Predictive Factors for Red Blood Cell Transfusion in Children Undergoing Noncomplex Cardiac Surgery

Muj Mulaj, MD, David Faraoni, MD, FCCP, Ariane Willems, MD, MS, Cristel Sanchez Torres, MD, and Philippe Van der Linden, MD, PhD

Department of Anesthesiology, Centre Hospitalier Universitaire Brugmann and Queen Fabiola Children’s University Hospital, Brussels, Belgium

Background. Red blood cell (RBC) transfusion is frequently required in pediatric cardiac surgery and is associated with altered outcome and increased costs. Determining which factors predict transfusion in this context will enable clinicians to adopt strategies that will reduce the risk of RBC transfusion. This study aimed to assess predictive factors associated with RBC transfusion in children undergoing low-risk cardiac surgery with cardiopulmonary bypass (CPB).

Methods. Children undergoing surgery to repair ventricular septal defect or atrioventricular septal defect from 2006 to 2011 were included in this retrospective study. Demography, preoperative laboratory testing, intraoperative data, and RBC transfusion were reviewed. Univariate and multivariate logistic regression analysis were used to define factors that were able to predict RBC transfusion. Then, we employed receiver operating characteristic analysis to design a predictive score.

Results. Among the 334 children included, 261 (78%) were transfused. Age (<18 months), priming volume of the CPB (>43 mL/kg), type of oxygenator used, minimal temperature reached during CPB (<32°C), and preoperative hematocrit (<34%) were independently associated with RBC transfusion in the studied population. A predictive score 2 or greater was the best predictor of RBC transfusion.

Conclusions. The present study identified several factors that were significantly associated with perioperative RBC transfusion. Based on these factors, we designed a predictive score that can be used to develop a patient-based blood management program with the aim of reducing the incidence of RBC transfusion.

© 2014 by The Society of Thoracic Surgeons

Material and Methods

After obtaining approval by the local ethics committee (Queen Fabiola Children’s University Hospital Ethic Committee), we performed a retrospective analysis of our departmental database, which included all consecutive children who underwent cardiac surgery with CPB between January 2006 and December 2011. We included all children scheduled for VSD or AVSD repair surgery.

The Appendix can be viewed in the online version of this article [http://dx.doi.org/10.1016/j.athoracsur.2014.04.089] on http://www.annalsthoracicsurgery.org.
Children in a moribund state (American Society of Anesthesiology 5), and Jehovah’s Witnesses were excluded from our analysis. The local ethics board waived the requirement for written informed consent given the retrospective nature of the protocol.

The same 2 surgeons performed all procedures during the study period. A senior anesthesiologist systematically performed preoperative evaluation. Preoperative laboratory testing included hemoglobin level, hematocrit, platelet count, coagulation assays (including fibrinogen level measured by the Clauss method [10]), creatinine level, blood urea nitrogen, and liver enzymes.

In the operating room, standard monitoring included pulse oximetry, 5-lead electrocardiogram, noninvasive arterial pressure, arterial and central venous pressure, urinary output, and cutaneous and rectal temperature probes. Intravenous anesthesia based on midazolam, sufentanil, and rocuronium was preferred in all children. All patients received cefazolin 25 mg/kg, methylprednisolone 30 mg/kg after anesthesia was induced. Aprotinin was systematically used before 2008 [11]; tranexamic acid was used thereafter. Before aortic cannulation, 4 mg/kg unfractionated heparin (UFH) was administered to reach an activated clotting time greater than 480 seconds. Anticoagulation level was regularly checked during CPB using repeated activated clotting time measures, and additional UFH boluses were administered to maintain activated clotting time greater than 480 seconds throughout the entire CPB.

During the study period, the CPB circuit was primed primarily with 6% hydroxyethyl starch (130/0.4) in 0.9% sodium chloride (Voluven; Fresenius-Kabi Gmbh, Bad Homburg, Germany), 20% mannitol (1.5 mL/kg), sodium bicarbonate (20 mEq/L), and UFH (50 mg/L). Different models of oxygenator chosen based on body weight were used during the study period. In addition, new “miniaturized” oxygenators, which require a smaller prime volume, were introduced in our department in 2008.

