to the PICU during the study period

- Abnormal postoperative bleeding (presence of bleeding of more than 10% of the circulating blood volume within the first six hours after the surgery).

### *3.3. Exclusion Criteria*

- Presence of congenital coagulopathy;

- Patients with pre-existing acquired coagulopathy [defined as a platelet count $< 100 \times 10^9$/L, activated thromboplastin time (aPTT) >45 seconds, prothrombin time (PT) < 70%, fibrinogen < 100 mg/dL];

- Patients with kidney disease (creatinine level >1.5 mg/dL and/or hemodialysis) or liver disease [aspartate aminotransferase (AST) and alanine aminotransferase (ALT) twice its normal value].

### *3.4. Elimination Criteria*

- Incomplete clinical records

### *3.5. Clinical Data Collection*

The following information was prospectively collected: sex, age, weight and height (length when appropriate) at the time of surgery, preoperative and postoperative tests, anesthetic risk (ASA score: I - VI), surgical complexity according to the RACHS-1 Classification, type of congenital heart defect, previous sternotomy, need for aortic clamping (AC) and/or circulatory arrest (CA), the time of AC and CA when applied, initial ACT (activated clotting time) in seconds, presence of profound hypothermia (less than 25°C), the time of CBS (cardiopulmonary bypass) > 90 minutes, need for reoperation after bleeding during surgery, and transfusion of blood products (plasma, erythrocyte concentrate, cryoprecipitate and/or platelets) during the surgery.

### *3.6. Ethics*

Approval number R-2014-3603-54 by the local scientific research and ethics committee was obtained.

### *3.7. Statistical Analysis*

Using SPSS version 22.0 for Windows, a descriptive analysis was performed by calculating frequencies, percentages, median and ranges for qualitative and quantitative variables, respectively. We performed a bivariate analysis using chi-square, student's t-test and Mann-Whitney U test, when appropriate. All variables with a $P < 0.05$ were introduced into a multivariate unconditional logistic regression analysis to identify independent risk factors for bleeding of more than 10% between the cases and controls. Adjusted odds ratios (aORs) and 95% confidence intervals (95% CI) were obtained.

## 4. Results

The study involved 79 pediatric patients who had undergone cardiac surgery with cardiopulmonary bypass (CBS) during study period (1-year). Seven patients were excluded, leaving 72 patients for the present analysis. Twenty-four of these patients were included as cases, and 48 patients as "non-bleeding controls". (Appendix 1 in Supplementary File)

Of the total population analyzed (n = 72), 61.1% (n = 44) were males, with a median age of 19 months (range = 2 - 105 months) at the time of the surgery. As to the nutritional state, 58.3% (n = 42) had some degree of malnutrition, calculated according to the CDC tables of 2000. Likewise, ASA classification information was gathered, which was determined by the anesthesiologist during the presurgical evaluation. It was observed that 69.4% (n = 50) of the patients were class III ASA (Table 1).

Congenital cyanotic heart diseases represented 52.8% (n = 38) of the cases, whereas congenital acyanotic heart diseases were 47.2% (n = 34) (Table 1), with a median presurgical oxygen saturation of 90% (range = 26% - 100%) (Table 2). The most frequent congenital heart disease was ventricular septal defect, with a 34.7% (n = 25) frequency, followed by tetralogy of Fallot with a 19.4% (n = 14) frequency (Table 3).

Moreover, according to surgical complexity based on the risk adjusted classification for congenital heart surgery (RACHS-1), 79.2% (n = 57) of the patients underwent a RACHS-1 class 2 procedure (Table 1).

In terms of the surgical procedure, the CBS median time was found to be 100 minutes (range= 44-223 minutes), with a time longer than 90 minutes in 62.5% of the cases. Of the total patients, 90.3% (n = 65) underwent AC with a median time of 46.5 minutes (range= 0-123 minutes), and a time longer than 60 minutes was observed in 37.5% (n = 27) of the cases. Only 8.3% (n= 6) went into circulatory arrest (CA) with a maximum time of 57 minutes. The minimum median rectal temperature during perfusion was 26°C (range = 16.4-35.3°C), and 29.2% (n = 21) of the patients had profound hypothermia with temperatures less than 25°C. The surgery duration was also reviewed and had a median time of 257.7 minutes (range = 90 - 480 minutes). The median time of surgical wound closure at the end of CBS was 60 minutes with a maximum time of 7200 minutes, which corresponds to a late closure of the sternotomy, performed days after the surgical procedure. Trans-surgical bleeding was also recorded and the median volume was 110 mL (14.7 mL/kg) (range = 15 - 1430 mL). In terms of the ACT measured during CBS, the median initial value was 137 seconds (range = 104 - 213 seconds) and the median final value was 140 seconds (range = 110 - 195 seconds). The difference between both values was expressed as a percentage, and the median value was 2.2% (range = 0% - 50.4%). Also, 44.4% (n = 32) of the patients had an initial ACT > 140 seconds (Tables 1 and 2).

