CHD

Aspirin unresponsiveness predicts thrombosis in high-risk pediatric patients after cardiac surgery

Sirisha Emani, PhD, Bethany Trainor, RN, David Zurakowski, PhD, Christopher W. Baird, MD, Francis E. Fynn-Thompson, MD, Frank A. Pigula, MD, and Sitaram M. Emani, MD

Objective: Thrombosis occurs in up to 26% of patients with congenital heart disease after cardiac surgery and is associated with increased morbidity and mortality. Aspirin is commonly administered to reduce the risk of thrombosis, yet aspirin responsiveness is rarely assessed. In this study, we hypothesize that inadequate response to aspirin is associated with increased risk of thrombosis after selected congenital cardiac procedures considered to be high risk for thrombosis.

Methods: Patients undergoing high-risk congenital cardiac surgery who received postoperative aspirin (N = 95) were studied. Response to aspirin was determined using the VerifyNow system several days after administration. Patients were monitored prospectively for 30 days for the development of a thrombosis event and the relationship between aspirin unresponsiveness and a thrombosis event was determined by the Fisher exact test.

Results: Rate of aspirin unresponsiveness (≥550 aspirin reaction units [ARU]) was 10 of 95 (10.5%) and was highest in patients weighing less than 5 kg given 20.25 mg/d of aspirin. Thrombosis events occurred in 7 patients (7.4%). Thrombosis was observed in 6 of 10 (60%) patients who were unresponsive to aspirin, compared with 1 of 85 (1.2%) patients who were responsive to aspirin ($P < .001$). In 2 patients who were unresponsive to the initial aspirin dose, an increase in dose resulted in an adequate therapeutic aspirin response (ARU < 550), suggesting insufficiency rather than true resistance in a subset of patients.

Conclusions: Postoperative thrombosis is associated with aspirin unresponsiveness in this patient population. In high-risk patients, monitoring of aspirin therapy and consideration of dose adjustment or alternative agents for unresponsive patients may be justified and warrants further investigation in a prospective trial. (J Thorac Cardiovasc Surg 2014;148:810-6)

Pediatric patients undergoing cardiac surgery are at higher risk for thrombosis than the general pediatric population.[1,2] Thrombosis rates reported in the literature range from 10% to 20%; the risk factors for thrombosis include young age, single ventricle circulation, and duration of central venous catheters.[3-6] Antiplatelet therapy with aspirin is commonly used to reduce thrombosis after high-risk cardiac surgical procedures that require either insertion of prosthetic material or prosthetic valves into the circulation or significant reconstruction of coronary arteries.

Aspirin resistance has been reported in up to 26% of pediatric patients with cardiovascular defects undergoing surgical procedures, and significant interpatient variability in response to a particular dose of aspirin exists.[7] Unpredictable aspirin responsiveness in pediatric patients may be caused by either inadequate dosing or true pharmacologic resistance. Measurement of platelet inhibition confirms the efficacy of aspirin, but is rarely performed in this population. This study tests the hypothesis that significant interpatient variability in aspirin responsiveness exists with the current dosing regimen used at our institution. Furthermore, we hypothesize that, among patients considered to be at high risk for thrombosis, the rate of thrombosis events is higher in patients who are unresponsive to aspirin compared with those who are responsive.

METHODS

Patients and Study Design

Pediatric and young adult patients with congenital heart disease (age <18 years) undergoing cardiac surgery at Boston Children's Hospital between January 1, 2013, and May 10, 2014, who were considered to be at high risk for thrombosis and deemed appropriate for aspirin therapy were enrolled into a prospective observation study after initiation of aspirin. Varying doses of aspirin (20.25, 40.5, or 81 mg/d) were administered orally or via nasogastric tube after postoperative bleeding complications were stabilized. Patients considered to be at high risk for thrombosis included those undergoing implantation of prosthetic material into the circulation (Blalock-Taussig shunt, stage 1 palliation, Fontan procedure, intracardiac baffles) and those undergoing coronary artery reconstruction (arterial switch operation, coronary artery unroofing, or reimplantation procedures). Exclusion criteria included: (1) coadministration of additional antiplatelet agents (clopidogrel, prasugrel); (2) inability to collect a blood sample; and (3) documented thrombosis before initiation of aspirin therapy. This

From Boston Children's Hospital, Boston, Mass.

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Address for reprints: Sitaram M. Emani, MD, 300 Longwood Ave, Building: 273 Bader, Boston, MA 02115 (E-mail: sitaram.emani@cardio.chboston.org).

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Abbreviations and Acronyms
ARU = aspirin reaction units
IQR = interquartile range

prospective study was approved by the Boston Children's Hospital Institutional Review Board and signed consent was obtained.

VerifyNow Aspirin Platelet Function Testing

Aspirin responsiveness was measured using the VerifyNow system (Accumetrics, San Diego, Calif) for quantitative measurement of platelet aggregation. This test incorporates activation of platelets in a sample of whole blood by addition of an agonist, arachidonic acid, and measures platelet aggregation to fibrinogen-coated beads in a premade testing cassette. Platelet aggregation leads to increased light transmittance recorded as aspirin reaction units (ARU). Values less than 550 ARU indicate aspirin responsiveness; values of 550 ARU or higher indicate unresponsiveness.