When preparing the CPB prime, the hematocrit on bypass was calculated based on the volume of the prime and the estimated blood volume (EBV) of the patient. Packed RBCs were added to the prime when calculated hematocrit after cardioplegia (crystalloid cold balanced solution enriched in potassium chloride [30 mmol/L]) was estimated to fall below 20%. During CPB, body temperature was decreased according to the aortic clamp duration and surgical complexity. All patients were rewarmed to greater than 35.5°C before weaning from CPB. After weaning, modified ultrafiltration (MUF) was used to increase the hematocrit of the residual blood volume in the circuit.

Our RBC transfusion policy was standardized in agreement with the Anesthesiology Department and the Pediatric Intensive Care Unit (PICU). After separation from CPB, RBCs were transfused to maintain a hematocrit greater than 24%. In addition, RBC transfusion was considered in cases of abnormal bleeding or persistent lactic acidosis, in order to increase oxygen delivery after optimizing cardiac output with inotropes, vasoactive agents, or both.

Recorded data, including age (months), preoperative weight (kg), height (cm), preoperative oxygen saturation (%), American Society of Anesthesiology, and the risk adjustment for congenital heart surgery (RACHS) [12]. The RACHS score uses 6 categories of surgical risk, ranging from 1 (lowest) to 6 (highest). We also recorded the incidences of preoperative cardiac failure and previous cardiac surgery with or without sternotomy. Preoperative laboratory testing was included in the analysis; hemoglobin level (g/dL), hematocrit (%), platelet count (×10^7/µL), fibrinogen level (mg/dL), prothrombin time (seconds), activated partial thromboplastin time (seconds), creatinin level (mg/dL), and blood urea nitrogen (mg/dL). Finally, the degree of hemodilution was measured in mL/kg using the ratio between the CPB prime volume (mL/kg), and the patient’s EBV (mL/kg) [13]. The type of oxygenator, use of MUF, and amount of MUF (mL/kg) were also recorded. The RBC transfusion was defined as any intraoperative exposure to RBCs (during or outside CPB), as well as exposure during the entire PICU stay. We weighed sponges and measured surgical suction and chest tube drainage to calculate intraoperative and postoperative blood loss. We also calculated blood losses from the patients’ EBV, preoperative and postoperative hematocrit (day 1), and the volume of RBCs transfused. No washed or unwashed cell salvage system was used during the study period.

Statistical Analysis

We used the Shapiro-Wilk normality test to assess continuous variables for normality. Because of the non-Gaussian distribution of the population, data are presented as median and interquartile range [25th percentile to 75th percentile]. Categoric variables are expressed as number and percentage (%). Groups were compared using the Wilcoxon rank sum test for continuous variables and the χ² test for categoric variables.

Univariate logistic regression analysis was performed for all possible determinants of RBC transfusion. We defined, a priori, that all variables with a p value less than 0.05 were considered relevant and included in the stepwise multivariate logistic regression analysis. This second analysis was used to define factors that were able to predict RBC transfusion in children undergoing VSD or AVSD repair surgery.

Next, we built separate receiver operating characteristic (ROC) curves for variables that significantly predict RBC transfusion. Results are expressed as area under the ROC curve with 95% confidence intervals (95% CI), Youden criterion, sensitivity, and specificity. Finally, those parameters were used to design a predictive score of RBC transfusion, which was validated using another ROC curve analysis. This analysis aimed to determine the sensitivity, the specificity, and the percentage of children correctly classified in the “transfused group,” as well as the positive and negative predictive values and likelihood ratios.

Statistical analyses were performed using STATA version 13.1 for Mac OS (StataCorp, College Station, TX) and GraphPad Prism 6 version 6.0d for Mac OS.
We observed that age (months), priming volume of the CPB (mL/kg), type of oxygenator used, minimal temperature reached during CPB (°C), and preoperative hematocrit (%) remained independently associated with RBC transfusion in the study population (Table 2).

