Antithrombin Concentrate Use in Children Receiving Unfractionated Heparin for Acute Thrombosis

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Objective To characterize features of antithrombin concentrate (ATC) use in children receiving unfractionated heparin (UFH) therapy for acute thrombosis.

Study design All pediatric patients at Texas Children's Hospital who received ATC in the context of UFH therapy for acute thrombosis during February 2011 to May 2013 were analyzed.

Results Fifty-one children received ATC during UFH therapy for acute thrombosis. Median age was 3 months (IQR 1 to 18 months). Clinical indications included venous (53%), arterial (37%), venous and arterial (6%), and intracardiac (4%) thrombosis. Median baseline antithrombin (AT) level was 61% and UFH dose was 26 U/kg/h. The median dose of ATC was 49.9 IU/kg (IQR 32.6 to 50.0 IU/kg). Although most patients (86%) did not undergo a change in UFH dose, there was a significant increase in both AT and anti-factor Xa level after the first dose of ATC ($P < .001$ for both). There was no correlation between ATC dose or increment in AT level above baseline and the achievement of targeted anticoagulation by anti-factor X activity level. Adverse bleeding events occurred in 10% of patients.

Conclusions There was a significant change in AT and anti-factor Xa activity level after a single dose of ATC despite little to no change in dose of UFH. ATC appears to facilitate anticoagulation with UFH in some children with acute thrombosis but the degree of response is variable and dependent on factors identified in this study. Bleeding and other theoretical risks must be carefully considered. *(J Pediatr 2015;167:645-9)*.

Unfractionated heparin (UFH) is a large repeating disaccharide polyanion with heterogeneous molecular weight that binds to and causes a conformational change in antithrombin (AT).[1] This conformational change potentiates AT's inhibition of activated coagulation proteins. UFH binds nonspecifically to many proteins and cells, leading to interindividual variation in pharmacokinetics and pharmacodynamics. Given this pharmacologic unpredictability, in clinical practice, the effect of UFH is monitored and typically titrated to achieve an anti-factor Xa activity level within a range of 0.35 to 0.7 U/mL.[2]

UFH is commonly used to treat acute thrombosis. However, there is uncertainty about the optimal management of children, especially when large doses of UFH fail to achieve targeted level of anticoagulation. In adults on cardiopulmonary bypass, such difficulties are often ascribed to relative AT deficiency and managed through administration of AT concentrate (ATC).[3-5] Because young infants and children also exhibit relatively low circulating AT levels secondary to developmental hemostasis,[6] administration of ATC is rational and is recommended in published guidelines to facilitate UFH therapy.[7] Despite increasing use of ATC in children, data to support this strategy are scarce.[8]

Texas Children's Hospital (TCH) is a large tertiary care children's hospital with a substantial number of critically ill patients who receive UFH for treatment of acute thrombosis. Although actual practice among providers is variable, a common practice at TCH is to consider administration of ATC when a patient has AT levels <70% in the setting of difficult achievement of therapeutic UFH effect. The present study reviews the use of ATC to enhance UFH therapy in children with acute thrombosis. We focused on the effect of ATC administration on AT and anti-factor Xa levels and the occurrence of bleeding and other adverse events.

Methods

This institutional review board-approved retrospective cohort study was conducted at TCH between February 2011 and May 2013. This study included young infants and children ≤18 years of age who received human-derived ATC (Thrombate III; Grifols, Los Angeles, California) while on anticoagulation with UFH for acute thrombosis. Investigators identified eligible patients retrospectively through

aPTT	Activated partial thromboplastin time
AT	Antithrombin
ATC	Antithrombin concentrate
TCH	Texas Children's Hospital
UFH	Unfractionated heparin

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electronic pharmacy records. Patients on extracorporeal life support were not included. Diagnosis of acute thrombosis was confirmed by imaging. Data recorded included patient demographics (age and sex), hospital area, dose event details (date, time, and place of administration, dose volume), laboratory values before and after the first dose of ATC including anti-factor Xa, activated partial thromboplastin time (aPTT) and AT level, and mortality at 28 days after administration of the first dose of ATC.

Anticoagulation with UFH was initiated in all patients for treatment of acute thrombosis and managed in accordance with current pediatric practice guidelines.[2] In order to determine and safely maintain anti-factor Xa activity within the targeted range of 0.35-0.7 U/mL, anti-factor Xa, aPTT, and AT levels were drawn post-ATC administration. The precise timing of such testing in relation to ATC infusion varied considerably depending on clinician preference. The AT level was measured using a chromogenic assay and STA-Stachrom AT III kit reagents (Diagnostica Stago, Asnieres, France). Anti-factor Xa activity was measured using STA-Liquid anti-factor Xa assay (Diagnostica Stago), which does not use exogenous AT.

