Catheter-Related Venous Thrombosis in Hospitalized Pediatric Patients with Inflammatory Bowel Disease: Incidence, Characteristics, and Role of Anticoagulant Thromboprophylaxis with Enoxaparin

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Objective To describe the incidence and characteristics of central venous catheter (CVC)-related thrombosis in hospitalized pediatric patients with active inflammatory bowel disease (IBD) and report the potential usefulness of anticoagulant thromboprophylaxis (AT).

Study design We conducted a retrospective study of patients who were admitted to our children's hospital in the last 2 years with active IBD and required a CVC and identified all patients with an objectively confirmed symptomatic CVC-related thrombosis. To assess the usefulness of a recently implemented institutional AT protocol, we compared the frequency of CVC-related thrombosis, nadir hemoglobin, and red blood cell transfusion requirements in patients who received AT with those who did not during the study period.

Results A total of 40 patients with IBD who required 47 consecutive hospitalizations were included. AT was administered during 24 of 47 hospitalizations (51%). Patients who received AT were similar to those who did not receive AT with regard to demographics, IBD phenotypes, extent of colonic involvement, and thrombotic risk factors. CVC-related thrombosis occurred in 5 of 23 hospitalizations (22%) in which AT was withheld compared with 0 of 24 hospitalizations (0%) in which patients received AT ($P = .02$). The red blood cell transfusion requirements and nadir hemoglobin were not significantly different between the 2 groups.

Conclusions We observed a high incidence of CVC-related thrombosis in hospitalized children with IBD. Administration of AT in our population was associated with significant reduction in CVC-related thrombosis without evidence of increased bleeding. *(J Pediatr 2018;■■:■■-■■).*

The incidence of pediatric inflammatory bowel disease (IBD) and the rate of hospital admissions for children and adolescents owing to IBD are both increasing.[1,2] Pediatric patients with IBD are at increased risk for developing venous thromboembolism (VTE).[3,4] Although the exact mechanism for the increased risk of VTE in this population has not been well-established, this risk is greater during states of disease flare, and especially with significant colonic involvement.[5-7] Moreover, inpatients of all age groups with IBD who develop VTE are at increased risk for VTE recurrence and in-hospital mortality compared with hospitalized non-IBD patients.[4,8,9] Risk factors for VTE in children with IBD include dehydration, immobilization, surgery, infection, parenteral nutrition, systemic steroids, and, most important, the placement of central venous catheters (CVCs).[10-13]

During states of severe disease flare, pediatric patients with IBD often require an indwelling CVC owing to the need for multiple intravenous mediations and parenteral nutrition. CVCs are known to be a strong independent risk factor for venous thrombosis.[14,15] The development of CVC-related thrombosis in this population can lead to significant morbidity and mortality, as well as considerable health care costs as a result of pulmonary embolism, embolic stroke, bloodstream infection, loss of venous access, and the development of post-thrombotic syndrome.[14,16,17]

Guidelines from the American College of Chest Physicians recommend routine anticoagulant thromboprophylaxis (AT) for adult patients requiring hospitalization for acute medical illness who are at increased risk of VTE and have no contraindication for AT.[18] Interestingly, the 2008 edition but not the current 2012 edition of the American College of Chest Physicians guidelines mentioned IBD as a risk factor for VTE.[19] More recently, the Canadian Association of Gastroenterology published consensus statements for the prevention of VTE in IBD patients recommending AT in hospitalized adult patients with moderate

AT	Anticoagulant thromboprophylaxis
CVC	Central venous catheter
DVT	Deep vein thrombosis
IBD	Inflammatory bowel disease
PICC	Peripherally inserted central catheter
RBC	Red blood cell
VTE	Venous thromboembolism

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to severe IBD flares without severe bleeding.[20] For pediatric patients admitted with IBD flare, AT was recommended in patients with a history of VTE and in overweight adolescents who undergo surgery.[20]

As a part of a quality improvement program, a surveillance system for identifying hospital-associated VTE was established at our institution. Data from the surveillance system suggested a high frequency of venous thrombotic events in inpatients with IBD. After multidisciplinary discussions, we implemented a protocol to consider AT with enoxaparin after CVC placement in any patient admitted to our institution with active IBD. The aim of this retrospective study was to describe incidence and characteristics of CVC-related thrombosis in hospitalized pediatric patients with active IBD and report the usefulness of AT with enoxaparin.