Each variable, with the exception of oxygenator type, was used to build ROC curves. Table 3 describes the parameters obtained with these analyses. We observed that age less than 18 months, priming volume more than 43 mL/kg, minimal temperature on bypass less than 32°C, and preoperative hematocrit less than 34% were able to predict children at risk of RBC transfusion. We attributed 1 point for each variable using these cutoffs, and calculated a 4-point predictive score for each child. Figure 1 shows the percentage of patients with each score that were transfused with RBCs. Using ROC curve analysis (Fig 2), we observed that a score 2 or greater was the best predictor of RBC transfusion, with 95% sensitivity and 74% specificity (Table 4). The positive predictive value of this score is 0.93 (95% CI, 0.89 to 0.96), and the negative predictive value is 0.81 (95% CI, 0.69 to 0.89).

### Table 1. Demographic Data

<table>
<thead>
<tr>
<th>Variables</th>
<th>Population (n = 334)</th>
<th>Transfused (n = 261)</th>
<th>Nontransfused (n = 73)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (months)</td>
<td>13 [6–28]</td>
<td>11 [5–18]</td>
<td>46 [24–75]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>7 [5–10]</td>
<td>6 [5–8]</td>
<td>14 [10–20]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>70 [61–84]</td>
<td>67 [59–75]</td>
<td>99 [79–118]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male (%)</td>
<td>150 (45)</td>
<td>115 (47)</td>
<td>34 (44)</td>
<td>0.68</td>
</tr>
<tr>
<td>ASA (%)</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2</td>
<td>53 (16)</td>
<td>22 (8)</td>
<td>31 (42)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>267 (80)</td>
<td>227 (87)</td>
<td>40 (55)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>14 (4)</td>
<td>12 (5)</td>
<td>2 (3)</td>
<td></td>
</tr>
<tr>
<td>Preoperative SpO2 (%)</td>
<td>97 [94–99]</td>
<td>97 [93–99]</td>
<td>98 [95–100]</td>
<td>0.02</td>
</tr>
<tr>
<td>Preoperative cardiac failure (%)</td>
<td>82 (25)</td>
<td>74 (28)</td>
<td>8 (11)</td>
<td>0.003</td>
</tr>
<tr>
<td>RACHS (%)</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2</td>
<td>220 (66)</td>
<td>167 (64)</td>
<td>53 (73)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>111 (33)</td>
<td>92 (35)</td>
<td>19 (26)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4 (1)</td>
<td>3 (1)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Aortic clamp duration (min)</td>
<td>42 [28–70]</td>
<td>45 [31–72]</td>
<td>36 [21–55]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CPB duration (min)</td>
<td>83 [64–113]</td>
<td>86 [68–114]</td>
<td>73 [53–100]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Surgery duration (min)</td>
<td>176 [151–206]</td>
<td>176 [152–206]</td>
<td>172 [147–206]</td>
<td>0.42</td>
</tr>
<tr>
<td>Priming volume (mL/kg)</td>
<td>57 [43–77]</td>
<td>63 [51–82]</td>
<td>35 [28–42]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MUF (%)</td>
<td>327 (98)</td>
<td>259 (99)</td>
<td>68 (93)</td>
<td>0.007</td>
</tr>
<tr>
<td>MUF (mL/kg)</td>
<td>28 [20–37]</td>
<td>29 [21–39]</td>
<td>24 [17–32]</td>
<td>0.003</td>
</tr>
<tr>
<td>Preoperative Hb (g/dL)</td>
<td>11.8 [10.1–12.9]</td>
<td>11.5 [10.0–12.8]</td>
<td>12.4 [11.7–13.2]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Preoperative Hct (%)</td>
<td>36.3 [33.6–39.1]</td>
<td>35.5 [32.3–38.7]</td>
<td>37.8 [35.6–40.3]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Preoperative platelets (10⁹/mm³)</td>
<td>360 [298–446]</td>
<td>372 [303–479]</td>
<td>327 [286–384]</td>
<td>0.003</td>
</tr>
<tr>
<td>Preoperative fibrinogen (mg/dL)</td>
<td>280 [241–324]</td>
<td>284 [240–326]</td>
<td>275 [249–305]</td>
<td>0.48</td>
</tr>
<tr>
<td>Preoperative creatinine (mg/dL)</td>
<td>3.0 [2.5–4.0]</td>
<td>3.8 [3.0–5.0]</td>
<td>3.0 [2.4–3.5]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Preoperative BUN (mg/dL)</td>
<td>27 [20–33]</td>
<td>25 [19–33]</td>
<td>28 [25–33]</td>
<td>0.03</td>
</tr>
</tbody>
</table>

