Development of a specific algorithm to guide haemostatic therapy in children undergoing cardiac surgery

A single-centre retrospective study

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BACKGROUND Although rotational thromboelastometry (ROTEM) is increasingly used to guide haemostatic therapy in a bleeding patient, there is a paucity of data guiding its use in the paediatric population.

OBJECTIVE The objective of this study is to develop an algorithm on the basis of ROTEM values obtained in our paediatric cardiac population to guide the management of the bleeding child.

DESIGN A retrospective analysis.

SETTING Department of Anaesthesiology, Queen Fabiola Children’s University Hospital. Data were collected between September 2010 and January 2012.

PATIENTS All children who underwent elective cardiac surgery requiring cardiopulmonary bypass (CPB) were reviewed.

INTERVENTION None.

MAIN OUTCOME MEASURES Significant postoperative bleeding was defined as blood loss more than 10% of the child’s estimated blood volume within the first six postoperative hours, dividing our population according to high blood loss (HBL) or low blood loss (LBL). Factors independently associated with postoperative bleeding determined the bleeding probability. Receiving operating characteristics (ROC) curves were constructed with the aim of determining relevant ROTEM parameters (including clot amplitude 10 min after administration of protamine [A10]) to be used in our algorithm. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were determined for the developed algorithm.

RESULTS One-hundred and fifty children were included in our study. Univariate and multivariate logistic regression analysis revealed that preoperative weight (kg), presence of a cyanotic disease (yes/no) and wound closure duration (min) were independent predictors of postoperative bleeding. Analysis of our ROTEM parameters revealed that clotting time (CT) / C21 / 111 s, A10 / C20 / 38 mm measured on the EXTEM and A10 / C20 / 3 mm obtained on the FIBTEM tests were the three relevant parameters to guide haemostatic therapy. If the ROTEM-based algorithm was applied according to the bleeding risk (n = 65), 27 out of 29 of the HBL and 24 out of 36 of the LBL group would have been treated.

CONCLUSION This study describes an algorithm starting with the detection of abnormal bleeding in which ROTEM could be used to guide haemostatic therapy in bleeding children after CPB. Further studies are needed to test the efficacy of this specific algorithm-based approach.

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Introduction

Coagulopathy induced by cardiopulmonary bypass (CPB) is a major cause of excessive blood loss after cardiac surgery.1 It is characterised by a complex interaction between haemodilution, tissue factor and fibrinolysis activation, and consumption of clotting factors. Administration of unfractioned heparin (UFH), both protamine underdosage and overdosage and homeostatic disturbances (hypothermia, hypocalcaemia and acidemia) can also contribute to the increased bleeding risk.2 The paediatric population is at even higher risk of
coagulopathy due to a higher ratio between the prime and circulating blood volume, the relative immaturity of the haemostatic system, the presence of cyanotic disease and the greater complexity of the procedures performed.\(^4\) Rotational thromboelastometry (ROTEM; TEM International GmbH, Munich, Germany) is increasingly used to monitor coagulation status during and after cardiac surgery.\(^5\) It has been proposed to guide haemostatic therapy in the bleeding patient.\(^6\) In the paediatric cardiac population, however, only sparse data on the use of ROTEM are available. Clinically important interindividual variability has been reported with the use of such monitoring and the definition of a precise cut-off between normal and abnormal values remains difficult.\(^7\) In addition, the routine use of ROTEM in all children undergoing cardiac surgery may not be cost-effective. Indeed, as ROTEM is unable to accurately predict postoperative blood loss and transfusion requirements, its use may lead to the treatment of children who do not bleed.\(^8\) Therefore, clinical parameters that could predict postoperative blood loss and detect abnormal bleeding should be considered as the first step of an algorithm-based approach. In addition, this algorithm should be developed considering relevant ROTEM cut-off values, specifically determined in the paediatric population.\(^9\)

The aim of this study was to develop an algorithm, based on the retrospective analysis of our paediatric cardiac population, which could be used to guide management strategy for the bleeding paediatric patient.

**Materials and methods**

The local ethics committee approved this study, but waived the requirement for written informed consent due to its retrospective design (Queen Fabiola Children’s University Hospital Ethics Committee, 15 Avenue JJ Crocq, 1020 Brussels, Belgium CEH 06/11, Chairperson Dr Grosassser J, accepted 25 May 2011).

