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**Multivariable predictors of substantial blood loss in children undergoing craniostomy repair:
Implications for risk stratification**

Running head (short title): Predictors of substantial bleeding in craniostomy repair

Research report

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What is already known:

- Substantial blood loss and associated coagulopathy are serious complications during the surgical treatment of craniosynostosis.

What this article adds:

- This study determines the predictive accuracy of thromboelastography and the platelet fibrinogen product in risk stratifying patients with substantial blood loss, which may lead to better allocation of blood products.

Abstract

Background: Operative treatment of craniosynostosis is associated with substantial blood loss, often requiring transfusion of packed red blood cells (PRBC) and coagulation products.

Aims: Analysis of thromboelastographic (TEG) parameters and platelet fibrinogen product to determine predictors of substantial blood loss, need for PRBC transfusion and coagulation products to improve risk stratification.

Methods: With IRB approval, we enrolled 120 children undergoing craniosynostosis repair with a standardized anesthetic, fluid management and TEG measurements at predefined times. Primary outcomes were intraoperative blood loss, need for PRBC transfusion and coagulation products. Multivariable logistic regression and receiver operating characteristic (ROC) curve analysis was applied to determine independent predictors of substantial blood loss and need for coagulation products.

Results: One hundred eighteen children were included in the analysis. Forty-four required PRBC transfusion (median 26 mL/kg; IQR: 22-42) with median blood loss of 56 mL/kg (IQR: 43-83). Factors associated with PRBC transfusion included type of surgery, duration of surgery, and three TEG parameters, α -angle, MA and K-time (all $P < 0.001$). A predictive algorithm was developed by subgroup analysis of cranial vault reconstruction (CVR) patients for substantial intraoperative blood loss (defined as ≥ 60 mL/kg) and need for coagulation products with ROC-derived cut-off values: platelet fibrinogen product < 343 , α -angle < 62 degrees, MA < 55 mm, K-time > 2.1 min. The best prognostic combination included at least 2 of these 4 predictors (sensitivity 89%, specificity 90%). Multivariable regression identified MA as the only independent predictor of coagulation product administration ($P < 0.001$) and ROC analysis identified MA < 46 mm as the optimal cut-off (sensitivity 86%, specificity 94%).

Conclusions: Risk for substantial intraoperative blood loss can be assessed using TEG parameters and platelet fibrinogen product whereas the need for coagulation products is strongly related to low MA. Patients susceptible to substantial blood loss can be risk stratified based on their TEG/platelet fibrinogen product profile.

Keywords: Craniosynostosis, risk factors, hemorrhage, thrombelastography, blood component transfusion

Introduction

Craniosynostosis is defined as a premature closure of one or more calvarial sutures. Surgical intervention is indicated to improve appearance and prevent complications of increased intracranial pressure such as cognitive impairment, auditory and visual loss. Correction of craniosynostosis includes various surgical techniques, some of which are associated with substantial blood loss. Cranial vault remodeling is the historical gold standard for treating this condition and yields predictable results in terms of cranial shape and volume expansion. The technique involves wide scalp dissections with multiple osteotomies followed by reshaping and stabilization of these cranial bones. Consequently, these procedures are lengthy (4-6 hours), and almost universally require blood transfusion; estimated percentage of blood volume loss ranges from 25% (open linear strip craniectomies, Pi (π) – procedure) to as high as 500% (total calvarial vault remodeling), and is associated with increased perioperative morbidity.(1-6) In the last two decades, less invasive alternatives have evolved to treat infants with craniosynostosis.(1, 7) One such technique, endoscopically assisted strip craniectomy has been offered to young infants (< 6 months of age) at our institution since 2004. The fused suture is accessed through small incisions and, with the use of an endoscope for visualization, the affected suture(s) is removed. Endoscopic assisted strip craniectomies have comparable cosmetic and volumetric outcomes to open cranial vault remodeling techniques, but with less operative time, blood loss and length of hospitalization.(8, 9)