ASA = American Society of Anesthesiology; BUN = blood urea nitrogen; CPB = cardiopulmonary bypass; Hb = hemoglobin; Hct = hematocrit; min = minutes; Min. Temp. = minimal body temperature; MUF = modified ultrafiltration; RACHS = risk adjustment for congenital heart surgery; SpO2 = oxygen saturation as measured by pulse oximetry; Vol. = volume.
Our results confirm that, among the pediatric cardiac population, blood loss or preoperative hemoglobin levels are not the only variables that determine the need for perioperative blood transfusion. Predictors of blood transfusion include patient-related, procedure-related, and process-related factors that can interfere between each other [4]. In a recent study of more than 2,000 consecutive children undergoing cardiac surgery with CPB, Richmond and colleagues [8] observed that CPB prime volume, preoperative hemoglobin value, minimal temperature during CPB, and operative risk (defined by the RACHS) were independently associated with RBC transfusion. These results demonstrated that the complexity of the congenital repair according to the RACHS must be taken into account when assessing predictors of blood transfusion in the global pediatric cardiac surgery population. Our study focused on children undergoing VSD or AVSD repair surgery, 2 procedures with relatively low risk of severe intraoperative complications, which in turn reduces the risk of increased RBC transfusion due to procedure-related factors. However, our population was considered at high risk for perioperative RBC transfusion because of patient-related and process-related factors; a high incidence of preoperative anemia related to age and preoperative hematocrit, and a high degree of hemodilution owing to a high ratio between the EBV and prime volume.

Our study identified 3 potentially modifiable factors associated with RBC transfusion; anemia, hemodilution, and hypothermia. Anemia (defined according to preoperative hematocrit) is easy to assess preoperatively. In the adult cardiac population, a multicenter cohort reported that 22% to 30% of patients scheduled for a cardiac surgery with CPB were anemic [14]. Anemia in this population was associated with an increased risk of acute kidney injury and increased incidence of early and late mortality [15]. As a consequence, preoperative identification of anemia is now integrated into different multidisciplinary “patient blood management” approaches [16]. In adults, there is growing evidence that preoperative hemoglobin optimization is feasible using iron supplementation, with or without the administration of recombinant human erythropoietin (rhEPO) [17, 18]. Obviously, the exact incidence of preoperative anemia and iron deficiency remains to be determined in children undergoing cardiac surgery, and additional studies are needed to assess whether preoperative detection and treatment of anemia might reduce the incidence of RBC transfusion in this population. Only 2 small studies have evaluated the effect of preoperative rhEPO administration in children undergoing cardiac surgery. Although these studies did not have the power to assess the effect of rhEPO administration on the incidence of RBC transfusion requirement, both reported that rhEPO treatment tended to increase the hematocrit nadir in the studied population [19, 20].

The degree of hemodilution appeared to play an important role in the need for RBC transfusion. This risk factor can be modified by using modern CPB circuitries,
which require a smaller prime volume. Ando and colleagues [21] reported that cardiac surgery with CPB can be initiated without RBCs in the CPB prime in greater than 70% of children weighing less than 5 kg that underwent VSD repair surgery using miniaturized systems. In this study, 95% of patients were not transfused during the perioperative period.

Hypothermia also appeared to be an independent risk factor for RBC transfusion. Hypothermia is still frequently used during pediatric open-heart surgery in order to protect organs such as the brain, the kidneys, and the heart from ischemic injury through a reduction of cellular metabolic rate [22]. Furthermore, hypothermia has been associated with a reduction in the whole body inflammatory response to CPB [23, 24]. Although a relationship between surgery duration and the degree of hypothermia could have been expected, our study did not reveal any such correlation between these 2 parameters. The relationship between hypothermia and the increased risk for RBC transfusion is complex and probably multifactorial. Although the effect of hypothermia on the coagulation system certainly plays a role, the present study was not designed to confirm such a relationship. Nevertheless, the benefit-to-risk balance of using hypothermia should be assessed in future well-designed prospective trials [25].

