Pediatric Heparin-Induced Thrombocytopenia: Prevalence, Thrombotic Risk, and Application of the 4Ts Scoring System

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Objective To characterize heparin-induced thrombocytopenia (HIT) at a single pediatric center including the prevalence and the accuracy of the 4Ts scoring system as a predictor of HIT.

Study design In this retrospective cohort study, we identified 155 consecutive patients <21 years old with sufficient data for 4Ts scoring. The 4Ts scoring system is a validated pretest tool in adults that predicts the likelihood of HIT using clinical features. Hospital-wide exposure to unfractionated and low molecular weight heparin was determined by querying the hospital pharmacy database.

Results The majority of patients with suspected HIT (61.2%) were on surgical services. Prediction of HIT risk using initial 4Ts scoring found 3 (2%) had high risk 4Ts scores, 114 (73%) had intermediate risk 4Ts scores, and the remaining 38 (25%) had low risk 4Ts scores. HIT was confirmed in 0/38 patients with low risk 4Ts scores, 2/114 patients with intermediate-risk 4Ts scores, and all 3 patients with high-risk 4Ts scores presented with HIT with thrombosis. Of 12 positive HIT screening tests, results were falsely positive in 66.6% of patients with intermediate risk 4Ts scores and 100% of patients with low risk 4Ts scores. The prevalence of HIT was 0.058% and HIT with thrombosis was 0.046% in pediatric patients on unfractionated heparin.

Conclusions The prevalence of HIT appears significantly lower in pediatric patients compared with adults. Application of the 4Ts system as a pretest tool may reduce laboratory evaluation for HIT in heparin-exposed children with low risk 4Ts scores, decreasing unnecessary further testing, intervention, and cost. *(J Pediatr 2015;166:144-50)*.

Heparin-induced thrombocytopenia (HIT) is a prothrombotic, immune-mediated complication of unfractionated and low molecular weight heparin (LMWH) therapy. HIT is characterized by moderate thrombocytopenia 5-10 days after initial heparin exposure, detection of platelet-activating anti-platelet factor 4 (PF4)/heparin antibodies, and an increased risk of venous and arterial thrombosis.[1-3] The diagnosis of HIT is complicated, and the management of patients with suspected HIT includes immediate discontinuation of all sources of heparin and the initiation of an alternative anticoagulant.

The term HIT has been used to describe 3 groups of patients: those for whom laboratory testing for HIT was sent because of clinical suspicion ("suspected HIT"), patients with expert clinician opinion HIT and positive laboratory testing (HIT), and HIT with thrombosis (HITT).[4]

In adult patients receiving heparin, the prevalence of HIT is reported to be 0.5-5%.[5,6] Studies of adults have noted thrombotic complications at the time of the diagnosis of HIT in 30%-60% of patients.[2,7] The risk of thrombosis continues for several days after heparin withdrawal with 50% of the remaining patients diagnosed with HIT subsequently developing a thrombotic event.[7,8] Prospective data on the prevalence of HIT and HITT in pediatric patients are lacking, however, published case series/reviews of HIT in children suggest that the prevalence of HIT may be lower than in adults (1.5%-3.7%) and as low as 0.33% in non-neonates receiving cardiopulmonary bypass.[9-13]

Laboratory testing for suspected HIT includes immunoassays for anti-PF4/heparin antibodies and functional assays for platelet aggregation or activation. Immunoassays detect anti-PF4/heparin antibodies via enzyme-linked immunosorbent assay (ELISA). Immunoassays are available in most medical centers.[14,15] Unfortunately, immunoassays have a poor specificity (74%-86%) and anti-PF4/heparin antibodies can be detected in patients without HIT.[4,5,8] Functional assays, including the gold standard ^{14}C-serotonin release assay (SRA), measure platelet-activating effects of anti-PF4/heparin antibodies with

ELISA	Enzyme-linked immunosorbent assay
HEP	HIT expert probability
HIT	Heparin-induced thrombocytopenia
HITT	HIT with thrombosis
LMWH	Low molecular weight heparin
OD	Optical density
PF4	Platelet factor 4
SRA	Serotonin release assay
UFH	Unfractionated heparin

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>95% sensitivity and specificity for HIT.[8,16] However, they are technically complex to perform and are not routinely available at most medical centers.

Given the limitations of laboratory testing for suspected HIT, clinical scoring systems such as the 4Ts[17-19] and HIT expert probability (HEP) scores[20] have been developed to assess the pretest probability of HIT. The utility of the 4Ts clinical scoring system has been prospectively evaluated in adult studies and has proven useful in identifying patients at low risk for HIT,[18,21-23] with a negative predictive value of 98%-100%.[18] To date, the 4Ts scoring system has not been validated in pediatric patients. The main objective of this study was to evaluate the 4Ts clinical scoring system as a predictor of HIT in children. Our secondary objective was to assess the prevalence of HIT among all heparin-exposed patients at our institution during the study period.