The considerable differences in blood loss observed in our craniofacial population provide an opportunity to study the effects of a wide range of blood loss on clot characteristics in infants and young children using thromboelastography (TEG). Although TEG and rotational thromboelastometry are increasingly integrated in diagnosis and treatment of bleeding in high risk adult populations, e.g. cardiac surgical procedures(10) and trauma management(11), data in infants and young children for non- cardiac surgical procedures are scarce.(12) In this cohort of children with craniosynostosis the objective of this investigation was to evaluate the use of TEG parameters and the platelet fibrinogen product on predicting substantial blood loss and need for packed red blood cell (PRBC) transfusion and coagulation products as primary outcomes. For the entire cohort of 118 patients, our goal was to determine significant factors associated with PRBC transfusion. In addition, for the high-risk subset of patients susceptible to large amounts of blood loss while undergoing cranial vault remodeling, we sought to determine predictors of substantial blood loss and the need for coagulation products. Finally, we sought to develop a predictive algorithm to risk stratify patients with respect to the probability of substantial bleeding.

Methods

Patient population

After approval by Boston Children's Hospital Institutional Review Board 120 patients with craniosynotosis were enrolled. Parents with infants younger than 6 months of age had been given the option of choosing either endoscopic strip craniectomy followed by helmeting or traditional cranial vault remodeling procedures (IRB number; CRX08-12-0602-6). Patients referred after 6 months of age underwent cranial vault remodeling. Those patients undergoing cranial vault remodeling were a subgroup of patients recruited for a previously reported randomized double-blind placebo controlled trial of tranexamic acid (TXA) who had a complete data set of TEG parameters performed during surgery (IRB number; 05-01-002).(13) Written informed consent was obtained from the parents or legal guardians of the cranial vault remodeling group and waived for the endoscopic strip craniectomy group by the Institutional Review Board.

Anesthesia management

The standard induction method of all patients was a sevoflurane mask induction in oxygen/air or oxygen/nitrous oxide with muscle relaxant to facilitate intubation. All patients received 2 peripheral IV catheters. A central venous catheter was only placed if peripheral IV access was unsatisfactory for volume administration. Radial arterial catheters were routinely inserted for all patients with cranial vault remodeling but not endoscopic strip craniectomy, except three due to cardiac/pulmonary co-morbidities.(8) Twenty-two of the thirty eight patients undergoing cranial vault remodeling procedures received TXA as a 15 minute loading dose infusion of 50 mg/kg TXA during induction of anesthesia followed by an infusion of 5 mg/kg/h TXA until the end of the surgery. (13) None of the patients undergoing endoscopic strip craniectomy received TXA. Maintenance of anesthesia consisted of sevoflurane or isoflurane in oxygen/air supplemented with fentanyl or sufentanil. All patients were mechanically ventilated to maintain normocapnia. Esophageal temperature was maintained between 35.5° and 36.5°C. All infants were monitored with precordial Doppler ultrasound (Dual-Frequency Doppler, Model 915-BL, Parks Medical Electronics, Aloha, Oregon) for venous air embolus per routine protocol for neurosurgical procedures at our institution.

Isotonic crystalloid solutions (lactated Ringer or normal saline) were used for replacement of fluid deficit and maintenance fluids. Blood loss was replaced with additional crystalloid solution 1:3 for the first 10% - 20% estimated blood volume lost and then 1:1 with human albumin 5% for the next 20% estimated blood volume lost and thereafter PRBC/coagulation products were used if needed. For endoscopic strip craniectomies the decision to transfuse PRBC was at the discretion of the anesthesia and neurosurgical staff based on their clinical assessment and hematocrit (HCT) measurements; an automatic transfusion trigger was not used. For cranial vault remodeling procedures decisions regarding maintenance of

intravascular volume and blood transfusion was guided by monitoring arterial blood pressure, HCT with a transfusion trigger of 25%, and arterial blood gas measurements performed every 30 min. PRBC were transfused if the HCT was less than 25% in increments of 10–15 mL/kg to increase the hematocrit by approximately 7–10% and achieve a target HCT of approximately 30% at the end of the surgery. Fresh frozen plasma (FFP), platelets, and cryoprecipitate were administered in accordance with the recommendations of the American Society of Anesthesiologists Task Force on Blood Component Therapy.⁽¹⁴⁾ Intraoperatively FFP was transfused in 10-15 mL/kg increments if PT/PTT measurements were prolonged 1.5 times normal, fibrinogen < 1 g/L, or in the presence of diffuse microvascular bleeding from the wound margins despite appropriate attempts at surgical hemostasis and/or absence of visible clots in the surgical field. Intraoperative blood loss was calculated by the anesthesia team using the preoperative and postoperative hematocrits and estimated hematocrit of transfused PRBC as previously described by Kearney et al. ⁽¹⁵⁾ and usually used in other studies for this population.^(6, 13, 16) In the ICU coagulation products were transfused (cryoprecipitate if fibrinogen < 1g/L, FFP if PT/PTT measurements were prolonged 1.5 times normal, and platelets if platelet count < 50-100 x10⁹/L) to treat continued surgical drain output at the discretion of the ICU team.