We then performed a retrospective review of data systematically recorded in our departmental database. All children (age ≤16 years) who underwent elective cardiac surgery with CPB between September 2010 and January 2012 were eligible for inclusion in this study. Exclusion criteria were Jehovah’s Witnesses; children in a moribund state; children who received haemostatic therapies [fresh frozen plasma (FFP), platelet concentrates or a combination of both] before protamine administration; and those in whom we did not perform a ROTEM after protamine administration due to technical problems.

During this study period, anaesthetic management was standardised. Monitoring included a five-lead electrocardiogram, pulse oximetry, noninvasive blood pressure, arterial and central venous pressure monitoring, urinary catheter and rectal and cutaneous temperature probes. Intravenous general anaesthesia (using midazolam, sufentanil and rocuronium) was generally preferred in all children. Children with univentricular physiology undergoing a cavopulmonary connection were anaesthetised with propofol or sevoflurane, remifentanil and atracurium. Tranexamic acid (TXA) was administered systemically according to our local dosing scheme (10 mg kg\(^{-1}\) loading dose before CPB, 10 mg kg\(^{-1}\) h\(^{-1}\) until the end of wound closure, 10 mg kg\(^{-1}\) in the CPB prime). In addition, all children received 30 mg kg\(^{-1}\) methylprednisolone and cefazoline 25 mg kg\(^{-1}\) after induction of anaesthesia. Before aortic cannulation, 4 mg kg\(^{-1}\) UFH was administered. Activated clotting time (ACT) (ACTII monitor; Medtronic BV, Kerkrade, The Netherlands) was used to guide UFH administration and to maintain the targeted ACT more than 480 s. At the end of CPB, protamine was administered at half of the total UFH dose administered during the whole CPB period. Adequate neutralisation was controlled using ACTII monitor comparing ACT measured in cartridge with and without heparinase (Medtronic BV).

Transfusion strategy was defined by a multidisciplinary approach. During CPB, red blood cells (RBCs) were transfused to maintain a haemoglobin concentration more than 70 g l\(^{-1}\). After CPB, RBCs were administered to maintain Hb between 70 and 100 g l\(^{-1}\) according to the clinical condition, the presence of cyanotic disease, pulmonary hypertension and cardiac dysfunction. In case of abnormal bleeding, defined by a clinical impression of diffuse bleeding without precise surgical origin, haemostatic variables were checked and corrected if required: temperature more than 36 °C; pH more than 7.35; ionised serum calcium concentration more than 1.03 mmol l\(^{-1}\); FFP was then administered at a dose of 15 ml kg\(^{-1}\). The same dose could be repeated in cases of persistent bleeding. In addition, platelets were administered in cases of significant blood loss associated with a platelet count less than 100 000 mm\(^{-3}\), as measured by our standard laboratory tests after protamine administration. Rotational thromboelastometry was performed 10 min after protamine administration (INTEM, EXTEM, HEPTEM and FIBTEM). The applied transfusion strategy was, however, not based on ROTEM parameters, but left to the discretion of the clinician in charge of the child who decided according to the clinical situation and the results of routine coagulation tests performed in our accredited central laboratory, which included activated partial thromboplastin time (APTT), prothrombin time (PT), fibrinogen level measured by the Clauss method and platelet count.

Demographic data and surgical characteristics were recorded, while the RACHS-1 (Risk Adjustment for Congenital Heart Surgery)\(^10\) score was used to classify surgical operating procedures. Cyanotic disease was defined as preoperative oxygen saturation less than 90%. Duration of the surgery was defined as the time between skin incision and the end of skin closure. Wound closure duration was defined as the time between
weaning from CPB and the end of skin closure. The weight of sponges and measurement of surgical suction determined intraoperative blood loss, while chest tube drainage was used in the postoperative period. Clinically significant postoperative bleeding was defined as a blood loss more than 10% of the child’s estimated blood volume (EBV) within the first 6 postoperative hours. This definition was adapted from the available literature, considering the 75th percentile of our population.6

Statistical analysis
Continuous variables were tested for normality with the Shapiro–Wilks test. Data are presented as median (interquartile range, IQR). Categorical variables are expressed as number (%).

