Journal of Cardiothoracic and Vascular Anesthesia ▮ (▮▮▮▮) ▮▮▮–▮▮▮

Contents lists available at ScienceDirect

ScienceDirect

journal homepage: www.jcvaonline.com

Original Article

Preoperative Thromboelastographic Profile of Patients with Congenital Heart Disease: Association of Hypercoagulability and Decreased Heparin Response

Zhe Amy Fang, MD, FRCPC*, Rachel Bernier, MPH*, Sirisha Emani, PhD†, Sitaram Emani, MD†, Gregory Matte, CCP, LP, FPP†, James A. DiNardo, MD*, David Faraoni, MD, PhD‡, Juan C. Ibla, MD*,[1]

*Divison of Cardiac Anesthesia, Department of Anesthesiology, Perioperative and Pain Medicine, Boston Children's Hospital, Harvard Medical School, Boston, MA

†Department of Cardiac Surgery, Boston Children's Hospital, Harvard Medical School, Boston, MA

‡Department of Anesthesiology and Pain Medicine, The Hospital for Sick Children, University of Toronto, Toronto, ON, Canada

Objective: To describe the demographic and thromboelastographic characteristics of patients with congenital heart disease presenting with decreased heparin response before cardiac surgery.

Design: Retrospective, observational study.

Setting: Single institution, tertiary, academic, university hospital.

Participants: The study comprised 496 pediatric and adult patients undergoing cardiac surgery for congenital heart disease.

Interventions: Retrospective review of medical records.

Measurements and Main Results: Data on preoperative thromboelastography (TEG), demographics, and response to heparin were collected retrospectively. Logistic regression analysis was used to study the association between TEG and response to heparin. Decreased heparin response (defined as activated clotting time < 480 s initial bolus of 300 U/kg heparin) was observed in 23.6% of patients presenting for surgery. Age distribution and preoperative coagulation profiles were similar for both nonresponders and responders to heparin. Preoperatively, nonresponders demonstrated all thromboelastrographic characteristics consistent with a hypercoagulable profile (shorter reaction time, K value, wider angle, and maximum amplitude). Univariate logistic regression identified all TEG variables significantly associated with decreased heparin response. After adjustment for age, procedure type, and the presence of cyanosis, a multivariate logistic regression model identified the TEG variable K (≤ 1.3 min) as being significantly associated with decreased heparin response (odds ratio 3.7; confidence interval 2.3-5.8; $p < 0.0001$).

Conclusions: Decreased response to heparin before cardiac surgery in patients with congenital heart disease is associated with preoperative hypercoagulability identified using a viscoelastic test. Additional studies are needed to better understand the etiology of decreased heparin response and potential clinical strategies to improve anticoagulation management.

Key Words: heparin resistance; pediatric cardiac surgery; congenital heart disease; thromboelastography; hypercoagulability

This study was supported by a Trailblazer Award, Department of Anesthesiology, Perioperative and Pain Medicine, Boston Children's Hospital, Boston, MA.

[1]*Address reprint requests to* Juan C. Ibla, MD, Division of Cardiac Anesthesia, Department of Anesthesiology, Perioperative and Pain Medicine, Boston Children's Hospital, 300 Longwood Avenue, Boston, MA, 02115.

E-mail address: juan.ibla@childrens.harvard.edu (J.C. Ibla).

REDUCED RESPONSE to heparin during cardiac surgery is defined as the inability to reach the target activated clotting time (ACT) before cardiopulmonary bypass (CPB) despite weight-adjusted doses of unfractionated heparin.[1,2] This phenomenon is common in adult patients presenting for cardiac

https://doi.org/10.1053/j.jvca.2017.12.013
1053-0770/

surgery and has been described to be associated with increased morbidity and mortality. In this study, severe heparin resistance was shown to be an independent predictor of death, with an odds ratio (OR) of 4.92.[3] Knapick et al postulated that increased thrombotic risk is associated with heparin resistance and was responsible for the increased mortality observed in their study.[3] The clinical risk factors predicting lack of heparin response in adult patients with coronary artery disease include preoperative exposure to heparin and the severity of preoperative symptoms.[3,4] The exact etiology of reduced heparin response in pediatric patients has been poorly described; however, heparin resistance is associated with low plasmatic antithrombin levels.[5] Lower levels of antithrombin result in decreased heparin binding to antithrombin and attenuated inhibition of thrombin activation necessary for full anticoagulation,[6,7] characterizing the clinical presentation of heparin resistance.