Regarding the anesthetic procedure, it was observed that 98.6% of the patients (n = 71) received blood products transfusion at the end of the CBS; 94.4% (n = 68) received erythrocyte concentrate, 63.9% (n = 46) received fresh frozen plasma (FFP), 80.6% (n = 58) received cryoprecipitates, and 75% (n = 54) received platelet concentrates (Table 1).

During the study, 33.3% (n = 24) of the patients suffered from postsurgical bleeding greater that 10% of the circulating blood volume within the first 6 hours after being admitted to the pediatric ICU. The median bleeding range was 9 to 745 mL. A total of 12.5% (n = 9) of patients died, and only 2 patients (2.8%) underwent another procedure because of bleeding (Tables 1 and 2).

Table 2 shows the behavior of the different studied variables between the two populations. It is remarkable that the group of patients who suffered from bleeding greater that 10% of CBV had a lower oxygen saturation percentage (84.5 vs. 93%), longer CBS time (113 vs. 89 minutes) and AC time (63.5 vs. 36 minutes), greater trans-surgical bleeding (150 vs. 100 mL), and a greater initial and final ACT value (147 - 145 vs. 135 - 136 seconds).

Presurgical and postsurgical tests were also considered. Appendix 2 in the supplementary file shows that the presurgical tests in both groups were within normal values. Nevertheless, our analysis highlights that the bleeding group presented higher hemoglobin (15 vs. 13.2 mg/dL) and hematocrit (44.1 vs. 38.4%) values. Regarding to postsurgical tests, patients in the bleeding group had lower hemoglobin (7.6 vs. 10.1 mg/dL), hematocrit (22.5 vs. 30.1%) and platelets (48.0 vs. 52.0 10ˆ3 /mL) values when admitted to the pediatric ICU.

The analytic study of the variables showed that the significant risk factors of bleeding greater that 10% of CBV within the first 6 postsurgical hours were cyanotic heart disease ($P < 0.01$), oxygen saturation percentage ($P = 0.03$), CBS time greater than 90 minutes ($P < 0.01$), AC time ($P < 0.01$), AC time greater than 60 minutes ($P = 0.01$), trans-surgical bleeding volume ($P = 0.04$) and initial ACT value ($P = 0.04$) with an initial ACT value greater than 140 seconds ($P < 0.01$) (Tables 1 and 2). Statistical significance according to the different types of heart disease was not calculated because of the wide diversity of the sample.

A recodification was done into two categories for the independent variables RACHS-1 and ASA because of irregularities observed in the patient distribution. However, after the analysis was performed, no statistical significance was observed (Table 4).

Aiming to determine the most important independent risk factors for postsurgical bleeding greater that 10% of CBV within the first 6 hours after being admitted to the pediatric ICU, a multivariate logistic regression model was made with all variables potentially associated with this outcome with a $P < 0.1$, in addition to sex, age, RACHS-1 scale, ASA classification, type of cyanotic/acyanotic heart disease, circulatory arrest, initial ACT > 140 seconds, hypothermia < 25°C, CBS time > 90 minutes and AC time > 60 minutes. In the analysis, the "ASA classification" and "circulatory arrest" variables were eliminated because of a higher than 30% correlation with other variables. It was revealed that CBS time > 90 minutes ($P = 0.04$) and initial ACT value >140 seconds ($P = 0.01$) represented the most important independent risk factors (Table 5). In addition, a stratified logistic regression analysis according the type of congenital heart disease was performed to identify independent risk factors associated with bleeding greater that 10% of CBV. The analysis demonstrated that CBS time > 90 minutes was the single most important independent risk factor ($P = 0.04$, OR 19.04, CI 95% 1.14 - 315.71) for patients with the acyanotic congenital heart disease. An initial ACT > 140 seconds was the most important independent risk factor for patients with cyanotic congenital heart diseases ($P = 0.02$, OR 7.63, CI 1.30 - 44.58) (Table 4).