For thromboelastography analysis (TEG®; Hemoscope, Niles, IL) 1.8 mL blood was collected after induction, at the end of the procedure and before administration of coagulation products. Traditional coagulation measurements including INR, PT, PTT, fibrinogen, and platelet count were determined before surgery in all infants and in infants with cranial vault remodeling before administration of coagulation products and at the end of the surgical procedure. The platelet fibrinogen product was defined as platelet count (10⁹ /L) times fibrinogen concentration (g/L).

All surgical procedures were performed by one of two plastic surgeons and a single neurosurgeon. Anesthesia management was provided by one of the study investigators (PMM, SMG).

Statistical Analysis

For outcomes including presence or absence of PRBC transfusion, intraoperative blood loss and need for coagulation products, univariate analysis included Fisher's exact test and Pearson chi-square for comparing categorical data and proportions including gender, ASA classification, type of surgical procedure, use of TXA, and the nonparametric Mann-Whitney U-test for assessing differences in medians and interquartile ranges for continuous variables such as age, weight, duration of surgery, platelet count, fibrinogen level, and TEG parameters. Among the 38 patients who underwent cranial vault remodeling, we applied multivariable logistic regression to identify independent predictors of substantial intraoperative blood loss (i.e., ≥ 60 mL/kg) and the need for coagulation products with the c-index used to judge the quality of model prediction and the Youden J-index in receiver operating characteristic (ROC) curve analysis to determine the optimal cut-off values for TEG parameters and the platelet fibrinogen product.⁽¹⁷⁾ We developed a ROC curve based on a simplified predictive algorithm according to the number of predictors (using their respective cut-off values) to characterize the accuracy (i.e., area under

the curve), sensitivity and specificity in classifying patients with and without substantial blood loss as well as those who required and did not require coagulation products.(18) Based on significant independent multivariable predictors, we derived the probability of substantial intraoperative blood loss with 95% confidence intervals. In addition, odds ratios and 95% confidence intervals were presented for significant multivariable predictors of substantial blood loss. Box-and-whisker plots were constructed to illustrate median values and interquartile ranges for TEG parameters and platelet fibrinogen product for comparing cranial vault remodeling patients according to blood loss and need for coagulation products. Statistical analysis was performed using IBM SPSS Statistics (version 23.0, IBM, Armonk, NY). Two-tailed values of $P < 0.05$ were considered statistically significant.

Power analysis revealed that a minimum sample size of 35 patients requiring PRBC transfusion would provide 90% power to detect differences of 1 standard deviation in each of the TEG parameters and 80% power for identifying factors predictive of substantial blood loss (version 7.0, nQuery Advisor, Statistical Solutions, Cork, Ireland).

Results

Study cohort and patient demographics

One hundred twenty patients with craniosynostosis were prospectively enrolled in this study. Two patients were excluded because of request for PRBC transfusion secondary to underlying comorbidity by the treating cardiologist/neonatologist. The schematic flow diagram in Figure 1 depicts the study cohort first stratified by PRBC transfusion and then by outcomes (substantial blood loss and need for coagulation products) for the surgical approaches. Forty-four patients (37%) in this cohort required PRBC transfusion, including all 38 patients undergoing cranial vault remodeling and 6 patients with endoscopic assisted strip craniectomy. Demographic information on the patients with and without PRBC transfusion is included in Table 1. Based on the entire cohort, patients who required PRBC transfusion had longer surgical procedures, were older and had higher body weight, although were not significantly different in terms of gender and ASA classification. The 44 patients who needed PRBC transfusion showed marked differences in TEG parameters (α -angle, MA, K-time) (all $P < 0.001$) compared to those not requiring transfusion. Moreover patients with PRBC transfusion had a significantly longer length of hospitalisation (median 3.2 days, range 1-7.2 days) compared to those patients ($n = 74$) without PRBC transfusion (median 1.3 days, range 1-3.5 days) ($P < 0.001$).

