Safety and Efficacy of Warfarin Therapy in Kawasaki Disease

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Objective To describe the safety and efficacy of warfarin for patients with Kawasaki disease and giant coronary artery aneurysms (CAAs, ≥8 mm). Giant aneurysms are managed with combined anticoagulation and antiplatelet therapies, heightening risk of bleeding complications.

Study design We reviewed the time in therapeutic range; percentage of international normalization ratios (INRs) in range (%); bleeding events, clotting events; INRs ≥6; INRs ≥5 and <6; and INRs <1.5.

Results In 9 patients (5 male), median age 14.4 years (range 7.1-22.8 years), INR testing was prescribed weekly to monthly and was done by home monitor (n = 5) or laboratory (n = 3) or combined (1). Median length of warfarin therapy was 7.2 years (2.3-13.3 years). Goal INR was 2.0-3.0 (n = 6) or 2.5-3.5 (n = 3), based on CAA size and history of CAA thrombosis. All patients were treated with aspirin; 1 was on dual antiplatelet therapy and warfarin. The median time in therapeutic range was 59% (37%-85%), and median percentage of INRs in range was 68% (52%-87%). INR >6 occurred in 3 patients (4 events); INRs ≥5 <6 in 7 patients (12 events); and INR <1.5 in 5 patients (28 events). The incidence of major bleeding events and clinically relevant nonmajor bleeding events were each 4.3 per 100 patient-years (95% CI 0.9-12.6). New asymptomatic coronary thrombosis was detected by imaging in 2 patients.

Conclusions Bleeding and clotting complications are common in patients with Kawasaki disease on warfarin and aspirin, with INRs in range only two-thirds of the time. Future studies should evaluate the use of direct oral anticoagulants in children as an alternative to warfarin. *(J Pediatr 2017;189:61-5).*

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Giant coronary artery aneurysms (CAAs) caused by Kawasaki disease (KD) underlie virtually all the morbidity and mortality in this illness. To decrease the risk of coronary thrombosis in patients with KD and giant CAA, American Heart Association (AHA) recommendations[1] suggest treatment with aspirin together with anticoagulation. For children older than age 1 year, the most commonly used anticoagulant is warfarin. Combined therapy with warfarin and aspirin would be expected to increase the risk of bleeding complications in young, active patients. However, few published studies have explored the safety of combined warfarin and aspirin use in children with KD. In this retrospective case series, we sought to describe our experience with combined warfarin and aspirin therapy in patients with KD and giant CAA.

Methods

Eligibility criteria for inclusion in this single-center retrospective review included a diagnosis of KD; presence of ≥1 giant CAA, defined here as having an internal lumen dimension of ≥8 mm; and management of international normalization ratio (INR) levels by our Cardiac Anticoagulation Monitoring Program between June 2009 and June 2015. Among 19 patients with giant CAA treated with warfarin and aspirin and followed at our institution from June 2009 to June 2015, 9 (47%) had their warfarin dosages managed by our institutional anticoagulation service and form the cohort for this report. We excluded from review those patients with giant aneurysms whose warfarin was managed by caregivers outside our institution or who

AHA	American Heart Association
CAA	Coronary artery aneurysm
CT	Computed tomography
ED	Emergency department
INR	International normalization ratio
KD	Kawasaki disease
PINRR	Percentage of INRs in range
TTR	Time in therapeutic range

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received low-molecular-weight heparin rather than warfarin. This study was conducted with the approval from the Boston Children's Hospital Institutional Review Board.

Medical history variables, including sociodemographic data, bleeding, and clotting events were obtained from review of medical records in the patients whose INR was managed here between January 2009 and June 2015. Beginning June 2011, all INR data on patients managed by our Cardiac Anticoagulation Monitoring Program team were systematically recorded in a prospectively maintained anticoagulation database (Alere Standing Stone; Alere Inc, Waltham, Massachusetts). In the 4-year period from June 2011 to June 2015, INR statistics were obtained from StandingStone and included the time in therapeutic range (TTR) and the percentage of INRs in range (PINRR). We obtained INR values in patients with bleeding or clotting events before June 2011 through medical record review. These statistics do not include INRs obtained during initiation and uptitration of warfarin to therapeutic range.