## 5. Discussion

Cardiac surgery with cardiopulmonary bypass (CBS) is a pathological state characterized by an increase in free radical synthesis caused by an exaggerated inflammatory response, edema, cell injury, and the development of a complex coagulopathy (11).

Postsurgical hemorrhage is one of the most important complications due to its association with an increase in morbidity and mortality, length of hospitalization, cost and exposure to allogenic blood products (2).

In the present study, we found that 33.3 % of the patients suffered this type of postsurgical bleeding in the evaluated period, exciding the amount described in published literature (5). One cause for this might be the type of pediatric population that our hospital focuses on (children under 5 years old), as well as the fact that drugs such as aprotinin, epsilon-aminocaproic acid (EACA) and tranexamic acid (TXA) are not used as they routinely are in other hospitals. Nonetheless, multicentric studies are needed to confirm this hypothesis.

From the studied variables, the ones that showed a significant result were the type of the cyanotic congenital heart disease and the oxygen saturation level before the surgery measured by pulse oximetry. This association has also been reported in other studies with pediatric patients, such as the studies conducted by Savan et al. and later by Faraoni et al. (4, 12-14).

The explanation for this association is that cyanotic children might have decreased platelet aggregation, prolonged bleeding with normal platelet count, and even mild chronic disseminated intravascular coagulation (DIC). The severity of these hematologic alterations is directly related to the degree of polycythemia (5). This alteration in blood clotting was confirmed by Osthaus et al. and Jensen et al. (15, 16) also reported a hypocoagulable state in children with the cyanotic heart disease related to an alteration in the fibrinogen activity.

Therefore, it is not surprising that the presence of a cyanotic heart disease is significantly correlated with postsurgical hemorrhage, probably due to a direct relation with a greater surgical complexity, degree of hypothermia, and heparin dosage (17). Studies have revealed a greater number of postsurgical complications associated with an AC time longer than 60 minutes and a CBS time longer than 90 minutes (5). Similarly, we observed a significant association between the previous values and bleeding greater than 10% of CBV.

In our study, it was observed that the initial ACT was significantly associated with postsurgical hemorrhage, probably due to the preexisting coagulopathy in children with heart disease. It is known that these children have importantly reduced clotting factor values as well as decreased platelet aggregation (8) and acquired loss of the Von Willebrand factor (6).

A significant association between time length for wound closure (greater than 64 minutes) and postsurgical hemorrhage (4) was not confirmed.

In 1998, Williams et al. (18) stated that blood loss and the need for blood transfusion varied inversely with age. Similarly, Miller et al. (19) also showed than children weight less than 8 kg had bleeding more than any other children. In contrast, in this study a statistical significance was not found for patient's weight or age as a risk factor in the development of postsurgical hemorrhage.

A similar situation occurs with the surgical complexity (evaluated through the RACHS-1 scale) and severity of the disease (evaluated through the American society of anesthesiologists [ASA] physical status classification) which, despite having statistical significance in the study by Savan et al. (4) did not show the same behavior in our study.

Other variables such as the degree of hypothermia and history of previous sternotomy, which were found to be determinants of bleeding in other studies such as the one performed by Williams et al. (18), were not found relevant in the present study.

Pre and postoperative laboratory tests were evaluated, and of note, those patients with postsurgical bleeding >

**Table 2.** Quantitative Characteristics of all Patients Included in the Study and According to the Development of Bleeding of More Than 10% of the CBV Within the First Six Hours Post Surgery