Methods

We conducted a retrospective chart review of all pediatric patients admitted between 2015 and 2017 to Children's National Health System with IBD (ulcerative colitis, Crohn's disease, or indeterminate colitis) who required CVC placement during their hospitalization. The study was approved by the Institutional Review Board at the Children's National Health System with waiver of informed consent. All CVCs in patients included in this study were single-lumen peripherally inserted central catheters (PICCs) that were placed in the upper extremity by interventional radiology under image guidance. Ultrasound guidance was used for vascular access and fluoroscopic guidance was used to confirm catheter tip location at the superior vena cava/right atrial junction. Catheter size was intentionally minimized and the majority of the PICCs placed were 3F in diameter. To identify study patients, we used radiology data mining software (MONTAGE Search and Analytics; Nuance communications Inc, Burlington, MA), which allows automated extraction of key words ("inflammatory bowel" or IBD or Crohn's or CD or "ulcerative colitis" or colitis or UC with search limited to all radiology procedure codes for CVC placement) from the unstructured radiology narrative in our radiology information system. CVC-related thrombotic events included in this study were identified prospectively using our surveillance system for identifying hospital-associated VTEs. The surveillance system was established at our center to detect hospital-associated VTEs in real time. This surveillance system relies on searching radiology reports using MONTAGE Search and Analytics (primary detection system) for specific key words (thrombosis or clot or thrombus or "deep vein thrombosis" or DVT or embolus or emboli or pulmonary embolism or occlusion) to identify inpatients who required imaging studies because of clinical concerns for VTE and the inpatient hematology consultation database (secondary detection system) followed by chart reviews of all possible cases to identify true VTE cases. Routine ultrasound screening to detect subclinical venous thrombotic events was not performed. A comprehensive thrombophilia panel was obtained in all patients with CVC-related thrombosis and included protein C activity, protein S activity, antithrombin activity, factor VIII activity, plasma homocysteine concentration, serum lipoprotein(a) concentrations, factor V Leiden mutation, factor II G20210A mutation, lupus anticoagulant assay, anticardiolipin antibodies (IgG, IgM, and IgA) and anti–beta-2-glycoprotein-I antibodies (IgG, IgM, and IgA).

AT Protocol

Initiation of AT with enoxaparin was determined at the discretion of the primary service in consultation with the inpatient thrombosis service. The first enoxaparin dose was administered on the same day, but after placement of CVC. The dose of enoxaparin was determined according to a weight-based institutional protocol. The starting dose for patients weighing less than 40 kg was 0.5 mg/kg per dose given subcutaneously every 12 hours. The dose was subsequently adjusted to achieve a target anti-factor Xa level of 0.1-0.3 U/mL. Anti-factor Xa levels were drawn 4-6 hours after patient had received at least 2 initial or adjusted doses. Patients weighing 40 kg or more received fixed enoxaparin dose of 40 mg subcutaneously every 24 hours without laboratory monitoring or dose adjustments. AT with enoxaparin was discontinued when the CVC was removed at the time of discharge.

Data Collection

Relevant demographic, clinical, laboratory, and radiologic data were collected from electronic medical records (Cerner PowerChart; Cerner Corporation, Kansas City, Missouri) into a Microsoft Excel database (Microsoft Corporation, Redmond, WA) for analysis. The entire study cohort included in the analysis consisted of 2 groups of patients who were admitted after implementation of our institutional AT protocol with an IBD flare and required CVC placement during their hospitalization. The first group included patients who received AT during hospitalization per our protocol. The second group included patients who did not receive AT during their hospitalization. In this group, AT was withheld by the primary service because of concerns about bleeding risk. The usefulness of AT was evaluated by determining the frequency of radiologically confirmed symptomatic CVC-related deep vein thrombosis (DVT), the proportion of patients requiring red blood cell (RBC) transfusions, the total number of RBC transfusions administered during hospitalization, RBC transfusions per day of hospitalization, and the nadir hemoglobin during hospitalization.

Statistical Analyses

Continuous variables are reported as median and IQR and compared using the Mann-Whitney *U* test. Categorical or binary data are reported as frequency and % and compared by Fisher exact test or χ^2 test as appropriate. Two-tailed values of *P* value less than .05 were considered statistically significant. Analysis of the data was performed using GraphPad Prism version 7.00 for Windows (GraphPad Software, La Jolla, California, www.graphpad.com).

Results

During the study period (2015-2017), 40 unique patients (median age, 14 years [IQR, 12-17]; 20 females) required 47

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