Predictors associated with blood loss requiring PRBC transfusion and need for coagulation product administration

Median blood loss (IQR) for the 44 patients requiring PRBC was 56 mL/kg (IQR 43-83 mL/kg) compared to 12 mL/kg (IQR 6-17 mL/kg) for the 74 patients not requiring PRBC transfusion ($P < 0.001$). Among patients who received PRBC transfusion the median amount of PRBCs was 26 mL/kg (IQR: 22-42

mL/kg). Factors significantly associated with PRBC transfusion by univariate analysis for the cohort of 118 patients include type of surgery, duration of surgery, and three TEG parameters, α -angle, MA and K (Table 1).

Given that PRBC transfusion was strongly associated with the type of surgical procedure (cranial vault remodeling), to identify predictors of substantial blood loss we focused our next sets of analyses on the subgroup of these 38 patients who underwent cranial vault remodeling (Table 2). The cut-off ≥ 60 mL/kg for substantial intraoperative blood loss was chosen as it pertained to the 50th percentile or median blood loss in this subgroup (IQR 46 – 87 mL/kg). Among patients in this subgroup who had blood loss < 60 mL/kg, the median PRBC transfusion was 22 mL/kg (IQR: 20-25 mL/kg) whereas in those with blood loss ≥ 60 mL/kg the median PRBC transfusion was 46 mL/kg (IQR: 34-57 mL/kg). The four significant univariate predictors of substantial blood loss ($n = 18$ out of 38) are the platelet fibrinogen product, and the TEG parameters α -angle, MA and K-time (all $P < 0.001$).

For the subgroup of patients undergoing cranial vault remodeling, who are susceptible to large amounts of blood loss, Table 3 shows the median and IQR of the five variables (the platelet fibrinogen product, α -angle, MA, K and R) significantly associated by univariate analysis with the need for perioperative coagulation product administration in 7 out of the 38 patients. The 31 patients not requiring coagulation products had a median blood loss of 55 mL/kg (IQR 43-63 mL/kg; range 26-118 mL/kg) with median PRBC transfusion of 25 mL/kg, (IQR 22-36 mL/kg; range 10-58 mL/kg) vs. the 7 patients requiring coagulation products had a median blood loss of 90 mL/kg (IQR 83-148 mL/kg; range 76-152 mL/kg; $P < 0.001$) with median PRBC transfusion of 52 mL/kg (IQR 40-71 mL/kg; range 30-75 mL/kg; $P < 0.001$).

Table 2, 3 and Supplementary Figure S1 A, B illustrate significant differences in median values of the platelet fibrinogen product between patients with substantial intraoperative blood loss ≥ 60 mL/kg vs. blood loss < 60 mL/kg (245 vs. 497, $P < 0.001$) and between patients receiving and not receiving coagulation products (161 vs. 403, $P = 0.007$). Table 2, 3 and Supplementary Figure S1 C, D also illustrate significant differences in the median values of MA between patients with substantial intraoperative blood loss ≥ 60 mL/kg vs. CBL < 60 mL/kg (48 mm vs. 58 mm, $P < 0.001$) and between patients receiving and not receiving coagulation products (44 mm vs. 57 mm, $P < 0.001$).

Simplified predictive algorithm for intraoperative substantial blood loss ≥ 60 mL/kg: A simplified predictive algorithm was developed as a clinical tool to predict the probability of substantial intraoperative blood loss ≥ 60 mL/kg among the subgroup of patients undergoing cranial vault remodeling. All four variables significant by univariate analysis (Table 2) were tested using multivariable logistic regression analysis to determine independent risk factors for blood loss ≥ 60 mL/kg and ROC analysis with the Youden J-index to identify the optimal cut-off value for each: platelet fibrinogen product < 343 , α -angle < 62 degrees, MA < 55 mm, and K-time > 2.1 min. This algorithm (Table 4) indicates that a patient with all 4 predictors present, has a theoretical probability of intraoperative blood loss ≥ 60 mL/kg of 92% (95% CI; 68-99%) which is consistent with the empirical data (12/13 patients = 92%). On the other extreme, the theoretical