| Studied Variables | Patients Included in the Study | | Patients With Bleeding of More Than 10% of the CBV Within the First Six Hours Post Surgery | | | | P[a] |
|---|---|---|---|---|---|---|---|
| | | | Yes | | No | | |
| | Median | Min-Max | Median | Min - Max | Median | Min - Max | |
| Age, months | 19.0 | 2.0 - 105.0 | 18.0 | 3.0 - 105.0 | 19.0 | 2.0 - 73.0 | 0.87 |
| Weight, g | 8.5 | 3.4 - 36.0 | 8.9 | 4.4 - 36.0 | 8.4 | 3.4 - 17.4 | 0.88 |
| Height, cm | 77.2 | 45.0 - 137.0 | 77.2 | 45.0 - 137.0 | 76.5 | 51.0 - 104.0 | 0.96 |
| Oxygen saturation (%) | 90.0 | 26.0 - 100.0 | 84.5 | 26.0 - 100.0 | 93.0 | 70.0 - 100.0 | 0.03 |
| Duration of surgery, minute | 257.5 | 90.0 - 480.0 | 265.0 | 190.0 - 480.0 | 255.0 | 90.0 - 390.0 | 0.61 |
| Time of CBS, minute | 100.0 | 44.0 - 223.0 | 113.0 | 52.0 - 223.0 | 89.0 | 44.0 - 184.0 | 0.06 |
| Time of AC, minute | 46.5 | 0.0 - 123.0 | 63.5 | 0.0 - 123.0 | 36.0 | 0.0 - 120.0 | < 0.01 |
| Time of CA, minute | 0.00 | 0.0 - 57.0 | 0.0 | 0.0 - 40.0 | 0.0 | 0.0 - 57.0 | 0.11 |
| Minimum rectal temperature (°C) | 26.0 | 16.4 - 35.3 | 25.5 | 16.4 - 33.0 | 26.0 | 18.0 - 35.3 | 0.10 |
| Time-wound closure, minute | 60.0 | 30.0 - 7200.0 | 60.0 | 30.0 - 7200.0 | 60.0 | 30.0 - 120.0 | 0.74 |
| Surgical bleeding | | | | | | | |
| mL | 110 | 15.0 - 1430.0 | 150.0 | 40.0 - 1430.0 | 100.0 | 15.0 - 570.0 | 0.04 |
| mL/kg | 14.7 | 1.76 - 83.1 | 17.7 | 4.6 - 83.1 | 12.8 | 1.7 - 69.5 | 0.09 |
| ACT | | | | | | | |
| Initial, seconds | 137.0 | 104.0 - 213.0 | 147.5 | 104.0 - 213.0 | 135.0 | 109.0 - 199.0 | 0.04 |
| Final, seconds | 140.0 | 110.0 - 195.0 | 145.5 | 116.0 - 191.0 | 136.5 | 110.0 - 195.0 | 0.26 |
| Differential initial/final (%) | 2.2 | 0.0 - 50.4 | 0.0 | 0.0 - 31.0 | 4.1 | 0.0 - 50.4 | 0.41 |
| Bleeding volume 6 hours postsurgical, mL | - | - | 96.5 | 9.0 - 745.0 | - | - | - |

Abbreviations: CBV, circulating blood volume; CBS, cardiopulmonary bypass; AC, aortic clamping; CA, circulatory arrest; ACT, activated clotting time.
[a] U-Mann Whitney.

**Table 3.** Types of Congenital Heart Disease in the Study Population, and According to the Presence of Bleeding of More Than 10% Within the First Six Hours Post Surgery[a]

| Congenital Heart Defect | Total Patients Included in the Study | Patients With Bleeding of More Than 10% Within the First Six Hours Post Surgery | |
|---|---|---|---|
| | | Yes | No |
| Tetralogy of Fallot | 14 (19.4) | 6 (25.0) | 8 (16.7) |
| Aortopulmonary window | 2 (2.8) | 1 (4.2) | 1 (2.1) |
| Interventricular septal defect | 25 (34.7) | 5 (20.8) | 20 (41.7) |
| Atrial septal defect | 3 (4.2) | 0 | 3 (6.3) |
| Patent ductus arteriosus | 1 (1.4) | 0 | 1 (2.1) |
| Total anomalous pulmonary venous connection | 6 (8.3) | 3 (12.5) | 3 (6.3) |
| Atrioventricular canal defect | 5 (6.9) | 2 (8.3) | 3 (6.3) |
| Ebstein's anomaly | 1 (1.4) | 0 | 1 (2.1) |
| Coronary artery anomalies | 2 (2.8) | 0 | 2 (4.2) |
| Pulmonary atresia, stenosis | 6 (8.3) | 4 (16.7) | 2 (4.2) |
| Transposition of the great arteries | 3 (4.2) | 1 (4.2) | 2 (4.2) |
| Double outlet right ventricle | 2 (2.8) | 1 (4.2) | 1 (2.1) |
| Hypoplastic right heart syndrome | 1 (1.4) | 0 | 1 (2.1) |
| Truncus arteriosus | 1 (1.4) | 1 (4.2) | 0 |

[a] Values are expressed as No. (%).

10% CBV had higher hemoglobin and hematocrit levels, although a significant difference was not observed. This finding contrasts with previous studies demonstrating that the degree of polycythemia in cyanotic patients correlates with a greater risk of postsurgical bleeding (5).