Hypercoagulability, defined as the propensity to venous or arterial thrombosis due to an abnormal and enhanced coagulation system,[8] is prevalent in patients with congenital heart disease.[9,10] The presence of hypercoagulability in patients with congenital heart disease is associated with several abnormalities in platelet aggregation and activation of the coagulation cascade.[11,12] Among patients with congenital heart disease, those with single ventricle physiology face the highest risk of hypercoagulability, abnormal clot formation, and long-term thrombotic complications.[13–16] The association of preoperative hypercoagulability and heparin response has not been identified previously in patients undergoing cardiac surgery and potentially is a significant risk factor affecting heparin dosing before cardiac surgery. On the other hand, the presence of hypercoagulability modifying heparin response has been described in pediatric patients with multiple myeloma. In this population, hypercoagulability and decreased response to heparin prophylaxis have been associated with the development of thrombotic events.[17,18] In addition, the association of hypercoagulability, abnormalities on thromboelastography (TEG), and thrombosis has been established for the pediatric sickle cell disease population.[19]

The objective of this article is to describe the demographic characteristics of patients presenting with decreased heparin response and to establish possible statistical associations between characteristics specific to congenital heart disease, preoperative coagulation parameters measured using TEG, and the binary outcome of decreased response to heparin. Overall, the authors hypothesized that patients presenting with preoperative TEG profiles consistent with hypercoagulability have decreased response to heparin before cardiac surgery.

Methods

With institutional review board approval (P-00000336), the authors reviewed the medical records of all pediatric and adult patients undergoing cardiac surgery with CPB at their institution from April 2015 to November 2016. A total of 1,498 records were reviewed; 1,151 had complete clinical data, of which 496 included preoperative TEG data. Patients were excluded if they did not require CPB, their indication for surgery did not include congenital heart disease, or their ACT values were not available. Statistical analysis presented in this study included only patients for whom TEG and clinical data were available, a total 496 patients. Preoperative TEG was performed on a blood sample collected from a central venous catheter in the operating room after the patient was anesthetized. TEG data that included reaction time (R), K value (K), α angle (A), and maximum amplitude (MA) variables were collected from the patient's medical record. Demographic data including age, type of procedure, presence of cyanosis, and ACT values after initial bolus of heparin before bypass also were collected. An ACT value of 480 seconds after the initial bolus of heparin is considered to be an adequate level of anticoagulation before initiation of CPB, in agreement with the authors' institutional policy and validated by multiple studies.[20,21] A patient's individual response to heparin was classified as nonresponder (NR) if ACT was < 480 seconds after the intravenous administration of 300 U/kg of heparin. If the ACT was > 480 seconds, the patient was classified as a responder (R). The patient's age at the time of surgery was analyzed in the following 5 subgroups: neonates < 30 days, infants < 1 year, children between 1 and 5 years old, children between 5 and 12 years old, and individuals 12 years of age and older, including adults. Similarly, surgical procedures were categorized into the following 5 groups: single ventricle repairs; 2 ventricular repairs; tetralogy of Fallot/pulmonary valve diseases; primary valvular lesions (tricuspid, mitral, and aortic); and combined procedures. In addition, the presence of preoperative cyanosis (defined as blood oxygen saturation level $< 85\%$ on room air) was incorporated into the analysis.

Cardiopulmonary Bypass, Anticoagulation, and Transfusion Protocols

Anesthesia and CPB management for all patients were standardized according to established departmental protocols. Intraoperative anticoagulation was initiated and maintained with unfractionated heparin to achieve an ACT > 480 seconds with a dose of 300 U/kg of heparin. ACT was measured with Hemochron Response (International Technidyne Corporation, Edinson, NJ) for all patients. A repeated dose of heparin was administered if the initial ACT was noted to be < 480 seconds. During CPB, ACT was maintained > 500 seconds with repeated doses of heparin. Priming of the CPB circuit was calculated based on the patient's estimated blood volume and total circuit volume to maintain a hematocrit $> 30\%$. A 1:1 mixture of packed red blood cells and fresh frozen plasma was used to prime the CPB circuit and maintain adequate intravascular volume during surgery. For patients weighing > 30 kg with an estimated dilutional hematocrit $> 30\%$, priming of CPB was performed with crystalloid or 5% albumin, according to institutional perfusion standards. An intraoperative red blood cell cell-saver system was used in every case to wash and reconstitute blood recovered from the surgical field and transfused both intraoperatively and postoperatively. Upon patient separation from CPB, heparin was reversed with protamine (4 mg/kg), and nonsurgical bleeding was treated with single or repeated platelet transfusions

Please cite this article as: Fang ZA, et al. (2018), https://doi.org/10.1053/j.jvca.2017.12.013