probability of substantial blood loss among patients with none of the 4 predictors is 10%, which is quite similar to the actual observed data (2 of 17 patients = 12%). The ROC curve in Figure 2A shows the predictive accuracy of substantial blood loss based on the number of predictors from the multivariable analysis. The model and the corresponding algorithm have excellent predictive accuracy as judged by the area under the curve (AUC = 0.894, 95% CI: 0.780-1.000, $P < 0.001$). The presence of at least 2 of the 4 predictors results in the best combination of sensitivity (89%) and specificity (90%). In patients with substantial bleeding, 89% (16 of 18) had at least 2 predictors and in patients without substantial bleeding 90% (18 of 20) had 0 or only 1 predictor. The odds ratios for each multivariable predictor, representing the estimated risk of substantial intraoperative blood loss, are shown in Table 4; the 95% CI lower boundaries reflect appreciable risk for each predictor.

Multivariable logistic regression identified MA as the only significant independent predictor of coagulation product administration (likelihood ratio test = 20.28, $P < 0.001$) with an excellent discrimination assessed by ROC analysis (Figure 2B: AUC = 0.945, 95% CI: 0.865-1.000, $P < 0.001$). The Youden J-index indicated an optimal cut-off value of MA < 46 mm; this cut-off has a sensitivity of 86% (6 of 7 patients requiring coagulation products were correctly classified) and a specificity of 94% (29 of 31 patients not requiring coagulation products are correctly classified based on having an MA $\geq$ 46mm). Therefore, the overall accuracy using MA < 46 mm in predicting the need for coagulation product administration is 92% (35 of 38 patients are correctly classified).

Discussion

In a cohort of craniosynostosis patients, we have demonstrated that patients at risk for substantial blood loss (≥ 60 mL/kg) and the potential need for coagulation products can be identified utilizing an algorithm comprised of 4 variables: the platelet fibrinogen product and three TEG parameters, α -angle, MA and K-time. Patients with all 4 predictors present (platelet fibrinogen product < 343, α -angle < 62 degrees, MA < 55mm, and K-time > 2.1 min), have a 92% (95% CI; 68-99%) theoretical probability of intraoperative blood loss ≥ 60 mL/kg. Patients having none of the 4 predictors, have a 10% (95% CI; 3-32%) theoretical probability of substantial blood loss. MA was identified as the only multivariable significant independent predictor of coagulation product administration with an optimal cut-off value of MA < 46 mm.

In this study the cut-off ≥ 60 mL/kg for substantial intraoperative blood loss was chosen as it corresponded to the 50th percentile or median blood loss (IQR 46 – 87 mL/kg) in the subgroup of patients with substantial bleeding. This reflects the loss of approximately one blood volume. Clot strength as assessed by rotational thromboelastometry is determined by the interaction of platelets and fibrinogen. For a given fibrinogen concentration clot strength will increase as platelet count increases until a platelet count of approximately $100 \times 10^9/L$ is reached at which point the effect of platelet count on clot strength plateaus. In contrast, for a given platelet count, clot strength will continue to increase as fibrinogen concentration increases without a plateau effect. (19, 20) Fibrinogen activity is critical to both clot strength

and the speed of clot initiation and clot propagation.(21) The median value of the platelet fibrinogen product and the MA measurements in patients without the need for coagulation products was 403 and 57 mm respectively while in patients requiring coagulation products it was 161 and 44 mm respectively (Table 3, Supplementary Figure S1B and S1D). The platelet fibrinogen product is a clinically useful indicator of bleeding and reduced clot strength in circumstances where TEG is unavailable. This finding is consistent with a previous study in children undergoing cardiac surgery demonstrating a rapid decrease in MA when fibrinogen decreases below 1g/L, platelet count decreases below $120 \times 10^9/L$ and the platelet fibrinogen product decreases to less than 100.(22)

In the acute setting of substantial bleeding during extensive cranial vault remodeling procedures the clinical utility of the traditional coagulation tests (PT, PTT, INR) is limited due to lengthy laboratory turnaround times. Furthermore, PT/PTT are performed on centrifuged plasma fractions and provide information of only isolated portions of the coagulation cascade and are poor predictors of increased bleeding.(23-25) In our institution it takes 45 to 60 minutes until traditional test results are available. On the other hand, TEG as a point of care test provides quickly available, comprehensive information about the real time coagulation process. Initial TEG results are available in 10 to 15 minutes and real-time observation of evolving clot formation is possible online using a bedside remote graphical display. The question arises if earlier goal-directed TEG-based hemostatic resuscitation with specific component therapy could have prevented further blood loss in our patients. A practical recommendation would be to perform baseline TEG analysis following induction of anesthesia with subsequent analysis after scalp dissection, and during craniotomy before blood transfusion. During time periods of excessive blood loss arterial blood gas and TEG analyses might be indicated every 30-60 minutes to guide specific component blood product administration.