Other studies, such as the one performed by Williams et al. (18) and later by Miller et al. (19) demonstrated that platelet count alterations at the end of CBS represent a risk factor for postsurgical bleeding. In our study, this association was not observed because postsurgical tests were conducted when the patients were admitted to the pediatric ICU, at which time 75% of the patients had already received platelet concentrates at the end of CBS by the anesthesiology team, modifying the results.

**Table 4.** Logistic Regression Analysis Stratified by Type of Congenital Heart Disease to Identify Independent Risk Factors Associated With Bleeding of More Than 10% of the CBV Within the First Six Hours Post Surgery

| Heart Disease Cyanotic/Acyanotic | Studied Variables | OR (CI 95%) | P Value[a] |
|---|---|---|---|
| **Acyanotic** | Profound hypothermia < 25°C | 0 | 0.99 |
| | Time of CBS > 90 minutes | 19.04 (1.14 - 315.71) | 0.04 |
| | Time of AC > 60 minutes | 1.29 (0.08 - 20.22) | 0.85 |
| | Initial ACT > 140 seg | 0.71 (0.04 - 11.91) | 0.81 |
| | RACHS-1 | 0 | 0.99 |
| **Cyanotic** | Profound hypothermia < 25°C | 1.70 (0.36 - 7.93) | 0.49 |
| | Time of CBS > 90 minutes | 2.20 ()0.17 - 28.32 | 0.54 |
| | Time of AC > 60 minutes | 3.07 (0.61 - 15.31) | 0.17 |
| | Initial ACT > 140 seg | 7.63 (1.30 - 44.58) | 0.02 |
| | RACHS-1 | 1.39 (0.21 - 9.21) | 0.72 |

Abbreviations: CBV, circulating blood volume; CBS, cardiopulmonary bypass; AC, aortic clamping; ACT, activated clotting time; RACHS, risk adjustment for congenital heart surgery.

[a] Adjusted for age, sex, and type of congenital heart disease (cyanotic/acyanotic).

**Table 5.** Analysis of Overall Logistic Regression to Identify Independent Risk Factors Associated With Bleeding of More Than 10% of the CBV Within the First Six Hours Post Surgery[a]

| Studied Variables | OR (CI 95%) |
|---|---|
| **Profound hypothermia < 25°C** | 1.13 (0.29 - 4.36) |
| **Time of CBS > 90 minute** | 5.66 (1.02 - 31.52) |
| **Time of AC > 60 minute** | 2.10 (0.62 - 7.12) |
| **Initial ACT > 140 seg** | 5.32 (1.49 - 19.01) |
| **RACHS-1** | 0.95 (0.20 - 4.52) |

Abbreviations: CBV, circulating blood volume; CBS, cardiopulmonary bypass; AC, aortic clamping; ACT, activated clotting time; RACHS, risk adjustment for congenital heart surgery.

[a] Adjusted for age, sex, and type of congenital heart disease (cyanotic/acyanotic).

In the same context, it was observed that allogenic blood products were transfused (Packed red blood cells, FFP, cryoprecipitate, platelet concentrates) at the end of CBS in almost all patients. Given that in only 50% of the patients who have hemorrhage the bleeding site can be surgically identified (in our population only two interventions were reported), treatment of these patients requires a major blood transfusion within the first hours in the pediatric ICU which contributes to an even greater increase in mortality and morbidity for this group (20).

The relevance of this study consists in the detection of risk factors in patients, which would be the first step in the development of a therapeutic algorithm for children with heart disease with postsurgical hemorrhage. Trans and postsurgical management for cardiac corrections should be optimize to include the administration of drugs such as aprotinin, EACA or TXA, and application of algorithm-based bedside clotting tests to guide hemostatic treatment (21, 22). Thromboelastography and rotational thromboelastometry have been useful in decreasing the exposure to hematic allogenic products lowering mortality and costs (10, 21, 23).

Our study provides a general view of the current situation of this postsurgical complication, and it might give guidelines for further studies that include the evaluation of costs and benefits related to the use of bedside clotting tests.

Finally, considering the retrospective nature of our study, bias cannot be excluded. To minimize this probability and based on the type of the study, a multivariate logistic regression analysis was performed to stratify risk by type of congenital heart disease. The results showed that an CBS greater than 90 minutes in children with the acyanotic congenital heart disease and an initial ACT greater than 140 seconds in children with the cyanotic congenital heart disease were the most important independent risk factors for developing postsurgical bleeding > 10% CBV within the first 6 hours in children who undergo the cardiac surgery with CBS.