First, univariate logistic regression analysis was performed for all possible determinants of postoperative bleeding. All variables with a P value less than 0.1 (defined ‘a priori’) were considered relevant and included in the multivariate logistic regression analysis. This second analysis was then used to define the factors that were independently associated with postoperative bleeding. These parameters were also used to calculate the bleeding risk as already validated in a previous study.9 It is important to note the present study differed from the previous one in that all children who received FFP or platelets before protamine administration were excluded in the present study. Receiver operating characteristics (ROC) curves were constructed with the aim of determining to determine a probability score that could be used to predict postoperative blood loss with the greatest specificity and sensitivity. This score was then used to define, a posteriori, the ‘at-risk’ population in whom ROTE M would have been recommended. Second, ROC curves were constructed with the ROTE M variables considered to be relevant for the construction of an algorithm that could be used to manage bleeding children: EXTEM clotting time (CT, s); EXTEM clot amplitude measured at 10 (A10, mm) and 20 min (A20, mm); and EXTEM maximum clot firmness (MCF, mm). Area under the ROC curve (AUC) with 95% confidence intervals (95% CI) and Youden criterion were calculated. To determine which factor (A10, A20 or MCF) would best predict abnormal postoperative blood loss, the areas under these three ROC curves were compared. The same statistical analysis was repeated for A10, A20 and MCF measured on the FIBTEM test.

Two authors (D.F. and P.VdL.) then independently applied the algorithm to the study population with the aim of determining the incidence of exposure to haemostatic agents. The same sequence was then repeated using the algorithm published by Romlin et al.12 in a comparable population.

Finally, we determined the incidence of haemostatic treatment administered following application of the algorithm in our population retrospectively classified into high blood loss (HBL) and low blood loss (LBL) groups. The same analyses were repeated in children in whom ROTE M would have been recommended using our probability score. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the algorithm were calculated for both situations.

A P value less than 0.05 was considered as statistically significant for all tests. Statistical analyses were performed with Prism 6 for Mac OS (version 6.0d; GraphPad Software Inc., San Diego, California, USA), STATA 13.1 for Mac OS (Stata Statistical Software version 13.1; StataCorp. 2013, College Station, Texas, USA) and MedCalc software for Windows (Version 12.3.0.0, MedCalc Software, Ostend, Belgium).

Results
From the 191 children screened for inclusion, we excluded 32 children less than 1 month of age because they received FFP in the CPB prime, and three others who received FFP before protamine administration for ‘abnormal’ bleeding. In addition, five children were excluded due to lack of data and one because he was placed on extracorporeal membrane oxygenation (ECMO) prior to surgery (Fig. 1). Demographic characteristics of the studied population are presented in Table 1.

Forty-eight variables that could be used to predict postoperative blood loss were examined in the univariate regression analysis, from which 23 matched the inclusion criteria and were included in the multivariate logistic regression model. From these analyses, preoperative weight (kg), the presence of a cyanotic disease (yes, 1/no, 0) and wound closure duration (min) remained

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the only variables independently associated with postoperative blood loss in this population (Table 2). These three parameters were then used to calculate our probability score using the following formula:

\[
P = \frac{1 + e^{-}\left(z \cdot \text{cyanotic disease} - 0.21 \cdot \text{weight} + 0.02 \cdot \text{wound closure duration} - 1.48\right)}{1},
\]

where \(z = \frac{1.6}{3}\) (cyanotic disease) – \(0.21\) (weight) + \(0.02\) (wound closure duration) – 1.48.

We observed that the calculated probability was significantly associated with postoperative blood loss (Fig. 2, AUC: 0.82, 95% CI 0.75 to 0.88; \(P < 0.001\)). Finally, we determined that a probability score at least 0.20 could predict postoperative blood loss with a sensitivity of 80% and a specificity of 69%. This cut-off value will be used as a first step of our algorithm to decide whether ROTEM tests should be performed or not.

