Measuring coagulopathy in pediatric craniofacial surgery

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Abstract

Complex cranial vault reconstruction (CCVR) for repair of craniosynostosis is a procedure associated with high risk of bleeding and resultant coagulopathy. The goal of this study was to describe lab parameters in a cohort of pediatric patients undergoing CCVR and identify if standard hematologic and coagulation laboratory results could predict blood loss. We found that standard hematologic and coagulation laboratory parameters predicted intraoperative and postoperative blood loss, but provided limited mechanistic information to improve our understanding of coagulopathy in craniofacial surgery. Future laboratory-based studies would be useful in providing a comprehensive model of coagulopathy in this population.

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Abbreviations

BL	*Blood loss*
CBL	*Calculated blood loss*
CCVR	*Complex cranial vault reconstruction*
EACA	ε-aminocaproic acid
EBV	Estimated blood volume
ERCV	Estimated red cell volume
HCT	Hematocrit
hr	Hour
kg	Kilograms
PT	*Prothrombin time*
PTT	*Partial thromboplastin time*
RBC	*Red blood cell*
TIC	*Trauma-induced coagulopathy*
TXA	*Tranexamic acid*

ABSTRACT

Complex cranial vault reconstruction (CCVR) for repair of craniosynostosis is a procedure associated with high risk of bleeding and resultant coagulopathy. The goal of this study was to describe lab parameters in a cohort of pediatric patients undergoing CCVR and identify if standard hematologic and coagulation laboratory results could predict blood loss. We found that standard hematologic and coagulation laboratory parameters predicted intraoperative and postoperative blood loss, but provided limited mechanistic information to improve our understanding of coagulopathy in craniofacial surgery. Future laboratory-based studies would be useful in providing a comprehensive model of coagulopathy in this population.

BACKGROUND

Complex cranial vault reconstruction (CCVR) is a surgery primarily performed in infants and young children for repair of craniosynostosis.[1] CCVR is an intricate and high-risk procedure involving extensive scalp dissection and multiple osteotomies, resulting in hemorrhage and need for transfusion.[2–4]Although coagulopathy related to CCVR has been attributed to dilutional anemia, there is emerging evidence for alternative mechanisms for disrupted hemostasis in highly invasive surgical procedures.[5–9] This type of "trauma-induced coagulopathy" (TIC) has been distinguished from simple hemodilution and hypothermia.[6,10–13] Additional contributing factors for coagulopathy in acute injury states include activation of protein C, endothelial injury, platelet dysfunction, complement activation, and altered fibrinolysis.[6,10,12,13]

CCVR is considered to be a type of controlled trauma.[14] As such, exploring the mechanisms of TIC in this population is key to improving outcomes. Control of hyperfibrinolysis through use of antifibrinolytics has been shown to improve bleeding outcomes.[15–17] Other mechanisms of TIC are being explored, but are not fully elucidated.[18–21] One limitation to such analysis is the inadequacy of standard clinical coagulation testing to provide a picture of global hemostasis.[19,21,22] Conventional pro-coagulant based assays prothrombin time (PT) and partial thromboplastin time (PTT) provide limited information about procoagulant protein function, but fail to capture other factors affecting hemostasis, including fibrinolysis, inflammation, and changes in platelet function.[8,19,23] However, the PT and PTT assays are relatively inexpensive, widely available, and provide rapid feedback. Currently, most clinical teams must rely on these assays to assess hemostatic function in CCVR patients and to decide on clinical interventions.

OBJECTIVES

The primary aim of this study was to describe lab parameters in CCVR patients and identify if conventional hematologic and coagulation laboratory results could predict blood loss (BL).

PATIENTS / METHODS

Study Design and Setting

This single-center retrospective cohort study was approved by Vanderbilt University Medical Center Institutional Review Board (#191843) with waiver of informed consent and HIPAA authorization. We identified 95 CCVR patients (birth to 12 years) between September 1, 2015 and December 31, 2019. Demographic, surgical, and laboratory data from date of surgery through 30 days postoperatively were collected. Primary outcome measures were hematologic and coagulation laboratory parameters: hematocrit, platelet count, fibrinogen activity, PT, and PTT. Secondary outcome measures were intraoperative and postoperative calculated blood loss (CBL).

Administration of Antifibrinolytics

From September 2015 to September 2017, patients received ε-aminocaproic acid (EACA) as their antifibrinolytic agent [loading dose 100 mg/kg followed by infusion at 33 mg/kg/hr]. Our institution switched from EACA to tranexamic acid (TXA) in October 2017 due to a national shortage of EACA. TXA was subsequently used for all CCVR patients [loading dose 10 mg/kg followed by infusion at 5 mg/kg/hr].

Transfusion protocols remained consistent across the study time period. The threshold for red blood cell (RBC) transfusion was a hemoglobin < 8 g/dL with a goal hematocrit [?] 30% by the end of the case.