### *5.1. Conclusions*

Postsurgical bleeding of > 10% CBV within the first 6 hours is a common complication (33%) in pediatric patients who undergo cardiac surgery with CBS treated in the pediatric intensive care unit at the pediatrics hospital of the national medical center (The Siglo XXI).

Risk factors associated with postsurgical hemorrhage such as the type of the cyanotic heart disease, oxygen saturation, CBS time > 90 minutes, AC > 60 minutes, intraoperative bleeding volume, and initial ACT > 140 sec were identified in this study. This allows the detection of subgroups of patients with a higher risk of postsurgical bleeding, making possible an appropriate treatment

## Supplementary Material

Supplementary material(s) is available here.

## References


1. Bano Rodrigo A, Dominguez Perez F, Fernandez Pineda L, Gomez Gonzalez R. Practice Guidelines of the Spanish Society of Cardiology in the postoperative course of congenital heart diseases. *Rev Esp Cardiol.* 2000;**53**(11):1496–526. doi: 10.1016/S0300-8932(00)75267-5.
2. Murphy GJ, Reeves BC, Rogers CA, Rizvi SI, Culliford L, Angelini GD. Increased mortality, postoperative morbidity, and cost after red blood cell transfusion in patients having cardiac surgery. *Circulation.* 2007;**116**(22):2544–52. doi: 10.1161/CIRCULATIONAHA.107.698977. [PubMed: 17998460].
3. Williams GD, Bratton SL, Ramamoorthy C. Factors associated with blood loss and blood product transfusions: a multivariate analysis in children after open-heart surgery. *Anesth Analg.* 1999;**89**(1):57–64. doi: 10.1213/00000539-199907000-00011. [PubMed: 10389779].
4. Savan V, Willems A, Faraoni D, Van der Linden P. Multivariate model for predicting postoperative blood loss in children undergoing cardiac surgery: a preliminary study. *Br J Anaesth.* 2014;**112**(4):708–14. doi: 10.1093/bja/aet463. [PubMed: 24394941].
5. Nichols DG, Cameron DE, Ungerleider RM, Nichols DG, Spevak PJ, Greeley WJ, et al. Critical Heart Disease in Infants and Children. 2 ed. Mosby Elsevier; 2006. pp. 367–78.
6. Jonas RA, Elliott MJ. Cardiopulmonary bypass in neonates, infants and young children. Oxford: Butterworth-Heinemann Ltd; .
7. Belisle S, Hardy JF. Hemorrhage and the use of blood products after adult cardiac operations: myths and realities. *Ann Thorac Surg.* 1996;**62**(6):1908–17. doi: 10.1016/S0003-4975(96)00944-7. [PubMed: 8957433].
8. Anthony CC, Frank L, Hanley GW, David L. Baltimore: Williams & Wilkins; 1998.
9. Johansson PI, Solbeck S, Genet G, Stensballe J, Ostrowski SR. Coagulopathy and hemostatic monitoring in cardiac surgery: an update. *Scand Cardiovasc J.* 2012;**46**(4):194–202. doi: 10.3109/14017431.2012.671487. [PubMed: 22375889].
10. Miller BE, Guzzetta NA, Tosone SR, Levy JH. Rapid evaluation of coagulopathies after cardiopulmonary bypass in children using modified thromboelastography. *Anesth Analg.* 2000;**90**(6):1324–30. doi: 10.1097/00000539-200006000-00011. [PubMed: 10825314].
11. Valenzuela-Flores AG, Valenzuela-Flores AA, Ortega-Ramirez JA, Penagos-Paniagua M, Perez-Campos JP. [Physiopathological alterations secondary to extracorporeal circulation in cardiac surgery]. *Cir Cir.* 2005;**73**(2):143–9. [PubMed: 15910709].