Unsurprisingly, CT measured on EXTEM and A10 measured on EXTEM and FIBTEM were significantly altered in the HBL cohort (Fig. 3). We observed that the AUC obtained for CT measured on EXTEM was 0.67 (95% CI 0.59 to 0.75; \(P < 0.001\)) (Fig. 4a) and we determined that a CT \(\geq 111\) s could predict postoperative blood loss with a sensitivity of 60% and a specificity of 74%. Figure 4b shows the ROC curves obtained for A10 obtained with the EXTEM test (AUC 0.74, 95% CI 0.66 to 0.81; \(P < 0.001\), A20 (AUC 0.71, 95% CI 0.69 to 0.83; \(P < 0.001\)) and MCF (AUC 0.76, 95% CI 0.68 to 0.83; \(P < 0.001\)). No statistical difference was observed between areas on the three ROC curves, which indicates that an A10 value \(\leq 38\) mm (sensitivity 88%, specificity 52%) should be preferred, as it is the first parameter to be obtained. The same analysis was performed with FIBTEM tests (Fig. 4C) with A10 (AUC 0.72, 95% CI 0.66 to 0.81; \(P < 0.001\)) and MCF (AUC 0.76, 95% CI 0.68 to 0.83; \(P < 0.001\)).

![Fig. 2](image)

**Table 1** Demographic characteristics of the studied population

<table>
<thead>
<tr>
<th>Variables</th>
<th>Population (n = 150)</th>
<th>Bleeding probability (\geq 0.2) (n = 65)</th>
<th>Bleeding probability &lt;0.2 (n = 85)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (months)</td>
<td>14 (5 to 40)</td>
<td>6 (3 to 12)</td>
<td>30 (11 to 63)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male</td>
<td>78 (52)</td>
<td>44 (88)</td>
<td>40 (67)</td>
<td>0.02</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>71 (60 to 98)</td>
<td>61 (55 to 70)</td>
<td>90 (68 to 107)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>7.7 (5.4 to 13.6)</td>
<td>5.7 (4.2 to 7.7)</td>
<td>12.3 (7.1 to 18.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ASA</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>0</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>102</td>
<td>39</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>36</td>
<td>26</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>RACHS-1</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1</td>
<td>11</td>
<td>0</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>64</td>
<td>34</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>56</td>
<td>16</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>14</td>
<td>11</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Preoperative SpO(_2) (%)</td>
<td>95 (85 to 97)</td>
<td>85 (77 to 95)</td>
<td>96 (95 to 97)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Surgery time (min)</td>
<td>215 (184 to 260)</td>
<td>250 (208 to 287)</td>
<td>200 (174 to 245)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number (%) requiring aortic cross-clamp</td>
<td>116 (77)</td>
<td>53 (82)</td>
<td>63 (74)</td>
<td>0.25</td>
</tr>
<tr>
<td>Aortic clamping time (min)</td>
<td>51 (38 to 71)</td>
<td>59 (38 to 76)</td>
<td>48 (36 to 64)</td>
<td>0.07</td>
</tr>
<tr>
<td>CPB time (min)</td>
<td>98 (74 to 129)</td>
<td>114 (80 to 152)</td>
<td>88 (71 to 115)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blood loss after 6 h (ml/kg(^{-1}))</td>
<td>4.8 (2.7 to 7.2)</td>
<td>6.9 (4.4 to 9.4)</td>
<td>3.8 (1.9 to 5.2)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are presented as median (IQR) or number (%). ASA, American Society of Anesthesiologists physical status; CPB, cardiopulmonary bypass; RACHS, Risk Adjustment for Congenital Heart Surgery.

![Fig. 2](image)

**Table 2** Results of multivariate logistic regression analysis

<table>
<thead>
<tr>
<th>Variables</th>
<th>B</th>
<th>Standard error</th>
<th>B/SE</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>-1.47</td>
<td>0.89</td>
<td>-1.66</td>
<td>0.096</td>
</tr>
<tr>
<td>Cyanotic disease (%)</td>
<td>1.62</td>
<td>0.47</td>
<td>3.48</td>
<td>0.001</td>
</tr>
<tr>
<td>Wound closure duration (min)</td>
<td>0.02</td>
<td>0.01</td>
<td>1.85</td>
<td>0.044</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>-0.21</td>
<td>0.06</td>
<td>-3.26</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

\(B\), coefficient; \(B/SE\), ratio between coefficient and standard error.
Algorithm-based management of bleeding children

Fig. 3

(a) Box and whisker plots showing the comparison between high blood loss and low blood loss groups for the clotting time measured on (a) EXTEM, (b) A10 measured on EXTEM and (c) FIBTEM. P < 0.05 for all comparisons. The box represents the first and third quartile, with the solid line within showing the median. The whiskers demonstrate the range of the data from maximum to minimum values, with the dots representing outliers outside this range.

