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Anticoagulation results in increased line salvage for children with intestinal failure and central venous thrombosis

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ABSTRACT

Purpose: The purpose of this study was to investigate whether anticoagulation (AC) results in thrombus resolution and increased line longevity in children with intestinal failure (IF) and catheter-associated central venous thrombosis (CVT).

Methods: A retrospective, single institution review was performed of children with IF who were dependent on parenteral nutrition with known CVT between 2006 and 2017. Frequency of catheter-related complications including infection, occlusion, and breakage were compared 18 months prior to and after starting AC. Thrombus resolution during anticoagulation was also determined. Data were analyzed using Poisson regression. p-Values <0.05 were considered significant.

Results: Eighteen children had ≥1 CVT, with the subclavian vein most commonly thrombosed (44%). All children were treated with low molecular weight heparin, and 6 patients (33%) had clot resolution on re-imaging while receiving AC. Bloodstream infections decreased from 7.9 to 4.4 per 1000 catheter days during AC ($p = 0.01$), and the number of infections requiring catheter replacement decreased from 3.0 to 1.0 per 1000 catheter days ($p = 0.01$). There were no significant differences in line occlusions or breakages.

Conclusion: Anticoagulation for children with intestinal failure and central venous thrombosis may prevent thrombus propagation, and decrease blood stream infections and line replacements. Further research is needed to determine optimal dosing and duration of therapy.

Level of Evidence: III; Retrospective Comparative Study.

Children with intestinal failure (IF) often require parenteral nutrition (PN) for extended periods of time, necessitating the use of long-term indwelling central venous catheters. Unfortunately, this makes them susceptible to catheter-associated complications such as central venous thrombosis (CVT), catheter breakage and occlusion, and central line associated blood stream infections (CLABSIs). Central venous thrombosis in these children is frequently catheter-related and is a major source of morbidity [1], with the loss of central access sites often resulting in transplantation evaluation because of the inability to deliver PN [2,3]. Venous thrombosis itself may predispose patients to additional catheter complications due to catheter-related sheaths composed of organized thrombus that forms around the tip of the catheter, resulting in catheter occlusion and acting as a medium for microbial growth and biofilm formation [4,5]. Once a CVT is identified, standard practice is to initiate anticoagulation therapy (AC) to resolve existing thrombus, and prevent formation of new clot.

The purpose of this study was to investigate the benefits of AC in children with IF and CVT in terms of thrombus resolution and the incidence of catheter-related complications.

1. Methods

1.1. Patients and study design

After study approval was obtained from the University of Texas Southwestern Medical Center Institutional Review Board, children on long-term PN for IF cared for by the Center for Intestinal Rehabilitation at Children's Health between 2006 and 2017 were reviewed retrospectively. Intestinal failure was defined as a primary gastrointestinal absorptive or motility disorder requiring at least 6 weeks of PN support to sustain normal growth. Children with IF were included if they were

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<18 years old, PN dependent, developed central venous thrombosis as documented by venous imaging, and were subsequently treated with AC. Central venous catheter complications were reviewed during two time periods, 18 months prior to, and 18 months after AC was initiated. Relevant clinical data was recorded, including duration of PN support, time to thrombosis, location of clot, the presence of thrombophilia, type and dose of AC, evidence of clot resolution on re-imaging, and reason AC was stopped. Measured outcomes included the number of CLABSIs, catheter occlusions, catheter breakages prior to and during AC therapy, and whether there was evidence of clot propagation or resolution.

1.2. Statistical analysis

Categorical variables were summarized using counts and percentages, and continuous variables were summarized using medians and interquartile ranges. Poisson regression was used for measures of association. A repeated measures subject effect was used to account for the dependency in the data. The number of catheter days was used as an offset variable to account for differences in the length of time each patient had a catheter. Data analysis was performed using SAS® software, Version 9.4. (Cary, NC, USA) with p-values <0.05 considered statistically significant.

2. Results

2.1. Study cohort and demographics

A total of 19 patients with IF developed central venous thrombosis while receiving PN and were treated with anticoagulation therapy between 2006 and 2017. One patient was excluded due to being lost to follow-up shortly after initiating therapy; therefore 18 patients were included in the final analysis. Baseline patient characteristics are listed in Table 1. Half (50%) of the children had IF due to short bowel syndrome, with the most common cause being necrotizing enterocolitis (22%). Patients were a median of 1.8 years (IQR 0.8–11.4 years) when central venous thrombosis was detected and had been receiving PN for a median of 414 days (IQR 176–882 days). Venous thrombosis was diagnosed most frequently with US (67%) or MRI (22%), with the subclavian vein being the most likely to be thrombosed (44%). Sixteen (89%) patients had a thrombophilia work-up after venous thrombosis was detected, and of those patients, 7 (44%) had a documented thrombophilia. This included anti-thrombin III deficiency (1 patient), Factor V Leiden mutation (1 patient), Prothrombin gene mutation (1 patient), protein S deficiency (1 patient) and both anti-thrombin III and protein C or S deficiency (3 patients).