A limitation to our study is the lack of a rigorous transfusion protocol. Although TEG data was available at the time the anesthesia/surgical team made the decision to initiate component therapy, a standardized treatment algorithm for goal-directed TEG-based hemostatic resuscitation with FFP, platelets, and cryoprecipitate was not utilized.

Conclusions:

Risk for substantial intraoperative blood loss can be identified using a combination of TEG parameters and the platelet fibrinogen product, whereas the need for coagulation products is strongly related to a low MA, portending reduced clot strength. If TEG measurements are not available the platelet fibrinogen product may be a clinically useful indicator of bleeding and reduced clot strength. Our results suggest that patients undergoing cranial vault remodeling who are susceptible to large amounts of blood loss can be risk stratified based on their TEG/platelet-fibrinogen product profile. Well-controlled studies for the

development and validation of a pediatric goal-directed TEG-based protocol for hemostatic resuscitation with specific component therapy are needed.

Ethics approval:

The study was conducted following the approval by the IRB in Boston Children's Hospital.

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Conflicts of interest:

The authors report no conflict of interest.

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Table 1. Factors Associated with PRBC Transfusion for Entire Patient Cohort (N = 118)

Variable	Need for PRBC Transfusion		Median Difference (95% CI)	P Value
	No (n = 74)	Yes (n = 44)		
Age (months)	3 (2-5)	15 (8-37)		<0.001*
Weight (kg)	6.2 (5.5-7.2)	11.0 (7.8-13.5)		<0.001*
Gender				0.84
Male	49 (66%)	28 (64%)		
Female	35 (34%)	16 (36%)		
ASA Classification				0.34
1	7 (10%)	8 (18%)		
2	47 (63%)	27 (61%)		
3	20 (27%)	9 (21%)		
Surgical Procedure				<0.001*
ESC	74 (100%)	6(14%)		
Cranial Vault Remodeling	0 (0%)	38 (86%)		
Duration of Surgery (min)	45 (40-53)	240 (188-293)		<0.001*
Postoperative TEG Parameters†				
α -angle (deg)	75 (71-78)	65 (58-69)	10 (8-15)	<0.001*
MA (mm)	66 (61-69)	55 (48-60)	11 (7-14)	<0.001*
K-time (min)	1.0 (0.8-1.2)	1.8 (1.4-2.6)	-0.8 (-1.5, -0.6)	<0.001*
R (min)	4.8 (3.9-6.1)	5.0 (3.8-6.4)	-0.2 (-0.5, 0.2)	0.66

Continuous variables are median (interquartile range). PRBC = packed red blood cells; ESC = endoscopic-assisted strip craniectomy; TEG = thromboelastography; CI = confidence interval.

*Statistically significant, Mann-Whitney *U*-test for continuous data, Fisher exact test for categorical data.

†TEG measurements used in the statistical analysis were those obtained at the end of the surgical procedure or preceding administration of coagulation products.

Table 2. Factors Associated with Substantial Intraoperative Blood Loss in the Subgroup of Patients Undergoing Cranial Vault Remodeling

	Calculated Blood Loss (mL/kg)
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Variable	<60 mL/kg (n = 20)	≥60 mL/kg (n = 18)	Median Difference (95% CI)	P Value
Age (months)	31 (17-41)	11 (8-18)		0.003*
Weight (kg)	12.8 (11.0-14.6)	9.1 (7.5-11.5)		0.003*
Gender				0.94
Male	12 (60%)	11 (61%)		
Female	8 (40%)	7 (39%)		
ASA Classification				0.54
1	4 (20%)	2 (11%)		
2	13 (65%)	11 (61%)		
3	3 (15%)	5 (28%)		
Duration of Surgery (min)	267 (229-306)	241 (231-296)		0.48
Use of TXA	13 (65%)	9 (50%)		0.51
Platelet count (10 ⁹ /L)	268 (235-340)	196 (157-228)	72 (52-120)	<0.001*
Fibrinogen (g/L)	2.03 (1.55-2.29)	1.40 (1.12-1.85)	0.63 (0.30-1.05)	0.021*
Platelet Fibrinogen Product	497 (358-723)	245 (174-329)	252 (135-357)	<0.001*
Postoperative TEG Parameters†				
α-angle (deg)	68 (65-72)	57 (50-62)	11 (7-18)	<0.001*
MA (mm)	58 (56-62)	48 (44-52)	10 (7-16)	<0.001*
K-time (min)	1.5 (1.3-1.9)	2.7 (2.2-3.4)	-1.2 (-2.7, -0.7)	<0.001*
R (min)	4.7 (3.0-6.0)	5.3 (4.5-7.3)	-0.6 (-2.5, 0.2)	0.11