(b) EXTEM-A10 (mm)

(c) FIBTEM-A10 (mm)

Fig. 4

Receiver operating characteristics curves for ROTEM tests. (a) Clotting time (CT) measured on the EXTEM (95% CI dotted lines); (b) amplitude measured at 10 min (A10, continuous line), 20 min (20, dotted line) and maximum clot firmness (MCF, dashed line) measured on EXTEM; (c) amplitude measured at 10 min (A10, continuous line), 20 min (20, dotted line) and maximum clot firmness (MCF, dashed line) measured on FIBTEM.

0.64 to 0.80; P < 0.001), A20 (AUC 0.73, 95% CI 0.65 to 0.81; P < 0.001) and MCF (AUC 0.74, 95% CI 0.66 to 0.82; P < 0.001). Again, no statistical difference was
observed between the three ROC curve areas. On FIB-TEM test, A10 value ≤ 3 mm should be used to predict postoperative blood loss with a sensitivity of 85% and a specificity of 62%. These parameters were used to construct the preliminary algorithm that will be tested in our population and compared with the algorithm published by Romlin et al.\textsuperscript{12} (Fig. 5).

On the basis of ROTEM values, we observed that application of our algorithm to the whole population would have led to the treatment of 32 of the 35 children with HBL (91%), although 63 of the 115 LBL group (55%) would have been treated. When the Romlin’s algorithm was applied to our population, 94% (33/35) of the HBL group would have been treated and 32 out of 36 of the LBL group would have received unnecessary treatment. When ROTEM analysis was performed according to the probability score we calculated ($n=65$), 27 out of 29 children included in the HBL group and 24 out of 36 included in the LBL group would have been treated with our algorithm. Using the Romlin’s algorithm, 29 out of 29 of the HBL group would have been treated and 32 out of 36 of the LBL group would have received useless treatment. The option with the best sensitivity and specificity was obtained when our own algorithm was applied only in children with a probability score of at least 0.20 (Table 3).

**Discussion**

This study has developed a specific algorithm, based on the characteristics of our population, which could be used to guide haemostatic therapy in bleeding children after CPB with an acceptable sensitivity and specificity.

Different authors have reported that both ROTEM and thromboelastography (TEG; Hemostasis system, 6 Faraoni et al.)

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**Table 3** Sensitivity, specificity, positive predictive value, negative predictive value of the studied algorithms

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total population</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tested algorithm</td>
<td>0.91 (0.77 to 0.98)</td>
<td>0.65 (0.57 to 0.72)</td>
<td>0.34 (0.24 to 0.44)</td>
<td>0.97 (0.93 to 0.99)</td>
</tr>
<tr>
<td>Romlin’s algorithm</td>
<td>0.94 (0.81 to 0.99)</td>
<td>0.96 (0.92 to 0.99)</td>
<td>0.33 (0.26 to 0.40)</td>
<td>0.97 (0.94 to 0.99)</td>
</tr>
<tr>
<td><strong>ROTEM Probability score ≥ 0.2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tested algorithm</td>
<td>0.93 (0.77 to 0.99)</td>
<td>0.33 (0.19 to 0.51)</td>
<td>0.53 (0.38 to 0.67)</td>
<td>0.86 (0.57 to 0.98)</td>
</tr>
<tr>
<td>Romlin’s algorithm</td>
<td>1.00 (0.88 to 1.00)</td>
<td>0.11 (0.03 to 0.26)</td>
<td>0.48 (0.35 to 0.61)</td>
<td>1.00 (0.40 to 1.00)</td>
</tr>
</tbody>
</table>