TTR was calculated for each patient through the Alere StandingStone database using the Rosendaal method,[2] in which INRs are assumed to change in a linear manner between measurements and the INR values on the days without measurements were interpolated. The percentage of time during which a patient had an INR within the designated target range was taken as the patient's TTR.[3]

The PINRR is defined as the percentage of INR values within the target range out of the total number of INR values, irrespective of a time period. PINRR was calculated as the number of INR measurements within therapeutic range divided by the total number of INR measurements multiplied by 100 to provide a percentage.

We also reviewed medical records, including clinic visits, visits to the emergency department (ED) and discharge summaries, and recorded adverse events including death, thrombosis, and bleeding events. Bleeding events were classified according to guidelines of the International Thrombosis and Hemostasis Society[4] into categories of major bleeding, clinically relevant nonmajor bleeding, and minor bleeding events, defined as follows. Major bleeding is defined as new onset, visible bleeding, or signs or symptoms suggestive of bleeding with confirmatory imaging techniques, which can detect the presence of blood (eg, ultrasound, computed tomography [CT], magnetic resonance imaging), together with ≥1 of the following criteria: (1) decrease in hemoglobin ≥2.0 g/dL over 24 hours; (2) bleeding that is retroperitoneal, pulmonary, intracranial, or otherwise involves the central nervous system; (3) bleeding that requires surgical intervention in an operating room or suite, including interventional radiology; and/or (4) fatal (ie, primary cause of death or contributes directly to death). Clinically relevant nonmajor bleeding is defined as overt bleeding for which blood product is administered and not directly attributable to the patient's underlying medical condition or bleeding that requires medical or surgical intervention to restore hemostasis, other than in an operating room. Minor bleeding is defined as any overt or macroscopic evidence of bleeding that does not fulfill the above criteria for either major bleeding or clinically relevant nonmajor bleeding. Menstrual bleeding resulting in a medical consultation and/or intervention is classified as a minor bleeding event.

Statistical Analyses

Descriptive statistics were used to describe characteristics of patients and their benchmarks for INR management. As the time on warfarin varied between patients, we calculated the incidence of events per patient-year on warfarin as well as CIs.

Results

Among 9 patients with giant CAA treated with warfarin and aspirin and followed by our institutional anticoagulation service between June 2009 and June 2015, 5 were male. Their median age was 14.4 years (range 7.1-22.8 years old). The frequency of testing varied from weekly or every other week (home testers) to monthly (laboratory testers). Testing was performed more frequently when INR values were out of range. Testing of INRs was performed using home monitors in 5 patients and by laboratories in 3 patients. One additional patient had a home machine for testing, but subsequently returned to laboratory testing because of insurance issues with obtaining test-strips. The median length of time on warfarin therapy was 7.2 years (range 2.3-13.3 years). The goal INR was either 2.0-3.0 (6 patients) or 2.5-3.5 (3 patients); a higher goal INR was prescribed for patients with a history of coronary thrombosis or with exceptionally large aneurysms (eg, internal lumen diameter approaching aortic dimension). All patients were treated with low dose aspirin in addition to warfarin. The general guideline for aspirin was 3-5 mg/kg/d rounded to the nearest one-half tablet. One patient was treated with triple therapy: warfarin, aspirin, and clopidogrel.

The median TTR was 59% (range 37%-88%), and the median PINRR was 68% (range 52%-98%). During this time period, 3 patients had an INR value ≥6.0 (4 events) and 7 patients had at least 1 INR level between 5 and 6 (12 total events). Among the 7 patients with high INRs, 4 had home monitoring, 2 were monitored in a conventional laboratory, and 1 alternated between home and hospital monitoring because of insurance issues. Five patients had at least 1 low INR (ie, <1.5, in 28 separate events). Among 28 instances in which the INR was <1.5, 2 instances were related to purposeful holding of anticoagulation for a procedure. Two patients never had INR values <1.5 or ≥5. No patient was in range 100% of the time. We documented coronary thrombotic and bleeding events on each patient during the course of their warfarin therapy (**Table**). Three of the 9 patients had major bleeding episodes, 1 of whom had 2 additional episodes of clinically significant nonmajor bleeding. The incidence for both major bleeding events and CRNM bleeding was 4.3 per 100 patient-years of warfarin (95% CI 0.9, 12.6).

Among 3 patients with major bleeding events, 1 (patient 2; **Table**) had an acute hemopericardium 11 days after discharge from coronary artery bypass surgery. The patient developed a cough and fever at home. A chest radiograph at an outlying hospital showed cardiomegaly. She was evaluated in