Table 1
Characteristics of children with intestinal failure and central venous thrombosis (2006–2017).

Description	Number
Patients, N	18
Male gender	9 (50%)
Diagnosis	
Short bowel syndrome	9 (50%)
Motility disorder	8 (44%)
Enteropathy	1 (6%)
Median age at CVT diagnosis, years (IQR)	1.8 (0.8–11.4)
Median PN duration prior to CVT, days (IQR)	414 (176–882)
Presence of symptoms related to clot	9 (50%)
Extremity swelling	5 (28%)
Extremity pain	2 (11%)
Skin changes	2 (11%)
Thrombophilia work-up performed	16 (89%)
Protein C, S & ATIII deficiencies	2 (13%)
Factor V Leiden mutation, Protein C & S deficiencies	1 (6%)
Protein C & ATIII deficiencies	1 (6%)
Protein S deficiency	1 (6%)
Prothrombin gene mutation	1 (6%)
ATIII deficiency	1 (6%)

Values presented as n (%) unless otherwise specified. CVT = central venous thrombosis; IQR = interquartile range; PN = parenteral nutrition; ATIII = anti-thrombin III.

2.2. Anticoagulation therapy and follow-up

Low molecular weight heparin was utilized for AC in all patients, with the most common starting dose being 1 mg/kg/d (72%, range 0.5–1.5 mg/kg). The dose was subsequently adjusted to achieve anti-factor Xa levels between 0.3–0.5 IU/mL. The majority of patients (78%) were re-imaged, at a median of 210 days (IQR 58–553 days) after starting AC (Table 2). Six patients (43%) had clot resolution on re-imaging, two of whom (33%) had thrombophilia; and five patients (36%) had an additional site of thrombus on re-imaging, three of whom (60%) had thrombophilia. Twelve patients completed AC therapy (67%) with a median duration of 300 days (IQR 123–1553 days). All of these patients had their CVC removed, and had completed PN therapy, prior to stopping AC. None of the patients experienced any bleeding complications while receiving anticoagulation therapy.

2.3. Catheter-related outcomes

The number of CLABSIs in patients who developed central venous thrombosis significantly decreased from 7.9 to 4.4 per 1000 catheter days ($p = 0.01$) when comparing 18 months prior to and after starting AC. In addition, the number of CLABSIs requiring catheter replacement also significantly decreased from 3.0 to 1.0 per 1000 catheter days ($p = 0.01$). There was no statistically significant difference in either the number of catheter occlusions or breakages while receiving AC compared to prior to initiating therapy (Fig. 1).

3. Discussion

Our study provides a longitudinal analysis of PN-dependent children with IF and CVT treated with low molecular weight heparin, in which we found a significant reduction in the incidence of CLABSIs and ultimately the number of CVCs removed for infection after initiating anticoagulation therapy. We also saw a trend towards reduction in line replacements for line occlusion, although it did not reach statistical significance. Additionally, we found that thrombus resolution occurred in about 40% of patients, while approximately the same amount experienced clot progression. Thrombophilia was common in our cohort, with more of these patients experiencing clot progression. This data suggests the importance of screening for and treating CVT in this patient population.

Children with IF who are PN dependent are a group of patients for whom line salvage is of utmost importance, but who are unfortunately at increased risk of developing CVT. Although it is recommended that a central venous catheter be removed when associated with CVT, this

Table 2
Low molecular weight heparin dosing and thrombus evaluation in patients with intestinal failure who were anticoagulated for central venous thrombosis (2006–2017).

Description	Number
Patients, N	18
LMWH dosage	
0.5 mg/kg	4 (22%)
1.0 mg/kg	13 (72%)
1.5 mg/kg	1 (6%)
Re-imaging after LMWH therapy	14 (78%)
Median time to re-imaging, days (IQR)	210 (58–553)
Thrombus absent on re-imaging	6 (43%)
New thrombus on re-imaging	5 (36%)
No change in thrombus on re-imaging	3 (21%)

Values presented as n (%) unless otherwise specified. LMWH = low molecular weight heparin; IQR = interquartile range.