Methods

This retrospective study was approved by the Boston Children's Hospital Institutional Review Board, which waived the need for informed consent. Patients with suspected HIT were identified from a database when clinical evaluation for HIT (ELISA testing) was sent at the discretion of their treating physician. A total of 176 consecutive patients with anti-PF4/heparin antibody testing were identified between October 1, 2007 and December 31, 2011. Sufficient clinical data for retrospective 4Ts scoring were available for 155 subjects. As several patients had repeat testing, a total of 191 samples were sent during this time period. Clinical information was collected by chart review.

To understand whether a procedure or underlying diagnosis contributes to risk of HIT, we categorized patients as medical or surgical, and cardiac or noncardiac. Cardiac medical patients were admitted for scheduled cardiac catheterization or medical management of fluid overload or systemic illness. Cardiac surgical patients were admitted for surgical repair. Patients included in the "other surgical" category underwent a variety of procedures including orthopedic surgery, lung or renal transplantation, and multivisceral organ transplantation. The group of "other medical" patients comprised a heterogeneous group of patients receiving critical care management of conditions associated with thrombocytopenia including vascular anomalies, sepsis physiology, and systemic chemotherapy for malignancy.

Definition of HIT/HITT

Patients were determined to have a diagnosis of possible HIT if they developed thrombocytopenia (platelet count fall >50% or platelet nadir ≥20 000 cells/μL) with recent or concurrent heparin exposure and the absence of other causes for thrombocytopenia, were positive PF4/heparin ELISA, and met expert consensus. Patients were determined to have possible HITT if they developed a thrombus in addition to meeting the above criteria. All patients with positive ELISAs were evaluated by 6 pediatric hematologists for expert consensus diagnosis.

Determination of Heparin Exposure

A Boston Children's Hospital Pharmacy database was queried for all orders of either unfractionated heparin (UFH) or LMWH during the study period. Systemic therapy orders, including subcutaneous UFH and LMWH prophylaxis orders, were counted. Nonsystemic doses (locks, flushes, continuous flushes, Port-a-caths, intra-arterial, and other line maintenance orders) were excluded. Remaining orders were recategorized by number of orders, number of admissions, and number of patients. The number of admissions including exposure to treatment or prophylactic doses of heparin was used as the denominator for prevalence calculations. Separate calculations were performed for UFH and LMWH exposures. No episodes of thrombosis with thrombocytopenia were identified in our database of all new thrombotic events requiring anticoagulation, aside from those with positive ELISA testing captured in this study.

4Ts Score

The Warkentin 4Ts scoring system[19] assigns scores based on the degree of *T*hrombocytopenia, the *T*iming of the fall in the platelet count, the presence of *T*hrombosis, and the absence of o*T*her explanations for the thrombocytopenia. Patients receive scores of 0-2 points for each of these categories before sending laboratory testing for HIT. In adults, the probability of HIT is predicted to be high in patients with scores greater than or equal to 6 points, intermediate in patients scoring 4-5 points, and low in patients scoring 3 or fewer points.[24] In our study, a 4Ts score was retrospectively assigned based on the clinical and laboratory findings at the time ELISA testing was sent. All patients in the ELISA database were scored by 1 reviewer who was blinded to the ELISA result at the time of scoring. Cases in question were reviewed with a senior hematologist and 4Ts scores for the 12 patients with positive ELISA results were also reviewed by a group of 6 pediatric hematologists at Boston Children's Hospital.

Laboratory Testing

During the study period, anti-PF4/heparin antibody testing was performed at a local reference laboratory (Massachusetts General Hospital, Boston, Massachusetts) using a commercial poly-immunoglobulin specific immunoassay (Asserachrom HPIA ELISA, Diagnostica Stago, Asnières, France). According to the manufacturer's instructions, an in-house control was run with every sample run and results were reported as positive if above the positive cut-off value, negative if below the negative cut-off value, and "negative but borderline, recommend repeat" if the values fell between the positive and negative cut-offs for that run. Quantitative ELISA optical density (OD) values were collected to assess if higher titer antibodies were more predictive of HIT, as described in adult HIT studies.[24-26]

During the period of this retrospective study, all laboratory studies were sent at the discretion of the treating clinician. Few confirmatory functional tests (SRA) were sent to our reference laboratory at the University of Pennsylvania and performed as described previously.[27,28] Given the absence