Continuous variables are median (interquartile range). PRBC = packed red blood cells; TXA = tranexamic acid; TEG = thromboelastography; CI = confidence interval.

*Statistically significant, Mann-Whitney *U*-test for continuous data, Fisher exact test for categorical data.

†TEG measurements used in the statistical analysis were those obtained at the end of the surgical procedure or preceding administration of coagulation products.

Table 3. Factors Associated with the Need for Perioperative Coagulation Products in the Subgroup of Patients Undergoing Cranial Vault Remodeling

Variable	Need for Coagulation Products		Median Difference (95% CI)	P Value
	No (n = 31)	Yes (n = 7)		
Age (months)	23 (13-40)	9 (8-12)		0.003*
Weight (kg)	11.6 (10.3-14.4)	8.6 (7.6-10.5)		0.004*
Gender				0.40
Male	20 (65%)	3 (43%)		
Female	11 (35%)	4 (57%)		
ASA Classification				0.86

1	5 (16%)	1 (14%)		
2	19 (61%)	5 (72%)		
3	7 (23%)	1 (14%)		
Duration of Surgery (min)	261 (232-300)	234 (224-297)		0.48
Use of TXA	20 (65%)	2 (29%)		0.11
Platelet count ($10^9/L$)	238 (201-306)	180 (74-236)	58 (24-95)	0.017*
Fibrinogen (g/L)	1.59 (1.23-2.13)	1.41 (1.02-2.08)	0.19 (-0.05, 0.30)	0.39
Platelet Fibrinogen Product	403 (270-609)	161 (134-332)	242 (148-330)	0.007*
Postoperative TEG Parameters†				
α -angle (deg)	66 (61-70)	49 (32-56)	17 (9-26)	<0.001*
MA (mm)	57 (50-60)	44 (31-46)	13 (8-20)	<0.001*
K-time (min)	1.8 (1.5-2.2)	3.3 (3.1-8.2)	-1.5 (-3.0, -1.0)	<0.001*
R (min)	4.7 (3.2-5.7)	8.0 (5.9-9.7)	-3.3 (-4.5, -1.4)	0.004*

Continuous variables are median (interquartile range). TXA = tranexamic acid; TEG = thromboelastography; CI = confidence interval.

*Statistically significant, Mann-Whitney *U*-test for continuous data, Fisher exact test for categorical data.

†TEG measurements used in the statistical analysis were those obtained at the end of the surgical procedure or preceding administration of coagulation products.

Table 4. Multivariable Predictors of Substantial Intraoperative Calculated Blood Loss for Patients Undergoing Cranial Vault Remodeling and Simplified Predictive Algorithm using Platelet Fibrinogen Product and TEG Parameters

Predictor and Optimal Cut-Off Value	Sensitivity (CBL $\geq$ 60 mL/kg)	Specificity (CBL < 60 mL/kg)	Odds Ratio (95% CI)
Platelet Fibrinogen Product < 343*	14/17 = 82%	16/19 = 84%	24.8 (4.4-143.3)
α -angle < 62 deg	14/18 = 78%	18/20 = 90%	31.5 (5.1-187.4)
MA < 55 mm	17/18 = 94%	17/20 = 85%	45.3 (6.7-207.0)
K-time > 2.1 min	14/18 = 78%	18/20 = 90%	30.2 (5.0-138.1)

Empirical Data using above Cut-Offs	Number of Patients	No. with CBL $\geq$ 60 mL/kg
All 4 predictors	13	12 (92%)
Any 3 predictors	3	2 (67%)
Any 2 predictors	2	2 (100%)
Any 1 predictor	3	0 (0%)
None of the 4 predictors	17	2 (12%)

Simplified Algorithm using Probability of CBL $\geq$ 60

Cut-Off†	mL/kg	95% CI
All 4 predictors	92%	68-99%
Any 3 predictors	79%	51-93%
Any 2 predictors	54%	30-76%
Any 1 predictor	27%	12-50%
None of the 4 predictors	10%	3-32%

CBL = calculated blood loss; TEG = thromboelastography; CI = confidence interval.