Measurement of Blood Loss

Since visual estimation of BL is grossly inaccurate in CCVR, CBL was used to quantify BL using a widely-accepted formula previously described in this population [2]: $\mathbf{EBV_{lost}(mL/kg) = ERCV_{lost}\ (mL)/[weight\ (kg)\ x\ HCT_{preop}/100]}$ where ERCV is estimated red cell volume, EBV is estimated blood volume, HCT is hematocrit, mL is milliliters, and kg is kilograms.

Data Collection and Statistical Analysis

Data were analyzed using a statistical software package (R 3.6.3). Wilcoxon rank sum test was used for continuous variables and Chi-square test for categorical variables. Ordinal logistic regression model was used to find the laboratory parameters associated with BL adjusting for age, weight, operative time, surgical vault category and syndromic status.

RESULTS AND DISCUSSION

In 95 pediatric patients undergoing CCVR for craniosynostosis, 47 patients received EACA and 48 patients received TXA. There were no differences in demographics, procedure category, operative time, or CBL between antifibrinolytic groups (Supplemental Table 1).[24] Perioperative hematologic and coagulation laboratory values were reviewed and the minimum or maximum value for each was recorded (Table 1). Preoperative laboratory values were within normal range on all patients and there were no differences between antifibrinolytic cohorts. Postoperative laboratory parameters are depicted in spaghetti plots in Supplemental Figure 1. Intraoperative hematocrit fell as expected with appreciated BL and did not fully recover for most patients, despite RBC transfusion intraoperatively in 59 patients (62%) and postoperatively in 22 patients (23%). No patients developed significant thrombocytopenia perioperatively. Hypofibrinogenemia was not seen and fibrinogen activity tended to increase postoperatively. PT and PTT were prolonged, consistent with TIC in this patient population; though reflecting only loss of procoagulant proteins. There was a trend toward a small peak in PT around 24-36 hours postoperatively, but this varied with several outliers. PTT tended to rise with time in the postoperative period but was only collected on a few patients (n=11).

CBL and transfusion rates in our cohort were similar to that reported in other large cohorts.[3,14,16,17,25] Intraoperative CBL for the cohort was 34 mL/kg, reflecting a percentage of total blood volume (BV) loss of 44%. Postoperative CBL was 12 mL/kg (total BV loss of 15%). We evaluated laboratory parameters to determine if they could be predictive of BL (Table 2). Intraoperative laboratory values did predict perioperative CBL. A lower intraoperative platelet count and fibrinogen predicted lower intraoperative CBL; lower intraoperative platelet count also predicted lower postoperative CBL. However, it is important to note that none of these patients were thrombocytopenic nor hypofibrinogenemic. In contrast, a higher intraoperative PT was associated with increased intraoperative CBL and a higher postoperative PTT was associated with increased postoperative CBL, possibly reflecting procoagulant protein losses or a more abnormal coagulation state. Postoperative laboratory values were not predictive of postoperative BL.

In our laboratory analysis, there was no significant difference in hematologic or coagulation laboratory parameters between patients receiving EACA vs. TXA. While there were no differences in laboratory parameters between the two cohorts, postoperative laboratory trends suggest ongoing disturbance of the hemostatic system beyond the operative period (Supplemental Figure 1). This includes an expected fall in hematocrit with a delayed improvement despite transfusion, a continuous rise in fibrinogen postoperatively, and in some patients, a persistently prolonged PTT. These results were limited by sampling in this observational study, not providing mechanistic data, but may provide an impetus for future laboratory investigation in this population.

Prior groups have looked at viscoelastic assays in pediatric CCVR as a potential alternative to monitoring standard coagulation assays.[19,21,30,31] Global assays of hemostasis, such as thromboelastography, potentially provide more useful information, but have their own limitations.[20,21,30–32] This testing was not performed

routinely in our cohort. Our data set was insufficient to draw firm conclusions about coagulopathy but suggests that future prospective laboratory-based studies looking at alternative coagulation assays may help elucidate some of the mechanisms of surgically-induced coagulopathy. Better understanding of the mechanisms of coagulopathy in CCVR has the potential to improve BL and surgical outcomes for children with craniosynostosis. A prospective study analyzing additional perioperative laboratory markers such as plasminogen activity, plasmin-antiplasmin complexes, markers of platelet activation by flow cytometry, and inflammatory cytokines would be beneficial in improving our understanding of TIC and BL in craniofacial surgery.

CONCLUSIONS

In this single center study, intraoperative standard hematologic and coagulation laboratory parameters predicted intraoperative and postoperative BL, but failed to provide a complete picture of the mechanisms of coagulopathy associated with BL in CCVR.

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RELATIONSHIP DISCLOSURE

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

AB and SR designed and coordinated the research. AB, PD, CL, MX and SR performed the research. All authors analyzed the data and contributed to the writing of the manuscript.

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FIGURE LEGENDS

Supplemental Figure 1 Spaghetti plots of postoperative laboratory values vs. time post-procedure. A) hematocrit levels (%) vs. time (minutes), B) platelet count (10^3/mcL) vs. time (minutes), C) prothrombin time (s) vs. time (minutes), D) partial thromboplastin time (s) vs. time (minutes), and E) fibrinogen (mg/dL) vs. time (minutes).

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