Data shown are number (95% CI). NPV, negative predictive value; PPV, positive predictive value.
Haemoscope Corporation, Niles, Illinois, USA) could be used at the end of CPB to guide the transfusion of blood products.\textsuperscript{13–15} In 2011, Hayashi \textit{et al.}\textsuperscript{16} observed that MCF and CT obtained on ROTEM correlated significantly with the amount of postoperative blood loss. However, only one case–control study has assessed the use of an algorithm on the basis of ROTEM in 100 children undergoing cardiac surgery.\textsuperscript{12} In this study, haemostatic therapy based on ROTEM analysis in bleeding children was associated with a significant decrease in RBC and FFP transfusion rates, although the frequency of administration of fibrinogen and platelets concentrates increased. Although the authors constructed the algorithm considering the presence of abnormal bleeding, they used cut-off values for ROTEM variables that were arbitrarily chosen without testing their relevance in the targeted population. As ROTEM does not accurately predict excessive postoperative bleeding, its indiscriminate use could increase the exposure of patients to unnecessary haemostatic treatment. Such an approach would be associated with an increased risk of transfusion-related complications and financial cost.\textsuperscript{14} For this reason, ROTEM should only be performed in a patient who is actually bleeding.

The results of our study confirmed that the routine use of ROTEM at the end of CPB would have increased the use of unnecessary haemostatic therapies to children who subsequently had low levels of postoperative bleeding. Currently, no ‘optimal’ criterion defining abnormal perioperative blood loss has been proposed in the literature. Some authors have defined abnormal bleeding as diffuse bleeding from capillary beds at wound surfaces, as assessed by the anaesthesiologist and surgeon inspecting the operative field and/or intraoperative blood loss exceeding 50 ml over 10 min.\textsuperscript{1,6,12,18} Rahe-Meyer \textit{et al.}\textsuperscript{19} used the weight of sponges to define the 5-min bleeding mass after CPB weaning and protamine administration. These authors used a threshold of 250 g to define abnormal blood loss. Even if this approach appears attractive, this threshold could not be applied in the paediatric population. In a recent study, we defined a simple probabilistic model, including preoperative body weight, the presence of cyanotic disease and the duration of wound closure (defined as the time between CPB weaning and the end of skin closure), which could be used to predict excessive postoperative blood loss in children undergoing cardiac surgery with CPB.\textsuperscript{9} Considering that the body weight and the presence of cyanotic disease are known preoperatively, duration of wound closure will be the main determinant of when the probability score will reach a value at least 0.20. At that moment, the child would be considered at risk of postoperative bleeding and ROTEM would be performed. When applied in this retrospective design, this approach allowed for the detection and the treatment of 77% of the children with HBL. Only 21% of the patients with LBL would have received unnecessary treatment. It is important to note that during the study period, the same surgeon performed all procedures, which could explain the homogeneity and the relevance of the parameter ‘duration of wound closure’.

The cut-off between normal and abnormal ROTEM values is difficult to define due to the huge interindividual variability observed with this monitoring technique.\textsuperscript{20} Although no statistical difference in baseline ROTEM has been reported between different age groups,\textsuperscript{20} the incidence of abnormal ROTEM values was increased in children with a congenital heart defect, especially in cases of cyanotic disease.\textsuperscript{4} In this study, we first defined cut-off values that could be used to develop a specific algorithm for our population. Interestingly, we observed that CT obtained on the EXTEM test and clot amplitude measured after 10 min (A10), obtained both on the EXTEM and the FIBTEM tests, were associated with high postoperative blood loss in our population. The sensitivity and specificity obtained for the different cut-off values are relatively low, which could be explained by the retrospective nature of our study in which some children considered as LBL should have received blood products during this period. However, the cut-off values we calculated for these parameters in our population differed significantly from those defined by the manufacturer, confirming that clinically relevant parameters need to be determined according to the specific nature of the studied population.

Interestingly, application of these cut-off values in our population-based algorithm, compared with the standard algorithm used by Romlin \textit{et al.},\textsuperscript{12} significantly decreased the exposure to unnecessary treatment in children who did not experience abnormal bleeding. These observations confirmed our hypothesis that algorithm-based strategies should be designed considering the specific characteristics of the studied population. Indeed, although the algorithm published by Romlin \textit{et al.}\textsuperscript{12} was prospectively tested, it was arbitrarily designed without consideration of the targeted population. In addition, this algorithm was applied both in neonates and older children, although the cause of the coagulopathy and the bleeding risk could differ between these two populations. If the application of the Romlin algorithm to our population is questionable, the goal of this analysis was to confirm that only an adequate algorithm, designed specifically for the targeted population, could be recommended.