For a couple of years, the patient blood management concept has been developed to optimize the perioperative management of patients at higher risk of requiring RBC transfusion [26]. Different approaches have been proposed based on the following 3 main pillars: preoperative optimization of the patient’s red blood cell mass; adoption of techniques that minimize perioperative blood loss; and implementation of strategies to increase each patient’s tolerance to anemia. With the aim of developing such a blood management program in our cardiac population, we set up a predictive score that could be easily employed to detect children at high risk for RBC transfusion. Using this score, we observed that patients with a score 2 or greater are at particular risk of requiring RBC transfusion during the perioperative period. The next steps of our approach would be to implement a multidisciplinary program to detect and correct preoperative anemia, to further modify our CPB devices in order to decrease the degree of hemodilution, and to implement a multifactorial strategy to minimize blood loss and treat coagulopathy [27].

Although this study is limited as a retrospective analysis, we targeted our analysis to a specific population with the objective of lowering the risk of bias caused by the complexity of the procedures and comorbidities. The validity of our model might have been affected by the fact that most RBC transfusions were administered during the CPB prime according to our departmental protocol, which aimed to maintain the hematocrit at greater than 20% after the administration of cardioplegia. Therefore, transfusion on CPB in this study depended strongly on each patient’s preoperative hematocrit and the volume of the CPB prime, 2 factors found to be independently associated with perioperative transfusion. However, our multivariate regression analysis confirmed that, in our population, no other factor (eg, intraoperative bleeding, CPB, and aortic clamp duration) predicted RBC transfusion better than those we reported. Although our CPB

<table>
<thead>
<tr>
<th>Score</th>
<th>Se</th>
<th>Sp</th>
<th>Correctly Classified</th>
<th>LR⁺</th>
<th>LR⁻</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥0</td>
<td>100</td>
<td>0</td>
<td>78.2</td>
<td>1.00</td>
<td>–</td>
</tr>
<tr>
<td>≥1</td>
<td>99.6</td>
<td>27.4</td>
<td>83.9</td>
<td>1.37</td>
<td>0.01</td>
</tr>
<tr>
<td>≥2</td>
<td>95.0</td>
<td>74.0</td>
<td>90.4</td>
<td>3.65</td>
<td>0.07</td>
</tr>
<tr>
<td>≥3</td>
<td>75.2</td>
<td>90.4</td>
<td>78.5</td>
<td>7.84</td>
<td>0.27</td>
</tr>
<tr>
<td>≥4</td>
<td>21.4</td>
<td>98.6</td>
<td>38.2</td>
<td>15.60</td>
<td>0.8</td>
</tr>
</tbody>
</table>

LR⁺ = positive likelihood ratio; LR⁻ = negative likelihood ratio; Se = sensitivity; Sp = specificity.

Fig 1. Histogram reporting the percentage of children transfused with red blood cells (RBCs) with respect to predictive score. Score 0, n = 21 children; score 1, n = 46; score 2, n = 64; score 3, n = 148; and score 4, n = 57.

Fig 2. Receiver operating characteristic (ROC) curve for the predicting score of red blood cell transfusion. Area under the ROC curve, 0.91; 95% confidence interval CI, 0.87 to 0.95.
circuities were modified in 2008 to reduce the prime volume, the year of surgery was not independently associated with RBC transfusion in our univariate regression and therefore could not be considered as a major bias. Rather, this observation tended to indicate that efforts should continue in such a direction. Finally, the predictive score designed in this study was only validated in an internal patient subset; it should be validated in an external population before its use can be generalized.

In conclusion, this study reported that age, CPB prime volume, oxygenator type, minimal temperature reached during CPB, and preoperative hematocrit were each independently associated with RBC transfusion in children undergoing VSD or AVSD repair surgery. Our predictive score can be used to develop a patient-based blood management program that aims to reduce the RBC transfusion requirement in the pediatric cardiac population.

This work was supported by the Department of Anesthesiology, CHU-Brugmann, QFCUH, Brussels, Belgium.

References