12. Kontras SB, Sirak HD, Newton WA. Hematologic abnormalities in children with congenital heart disease. *JAMA.* 1966;**195**(8):611–5. doi: 10.1001/jama.195.8.611. [PubMed: 5951759].
13. Komp DM, Sparrow AW. Polycythemia in cyanotic heart disease–a study of altered coagulation. *J Pediatr.* 1970;**76**(2):231–6. doi: 10.1016/S0022-3476(70)80167-6. [PubMed: 5410171].
14. Faraoni D, Van der Linden P. Factors affecting postoperative blood loss in children undergoing cardiac surgery. *J Cardiothorac Surg.* 2014;**9**:32. doi: 10.1186/1749-8090-9-32. [PubMed: 24512988].
15. Osthaus WA, Boethig D, Johanning K, Rahe-Meyer N, Theilmeier G, Breymann T, et al. Whole blood coagulation measured by modified thrombelastography (ROTEM) is impaired in infants with congenital heart diseases. *Blood Coagul Fibrinolysis.* 2008;**19**(3):220–5. doi: 10.1097/MBC.0b013e3282f54532. [PubMed: 18388502].
16. Jensen AS, Johansson PI, Bochsen L, Idorn L, Sorensen KE, Thilen U, et al. Fibrinogen function is impaired in whole blood from patients with cyanotic congenital heart disease. *Int J Cardiol.* 2013;**167**(5):2210–4. doi: 10.1016/j.ijcard.2012.06.019. [PubMed: 22727966].
17. Codispoti M, Ludlam CA, Simpson D, Mankad PS. Individualized heparin and protamine management in infants and children undergoing cardiac operations. *Ann Thorac Surg.* 2001;**71**(3):922–7. doi: 10.1016/S0003-4975(00)02586-8.
18. Williams GD, Bratton SL, Riley EC, Ramamoorthy C. Association between age and blood loss in children undergoing open heart operations. *Ann Thorac Surg.* 1998;**66**(3):870–5. doi: 10.1016/S0003-4975(98)00600-6. [PubMed: 9768944].
19. Miller BE, Mochizuki T, Levy JH, Bailey JM, Tosone SR, Tam VK, et al. Predicting and treating coagulopathies after cardiopulmonary bypass in children. *Anesth Analg.* 1997;**85**(6):1196–202. doi: 10.1097/00000539-199712000-00003. [PubMed: 9390579].
20. Khuri SF, Wolfe JA, Josa M, Axford TC, Szymanski I, Assousa S, et al. Hematologic changes during and after cardiopulmonary bypass and their relationship to the bleeding time and nonsurgical blood loss. *J Thorac Cardiovasc Surg.* 1992;**104**(1):94–107. [PubMed: 1614220].
21. Weber CF, Gorlinger K, Meininger D, Herrmann E, Bingold T, Moritz A, et al. Point-of-care testing: a prospective, randomized clinical trial of efficacy in coagulopathic cardiac surgery patients. *Anesthesiology.* 2012;**117**(3):531–47. doi: 10.1097/ALN.0b013e318264c644. [PubMed: 22914710].
22. Rahe-Meyer N, Hanke A, Schmidt DS, Hagl C, Pichlmaier M. Fibrinogen concentrate reduces intraoperative bleeding when used as first-line hemostatic therapy during major aortic replacement surgery: results from a randomized, placebo-controlled trial. *J Thorac Cardiovasc Surg.* 2013;**145**(3 Suppl):178–85. doi: 10.1016/j.jtcvs.2012.12.083. [PubMed: 23410777].
23. Hayashi T, Sakurai Y, Fukuda K, Yada K, Ogiwara K, Matsumoto T, et al. Correlations between global clotting function tests, duration of operation, and postoperative chest tube drainage in pediatric cardiac surgery. *Paediatr Anaesth.* 2011;**21**(8):865–71. doi: 10.1111/j.1460-9592.2011.03524.x. [PubMed: 21251146].