Platelet testing was performed after at least 2 doses of aspirin were administered to the patients. A sample of whole blood (2 mL) was drawn into a 3.2% sodium citrate vacuette tube (Greiner Bio-One, Monroe, NC) by direct venipuncture or from an indwelling catheter after collection of at least 5 mL of blood, and was incubated for at least 30 minutes (but no longer than 2 hours) at room temperature according to the manufacturer's recommendations. The sample was then loaded into the VerifyNow cartridge and analyzed by the system.

Assessment of a Thrombosis Event

Patients were followed prospectively to detect the occurrence of a thrombosis event within 30 days of initiation of aspirin. Weekly review of clinical records and imaging studies as well as direct interaction with care providers were used to detect thrombosis events. An echocardiogram was obtained within 2 weeks after surgery or before discharge in all patients according to standard clinical care protocol. Clinical thrombosis events (stroke, shunt thrombosis, limb ischemia) and evidence of thrombosis by imaging studies (echocardiography or cardiac catheterization) were recorded, and the interval to the event was documented. Variables believed to contribute to the risk of thrombosis (age, concomitant use of heparin) were also recorded.

Statistical Analysis

Distribution of continuous variables are represented as the median with the interquartile range (IQR) and comparisons were made using the independent Student *t* test. Categorical variables are expressed as percentages and compared using the Fisher exact test. Multivariate analysis was used to identify independent predictors of aspirin unresponsiveness and thrombosis. All statistical tests were 2-tailed.

RESULTS

Patient Characteristics

Although 110 patients met the initial inclusion criteria, only 95 were included in the study because of the inability to collect blood samples or the occurrence of a thrombosis event before initiation of aspirin. The general characteristics of the study population are shown in Table 1. Cardiac surgical procedures performed on patients given aspirin therapy in the postoperative period are listed in Table 1.

Median time from day of surgery to aspirin administration was 4 days with an IQR of 3 to 7 days. Aspirin testing was performed at a median of 4 days (IQR, 2-7 days) after initiation of aspirin. The median dose of aspirin administered was 6.5 mg/kg/d (IQR, 4.2-9 mg/kg/d). Although most of the patients received heparin in the immediate postoperative period, 28 of 95 patients (29.5%) were on heparin at the time of platelet testing. Unresponsiveness to aspirin therapy, defined as more than 549 ARU, was present in 10 of 95 (10.5%) patients. The rate of thrombosis after surgery in this cohort was 7 of 95 (7.4%), and the location of the thrombosis for each patient is listed in Table 1.

Effect of Aspirin Dose on Unresponsiveness

Aspirin dose administered in this cohort of patients was 20.25, 40.5, or 81 mg/d. The median age, weight and number of patients categorized by dosage are shown in Table 2. Of the 7 patients given 20.25 mg/d, 4 (57.1%) were unresponsive to aspirin therapy. All patients in this group were neonates less than 1 month old and weighed less than 5 kg. For patients receiving 40.5 and 81 mg/d of aspirin, 4 of 50 (8%) and 2 of 38 (5.3%) were unresponsive to aspirin therapy, respectively. Logistic regression indicated a significantly higher unresponsiveness rate for 20.25 mg/d versus 40.5 mg/d (57.1% vs 8%; $P = .003$) and 20.25 mg/d versus 81 mg/d (57.1% vs 5.3%; $P = .002$) but no difference between 40.5 mg/d versus 81 mg/d (8% vs 5.3%; $P = .56$). In 2 patients who were unresponsive to an initial aspirin dose of 20.25 and 40.5 mg/d, increasing the dose to 40.5 and 81 mg/d, respectively, resulted in an adequate response, suggesting insufficiency rather than true resistance in this subset of patients.

Relationship Between Aspirin Unresponsiveness and Thrombosis

Thrombosis was observed in 7 of 95 (7.4%) patients in this study. Thrombosis developed in 2 of 7 (28.6%) patients who received 20.5 mg/d, 3 of 50 (6%) patients who received 40.5 mg/d, and 2 of 38 (5.3%) patients who were given 81 mg/d (Table 2). Logistic regression indicated a significantly higher rate of thrombosis for 20.25 mg/d versus 81 mg/d (28.6% vs 5.3%; $P = .025$); no significant differences was observed between 40.5 mg/d versus 81 mg/d (6.1% vs 5.3%; $P = .69$). There was a trend toward a difference in the rates of thrombosis between patients given 20.25 mg/d versus 40.5 mg/d (28.6% vs 6%; $P = .06$); this difference was not statistically significant.

Thrombosis occurred more commonly in nonresponders compared with responders (Figure 1). Only 1 of 85 responders had a thrombosis event after the administration of aspirin, whereas 6 of 10 nonresponders had a thrombosis (1.2% vs 60%, respectively; $P < .001$). Multivariate logistic regression analysis indicated that, after adjusting for age ($P = .04$) and weight ($P = .76$), aspirin dose was an independent predictor of unresponsiveness ($P < .01$)