* Two of the 38 CVR patients did not have a measured platelet fibrinogen product.

† The multivariable logistic regression analysis adjusted for age as a covariate in the model.

Figure Legends

Figure 1: Schematic flow diagram showing the study cohort and stratification of surgical approaches and outcomes. The cohort consists of 118 craniosynostosis patients (80 endoscopic-assisted strip craniectomy, 38 cranial vault remodeling). Two patients were excluded because of request for packed red blood cell (PRBC) transfusion not due to blood loss but underlying comorbidity by the treating cardiologist/neonatologist. Overall, 44 patients had PRBC transfusion. In the high-risk cranial vault remodeling group, 18 patients had substantial blood loss and 7 received administration of coagulation products. PRBC = packed red blood cell; CBL = calculated blood loss; ESC = endoscopic-assisted strip craniectomy.

Figure 2: (A) Receiver-operating characteristic (ROC) curve showing the combined predictive accuracy of the four independent multivariable predictors of substantial blood loss (≥ 60 mL/kg) based on logistic regression among patients undergoing cranial vault remodeling. ROC analysis with the Youden J-index identified the optimal cut-off value for each of the four predictors: < 343 for platelet fibrinogen product, < 62 degrees for α -angle, < 55 mm for MA, and > 2.1 min for K-time. The ROC curve shows the relationship between sensitivity and specificity according to the number of predictors and the combined area under the curve (AUC) of 0.894, which is analogous to the c-index in logistic regression. The best combination of sensitivity and specificity pertain to at least 2 of the 4 predictors, showing a sensitivity of 89% and a specificity of 90%. The 45-degree dashed line represents the chance diagonal. This simplified algorithm based on the number of predictors clearly demonstrates excellent accuracy in predicting substantial intraoperative blood loss. **(B)** ROC curve based on maximum amplitude (MA) from TEG for predicting administration of coagulation products among craniosynostosis patients undergoing cranial vault remodeling. Here, MA was the only significant independent predictor of coagulation products using logistic regression and ROC analysis indicates excellent discrimination (area under the curve = 0.945, 95% confidence interval: 0.865-1.000, $P < 0.001$) and the Youden J-index identified an MA < 46 mm as the optimal cut-off; this cut-off has a sensitivity of 86% (6 of 7 patients who required coagulation products) and a specificity of 94% (29 of 31 patients not requiring coagulation products are correctly classified based on having an MA > 46 mm). The ROC curve for predicting the need to replenish coagulation

products in the high-risk group of patients undergoing cranial vault remodeling shows an excellent tradeoff between the true-positive rate (sensitivity) and the false-positive rate (1-specificity). The 45-degree dashed line is the chance diagonal, equivalent to random guessing or coin tossing; the optimal cut-off value of MA is denoted along the ROC curve and clearly shows excellent predictive accuracy.

Supporting information

Additional Supporting Information may be found in the online version of this article.

Supplementary Figure Legend

Figure S1: Box-and-whisker plots comparing median values of the platelet fibrinogen product in patients undergoing cranial vault remodeling between **(A)** patients with substantial intraoperative blood loss of ≥ 60 mL/kg versus < 60 mL/kg (245 vs. 497, $P < 0.001$) and **(B)** patients receiving and not receiving coagulation products (161 vs. 403, $P = 0.007$). Box-and-whisker plots comparing median values of maximum amplitude (MA) between **(C)** patients with substantial intraoperative blood loss of ≥ 60 mL/kg versus < 60 mL/kg (48 mm vs. 58 mm, $P < 0.001$) and **(D)** patients receiving and not receiving coagulation products (44 mm vs. 57 mm, $P < 0.001$). Lengths of the boxes represent the interquartile ranges (25th to 75th percentiles) and the lower and upper whiskers are the 2.5th and 97.5th percentiles. The nonparametric Mann-Whitney U-test was used to compare the groups.

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Figure 2A

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Figure 2B

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