Our study has several limitations. We performed a retrospective analysis of data collected from a single-centre departmental database and the results may not be applicable to other populations. The present study results should be considered as preliminary in nature and need to be validated in a much larger internal cohort. Further studies are needed to better define the relationship between sensitivity, specificity and postoperative
outcomes due to abnormal bleeding, in addition to the additional costs related to the use of point-of-care testing. The retrospective nature of this study could not guarantee the absence of bias. In order to decrease this bias as much as possible, we performed univariate and multivariate regression analyses, which are recommended in the case of a retrospective study. The retrospective nature of the analysis increased the risk of children being misclassified between HBL and LBL groups. We voluntarily did not review the transfusion data because this could have biased our interpretation. However, we have to keep in mind that some children included in the LBL group could have been transfused after the ROTEM analyses. We decided to adopt a definition of postoperative bleeding according to the distribution of blood loss observed after the first six postoperative hours. This definition was modified from the study published by Williams et al.\textsuperscript{11} and corresponds to the 75th percentile for blood loss in our population.\textsuperscript{9,21}

On the basis of the results obtained in this study, we designed an algorithm adapted to our population (Fig. 6). In the presence of a probability score of at least 0.20, we recommend that a ROTEM test should be performed. In addition, a clinical judgement of abnormal bleeding was considered with the aim of decreasing exposure to haemostatic treatment. Using this design, ROTEM will be performed only in children with ongoing bleeding.

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**Algorithm proposed for the management of bleeding in children undergoing cardiac surgery.**

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Algorithm-based management of bleeding children

The haemostatic agents proposed in our algorithm were defined according to our departmental practices. The choice between blood products and concentrate factors should be interpreted with caution. Both therapies have advantages and pitfalls. In a recent study, Rahe-Mayer et al. reported that in adults, fibrinogen concentrates could be used as a first-line therapy. However, no such study has been undertaken in the paediatric population. Hvas et al. observed that the addition of pooled platelets to whole blood obtained after CPB led to a complete correction of ROTEM, although clot stability was improved by the addition of fibrinogen, FFP and tranexamic acid. The results of this ex-vivo study could not be transposed to in-vivo management of a bleeding child and further well designed studies are needed to compare the effect of different haemostatic components on blood loss. We did not consider the use of platelet function assays in our algorithm. In a recent study, Hoftet et al. used multiple electrode aggregometry to assess platelet dysfunction in children undergoing cardiac surgery. The authors reported higher blood loss in cyanotic than in noncyanotic patients, despite better platelet aggregation. They concluded that platelet function assays alone might be unsuitable for predicting increased perioperative blood loss in children undergoing cardiac surgery. The same conclusion was formulated by Ranucci et al. Platelet function assays could not be considered in an algorithm-based approach in children until further studies have assessed their usefulness in this population. Finally, tranexamic acid was not considered in our algorithm because the drug was systematically administered according to our departmental dose scheme. Using this dose scheme, no hyperfibrinolysis was observed on ROTEM parameters. In addition, the sensitivity of ROTEM to detect hyperfibrinolysis in the perioperative period of cardiac surgery is still under discussion.

Despite the use of point-of-care testing and management algorithms, the incidence of unnecessary transfusion remains high. Romlin et al. reported that although a ROTEM-based algorithm significantly reduced the transfusion of RBCs and FFP, its use significantly increased the incidence of platelet and fibrinogen concentrate administration. The same results were highlighted in a study recently published by Haas et al. in children who underwent craniofacial surgery.

Our algorithm should be tested in a prospective study before it can be applied in routine clinical practice. It is also important to note that this algorithm was specifically designed for the studied population; we do not argue that it could be applied to others. In addition, dose–response analyses should be performed before we can recommend which haemostatic components should be used, as well as the optimal dosage of each of them.

In conclusion, this study described an algorithm starting with the detection of abnormal bleeding, in which ROTEM could be used to guide haemostatic therapy in bleeding children after CPB. Further studies are needed to test the efficacy of this specific algorithm-based approach, developed according to the characteristics of the targeted population, in order to decrease postoperative blood loss and transfusion requirements.

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