Platelet testing to guide aspirin dose adjustment in pediatric patients after cardiac surgery

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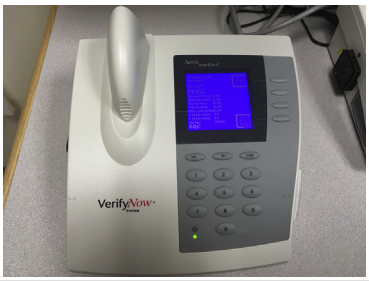
ABSTRACT

Objectives: Thrombosis is associated with increased morbidity and mortality in pediatric patients undergoing cardiac surgery. Although aspirin commonly is used for thromboprophylaxis, the utility of laboratory-based tests that assess aspirin efficacy have not been evaluated. We sought to determine the relationship between platelet aggregation testing and aspirin dose adjustment on thrombosis rates in this population.

Methods: Pediatric patients undergoing cardiac surgery who received aspirin and underwent platelet testing were studied retrospectively. Patients were excluded if they were treated with multiple agents or experienced thrombosis before the initiation of aspirin. Thrombosis events within 30 days after initiation of aspirin were recorded. Associations between aspirin responsiveness and thrombosis rate and aspirin dose adjustment and thrombosis rate were assessed with the use of multivariable logistic regression analysis.

Results: Suboptimal platelet response to aspirin was detected in 64 of 430 patients (15%) and thrombosis was detected in 11 patients (2.6%). Lack of aspirin responsiveness on initial testing was a significant risk factor for thrombosis ($P < .001$) independent of age, weight, diagnosis, and initial aspirin dose. Dose escalation based on aspirin testing was performed in 40 of 64 patients, and significantly lower rate of thrombosis was observed in patients who underwent dose escalation compared with those without dose escalation (0/40 vs 9/24, $P < .001$). By multivariable analysis, the only significant independent risk factor for thrombosis was failure to increase aspirin dose after initial unresponsiveness ($P < .001$).

Conclusions: Current practice of weight-based aspirin dosing may lead to subtherapeutic platelet inhibition in some children. Aspirin unresponsiveness is associated with increased risk of thrombosis after specific pediatric cardiac surgical procedures. Aspirin dose increase in unresponsive patients is associated with reduced risk of thrombosis. (J Thorac Cardiovasc Surg 2017;154:1723-30)



The Verify Now device allows automated testing of aspirin responsiveness in pediatric patients.

Central Message

Aspirin dose adjustment based on laboratory testing is associated with reduced risk of thrombosis in pediatric patients after cardiac surgery.

Perspective

Aspirin therapy is used frequently in pediatric patients after cardiac surgery. This study assesses the relationship between laboratory testing and clinical outcome of thrombosis in pediatric patients on aspirin therapy. A significantly greater rate of thrombosis was observed in patients with inadequate platelet inhibition, whereas dose escalation was associated with reduced thrombosis rate.

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Rates of thrombosis in pediatric patients undergoing congenital cardiac surgery range from 5% to 20%, and risk factors for thrombosis include neonatal surgery, single-ventricle physiology, and procedures that require insertion of prosthetic material into the circulation (shunts, baffles, or valves) or significant reconstruction of coronary arteries.[1] Patients considered to be at high risk for thrombosis after these procedures receive prophylaxis with aspirin (3-10 mg/kg/d) for several months to years postoperatively, and aspirin therapy is associated with reduced risk of thrombosis.[2] The efficacy of aspirin to

Scanning this QR code will take you to a supplemental video for the article.

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Abbreviations and Acronyms

AA = arachidonic acid
ARU = aspirin reaction units
AUC = Area under the curve
CI = confidence interval
CLIA = Clinical Laboratory Improvement Amendments
IQR = interquartile range
TEG-PM = thromboelastography with platelet mapping
UFH = unfractionated heparin

inhibit platelets can be assessed by assays that examine platelet aggregation in response to exogenous arachidonic acid (AA). Greater than 50% inhibition of AA-mediated platelet aggregation generally is considered to be indicative of laboratory testing-based aspirin responsiveness.[3]

Previous studies have highlighted significant interpatient variability in platelet response to weight-based aspirin dosing, with rates of aspirin unresponsiveness ranging from 10% to 26%.[4,5] Heterogeneity in aspirin response may reflect the inherent variability in platelet function across individuals.[6,7] Consistent with these findings, a recent prospective study in pediatric patients after high-risk cardiac surgery demonstrated a correlation of laboratory-based platelet inhibition with clinical outcomes of postoperative thrombosis.[8] However, the impact of testing-based aspirin dose titration on the incidence of postoperative thrombosis has not been studied.