Delta AT level was calculated by subtracting pre- from post-ATC AT levels. Delta anti-factor Xa was calculated similarly. To standardize the approach for patients who received multiple doses of ATC, only the first dose was analyzed. A typical institutional dosing practice for ATC is to administer 50 IU/kg but this is sometimes rounded up or down to the nearest vial size to avoid waste. Post-infusion laboratory monitoring values were only included in the analysis if they were obtained within 24 hours after ATC administration. Patients were assessed for adverse events, including bleeding, symptomatic thrombotic, and allergic events, within 72 hours post-ATC infusion. Acute major bleeding and clinically relevant non-major bleeding was assessed according to the criteria by Mitchell et al.[9]

Statistical Analyses

Summary statistics are provided for patient characteristics using frequency and percentage or median and 25th and 75th percentiles (IQR). AT, aPTT, and anti-factor Xa levels obtained pre- and post-ATC infusion were compared using the Wilcoxon signed-rank test. The median increment in Δ AT per IU/kg of ATC administered was calculated using 2 methods for a subgroup of patients (n = 44) whose UFH was unchanged before and after dosing with ATC: (1) dose response curve analysis in which Δ AT per IU/kg of ATC was determined from the slope of the linear regression line; and (2) median and IQR values calculated by dividing each Δ AT by dosage of ATC in IU/kg for each patient. A similar analysis was conducted using Δ anti-factor Xa activity. The analysis focused on anti-Xa level rather than aPTT because the latter was not uniformly obtained on all patients. To better inform dosing decisions, the time interval required for 50% reduction of the peak Δ AT level was calculated for the subgroup of patients who received an ATC dose of 50 ± 5 IU/kg. Other analysis included comparison of baseline characteristics for patients who did or did not attain anti-factor Xa levels within the targeted range after the first dose of ATC using Fischer exact or Wilcoxon rank-sum test as appropriate. Pearson and Spearman's correlation was used to evaluate associations for normally and non-normally distributed data, respectively. A P value <.05 was considered statistically significant.

Results

A total of 51 patients were studied. The baseline characteristics are summarized in **Table I**. Most patients (53%) had isolated venous thrombosis. The majority (n = 44, 86%) did not undergo a change in UFH dose between the pre- vs post-ATC checks of AT and anti-factor Xa activity level. The 28-day mortality was 4%.

ATC Dose Administered

The median first dose administered was 49.9 IU/kg (IQR 32.6 to 50.0 IU/kg). The median number of ATC doses that patients received was 3 (IQR 1 to 6). Patient age correlated with ATC dose administered (r = 0.29, P = .0404), with younger patients receiving higher doses per kg of ATC.

Response

Only patients whose UFH dosing remained unchanged between pre- vs post-ATC AT and anti-factor Xa activity levels were included in the response analysis (n = 44). There was a significant increase in AT, anti-factor Xa level and aPTT after ATC as shown in **Table II**. A dose response plot of ATC dose vs Δ AT showed a positive correlation (**Figure**, A). Increment in Δ AT was 0.5% per IU/kg of ATC administered based on the slope of the regression line. Using the second method, the median increment in Δ AT per IU/kg of ATC was 0.6%. A plot of time elapsed after ATC dosing vs Δ AT for a subgroup of patients (n = 16) who received 50 ± 5 IU/kg of ATC estimates a Δ AT 1 hour post-ATC of 41%, suggesting a recovery of 0.8% per IU/kg of ATC 1 hour after dosing (**Figure**, B). By 18 hours after administration of 50 ± 5 IU/kg of ATC, Δ AT had declined by roughly 50%.

Next, we performed a similar analysis using Δ anti-factor Xa level. A dose response plot of ATC dose vs Δ anti-factor Xa did not show a strong association (r = 0.1916, P = .2241). Increment in Δ anti-factor Xa was 0.002 U/mL per IU/kg of ATC administered based on the slope of the line. Using the second method, the median increment in Δ anti-factor Xa per IU/kg of ATC was 0.003 U/mL. A plot of Δ AT vs Δ anti-factor Xa failed to demonstrate an association between the variables (r = 0.05, P = .7989). Dose of UFH correlated with Δ anti-factor Xa, with higher doses of UFH being associated with larger Δ anti-factor Xa, but was not statistically significant (r = 0.29, P = .0612). Subgroup analysis of patients with the lowest baseline AT levels (<50%) also failed to demonstrate a significant relationship between Δ anti-factor Xa and either ATC dose or Δ AT.