**Table 1.** Clinical Characteristics of the Patients Included in the Study and According to the Development of Bleeding of More Than 10% of CBV in the First Six Hours Post Surgery[a]

| Variables | Total Patients Included in the Study, n = 72 | Patients With Bleeding of More Than 10% of CBV Within The First Six Hours Post Surgery | | P[b] |
|---|---|---|---|---|
| | | Yes (33.3%, n = 24) | No (66.6%, n = 48) | |
| **Sex** | | | | |
| Male | 44 (61.1) | 13 (54.2) | 31 (64.6) | 0.39 |
| Female | 28 (38.9) | 11 (45.8) | 17 (35.4) | |
| **Nutritional status (CDC)** | | | | |
| Normal | 30 (41.7) | 10 (41.7) | 20 (41.7) | 1.00 |
| Malnutrition | 42 (58.3) | 14 (58.3) | 28 (58.3) | |
| **Anesthetic risk (ASA score)** | | | | |
| ASA II | 3 (34.2) | 0 | 3 (6.3) | - |
| ASA III | 50 (69.4) | 16 (66.7) | 34 (70.8) | 0.71 |
| ASA IV | 15 (20.8) | 6 (25.0) | 9 (18.8) | 0.53 |
| ASA V | 1 (1.4) | 0 | 1 (2.1) | NC |
| ASA VI | 3 (4.2) | 2 (8.3) | 1 (2.1) | 0.21 |
| **Surgical complexity (RACHS-1)** | | | | |
| RACHS-1 # 1 | 3 (4.2) | 0 | 3 (6.3) | - |
| RACHS-1 # 2 | 57 (79.2) | 18 (75.0) | 39 (81.3) | 0.53 |
| RACHS-1 # 3 | 9 (12.5) | 3 (12.5) | 6 (12.5) | 1.00 |
| RACHS-1 # 4 | 3 (4.2) | 3 (12.5) | 0 | NC |
| **Type of congenital heart defect** | | | | |
| Acyanotic | 34 (47.2) | 6 (25.0) | 28 (58.3) | < 0.01 |
| Cyanotic | 38 (52.8) | 18 (75.0) | 20 (41.7) | |
| **Previous sternotomy** | | | | |
| Yes | 11 (15.3) | 3 (12.5) | 8 (16.7) | 0.74 |
| No | 61 (84.7) | 21 (87.5) | 40 (83.3) | |
| **Aortic clamping** | | | | |
| Yes | 65 (90.3) | 22 (91.7) | 43 (89.6) | 1.00 |
| No | 7 (9.7) | 2 (8.3) | 5 (10.4) | |
| **Circulatory arrest** | | | | |
| Yes | 6 (8.3) | 4 (16.7) | 2 (4.2) | 0.09 |
| No | 66 (91.7) | 20 (83.3) | 46 (95.8) | |
| **Initial ACT > 140 seconds** | | | | |
| Yes | 32 (44.4) | 16 (66.7) | 16 (33.3) | < 0.01 |
| No | 40 (55.6) | 8 (33.3) | 32 (66.7) | |
| **Profound hypothermia (less than 25°C)** | | | | |
| Yes | 21 (29.2) | 10 (41.7) | 11 (22.9) | 0.09 |
| No | 51 (70.8) | 14 (58.3) | 37 (77.1) | |
| **Time of CBS > 90 minutes** | | | | |
| Yes | 45 (62.5) | 21 (87.5) | 24 (50.0) | < 0.01 |
| No | 27 (37.5) | 3 (12.5) | 24 (50.0) | |
| **Time of AC > 60 minutes** | | | | |
| Yes | 27 (37.5) | 14 (58.3) | 13 (27.1) | 0.01 |
| No | 45 (62.5) | 10 (41.7) | 35 (72.9) | |
| **Reoperation after bleeding during surgery** | | | | |
| Yes | 2 (2.8) | 2 (8.3) | 0 | 0.10 |
| No | 70 (97.2) | 22 (91.7) | 48 (100.0) | |
| **Transfusion of blood products at the end of CBS** | | | | |
| Yes | 71 (98.6) | 23 (95.8) | 48 (100.0) | 0.33 |
| No | 1 (1.4) | 1 (4.2) | 0 | |
| **Transfusion of FFP during surgery** | | | | |
| Yes | 46 (63.9) | 16 (66.7) | 30 (62.5) | 0.72 |
| No | 26 (36.1) | 8 (33.3) | 18 (37.5) | |
| **Transfusion of EC during surgery** | | | | |
| Yes | 68 (94.4) | 23 (95.8) | 45 (93.8) | 1.00 |

| | | | | |
|---|---|---|---|---|
| No | 4 (5.6) | 1 (4.2) | 3 (6.3) | |
| **Transfusion of cryoprecipitate during surgery** | | | | |
| Yes | 58 (80.6) | 22 (91.7) | 36 (75.0) | 0.12 |
| No | 14 (19.4) | 2 (8.3) | 12 (25.0) | |
| **Transfusion of platelets during surgery** | | | | |
| Yes | 54 (75.0) | 18 (75.0) | 36 (75.0) | 1.00 |
| No | 18 (25.0) | 6 (25.0) | 12 (25.0) | |

Abbreviations: CBV, circulating blood volume; CDC, centers for diseases control prevention; ASA, American society of anesthesiologists; RACHS, risk adjustment for congenital heart surgery; ACT, activated clotting time; CBS, cardiopulmonary bypass; AC, aortic clamping; FFP, fresh frozen plasma; EC, erythrocyte concentrate.

[a] Values are expressed as No. (%).

[b] Chi-square Pearson.