The purpose of this study was to determine the association between platelet testing and thrombosis rates in pediatric patients at high risk for thrombosis after cardiac surgery. Furthermore, we sought to determine the differences in thrombosis rates between patients in whom platelet testing was used to escalate aspirin dose compared with patients in whom aspirin dosing was weight-based.

METHODS

Patients and Study Design

On the basis of previous observational studies, a clinical protocol was developed at Boston Children's Hospital to provide aspirin responsiveness testing in patients undergoing high-risk pediatric cardiac surgery beginning in 2013. Pediatric patients (age <18 years) with congenital heart disease undergoing cardiac surgery at Boston Children's Hospital between January 1, 2013, and February 15, 2016, were identified. Patients who were considered to be at high risk for thrombosis, received single-agent antiplatelet therapy with aspirin, and underwent aspirin responsiveness testing were analyzed retrospectively. Patients were included in the study if they were considered to be at high risk for postoperative thrombosis due to one or more of the following criteria: (1) age < 30 days at surgery; (2) single-ventricle physiology undergoing palliative surgery; (3) congenital heart disease requiring complex valve repair/replacement, intracardiac baffling, or ventricular assist device; or (4) surgery for coronary artery reconstruction. Patients were excluded if they underwent multimodal therapy with concomitant antiplatelet or anticoagulant medications (clopidogrel, low-molecular-weight heparin, or warfarin) or if they had a documented history of thrombosis before surgery. Patients were further excluded if thrombosis was documented after surgery but before aspirin administration or if aspirin was discontinued during their hospital course because of bleeding or other side effects. This study was approved by the Boston Children's Hospital Institutional Review Board.

VIDEO 1. Testing of aspirin responsiveness on the VerifyNow device. The video describes the basic operational testing procedure for assessing platelet function on blood sample using the VerifyNow system. Video available at: http://www.jtcvsonline.org/article/S0022-5223(17)31347-8/fulltext.

Anticoagulation Strategy

After cessation of bleeding after cardiac surgical procedure, patients received unfractionated heparin (UFH) for a period of 2 to 5 days until removal of central venous catheters. Although most patients received low-dose UFH (10 U/kg/h), patients undergoing aortopulmonary shunting for single-ventricle palliation or ventricular assist device received therapeutic UFH. After the initiation of parenteral feeding, aspirin (3-10 mg/kg/d) was administered either orally or via nasogastric tube. Aspirin was not initiated until resolution of thrombocytopenia (platelet count > 100). Doses typically were administered as fractions or multiples of 81 mg (20.25, 40.5, 81, or 162 mg) or 325-mg tablets.

VerifyNow Aspirin Responsiveness Testing

Laboratory-based testing for aspirin responsiveness was performed after at least 2 doses of aspirin had been administered. Testing was performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory (Cardiovascular Program Coagulation Laboratory) within Boston Children's Hospital. Aspirin responsiveness was measured with the VerifyNow system (Accumetrics Corp, San Diego, Calif) for quantitative measurement of platelet aggregation in response to exogenous AA as pervious described (Video 1).[9] Values < 550 aspirin reaction units (ARU) indicate impaired platelet aggregation in response to AA, suggesting therapeutic platelet inhibition; conversely, ARU ≥ 550 indicates subtherapeutic platelet inhibition.[9]

Thromboelastography With Platelet Mapping

A subset of patients early in the study period underwent additional platelet testing with thromboelastography with platelet mapping (TEG-PM; Haemonetics Corporation, Braintree, Mass) to validate results of VerifyNow testing when it was first introduced into clinical practice. Blood samples for the TEG-PM were obtained and tested as per the manufacturer's protocol.

Aspirin Dose Adjustment

Therapeutic decisions regarding dose adjustment were not prescribed by clinical protocol, although clinicians were provided a recommended algorithm for incremental dose adjustment based on VerifyNow as follows: if ARU ≥ 550 at daily doses of 20.25 mg, 40.5 mg, or 81 mg, then dose was