Patient Characteristics and Treatment Outcomes of Symptomatic Catheter-Related Arterial Thrombosis in Infants: A Retrospective Cohort Study

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Objective To describe the clinical characteristics, outcomes, and adverse events of treatment for symptomatic infant catheter-related arterial thrombosis.

Study design Single-center retrospective medical record review of 99 infants (age <365 days) with catheter-related arterial thrombosis, either following indwelling arterial catheter placement or cardiac catheterization, who were treated with anticoagulation over an 8-year span at a pediatric tertiary care center. Outcomes measured include thrombosis progression, bleeding events, and thrombus resolution following the treatment period.

Results Thromboses were secondary to indwelling arterial catheter placement in 51 (51.5%) and cardiac catheterization in 48 (48.5%). The median age at diagnosis of catheter-related arterial thrombosis was 52 days. All patients received therapeutic anticoagulation with either unfractionated heparin or low molecular weight heparin for a maximum of 28 days. Progression of catheter-related arterial thrombosis occurred in 8 (8.1%) patients. One (1%) major and 3 (3%) minor bleeding events occurred within the cohort. Complete thrombus resolution was observed in 60 (60.6%), partial resolution in 33 (33.3%), and no resolution in 6 (6.1%) following the treatment period. Factors associated with complete thrombus resolution included time from intervention to catheter-related arterial thrombosis diagnosis (median of 1 day vs 5 days in those who experienced thrombus resolution vs those who did not, $P = .035$), and iliac and/or femoral artery involvement ($P = .015$).

Conclusions Our treatment approach to infant catheter-related arterial thrombosis is safe and effective. Limitations of the study are its retrospective nature with a limited number of patients from a single institution. Additional prospective studies are needed to determine the optimal treatment approach to catheter-related arterial thrombosis in infants. *(J Pediatr 2021;231:215-22)*.

Arterial thrombosis in critically ill infants (age <365 days) are typically secondary to indwelling arterial catheters for invasive monitoring and cardiac catheterization in those with congenital heart disease. Acute and long-term consequences of catheter-related arterial thrombosis may include limb ischemia and necrosis, leg length discrepancy, claudication, and loss of vascular access site for future diagnostic and therapeutic interventions.[1-6]

Available literature describing the clinical and treatment characteristics and outcomes are limited, and there is a lack of evidence-based studies to guide therapy of infant catheter-related arterial thrombosis.[7-10] Consensus clinical practice guidelines suggests immediate removal of the indwelling arterial catheter and to initiate anticoagulation with unfractionated heparin (UFH) or low molecular weight heparin (LMWH) to complete a short course (5-7 days) of therapeutic anticoagulation, with consideration of thrombolysis or thrombectomy for those with limb- or organ-threatening arterial thrombosis.[11] However, this recommendation is based on limited data derived from a single-center case series and does not provide guidance for additional therapy in patients with persistent arterial occlusion. Options that clinicians must weigh when treating catheter-related arterial thrombosis include the length of anticoagulation therapy and use of antiplatelet or thrombolytic agents.

We performed a retrospective review at a large pediatric tertiary care center to evaluate the clinical characteristics, efficacy, and safety of our current institutional therapeutic strategy for infant catheter-related arterial thrombosis. Our review focused on arterial thrombosis in 2 infant patient populations,

ICD	International Classification of Diseases
LMWH	Low molecular weight heparin
PT	Prothrombin time
PTT	Partial thromboplastin time
UFH	Unfractionated heparin

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The authors declare no conflicts of interest. Portions of this study were presented at the American Society of Hematology/Oncology conference, May 2, 2019, New Orleans LA, USA; and accepted for the Thrombosis and Hemostasis Summit of North America, April 24, 2020, virtual meeting and presented as a poster presentation.

https://doi.org/10.1016/j.jpeds.2020.12.061

catheter-related arterial thrombosis caused by indwelling arterial catheter and cardiac catheterization, and outcomes recommended by the catheter-related arterial thrombosis Working Group of the International Society of Thrombosis and Haemostasis.[12]

Methods

We conducted a retrospective review of consecutive infants with symptomatic catheter-related arterial thrombosis between January 2010 and December 2018, from a large tertiary pediatric hospital (Texas Children's Hospital, Houston, Texas). Institutional standards of care for patients with arterial thromboses are consistent with the evidence-based clinical practice guidelines of the American College of Chest Physicians.[11] As per our institutional guidelines, indwelling arterial catheter placed in infants are flushed by a continuous heparin infusion (1 unit/hour of UFH; heparin concentration of 1 unit/mL administered at a rate of 1 mL/hour). Doppler ultrasonography was performed at the discretion of the treating medical provider following clinical suspicion of catheter-related arterial thrombosis. A catheter-related arterial thrombosis was defined as symptomatic if Doppler ultrasonography was performed and catheter-related arterial thrombosis diagnosed following new onset of any of the following clinical symptoms: change in color or temperature, swelling, poor perfusion, or decreased pulses. We did not perform screening Doppler ultrasonography of all patients following cardiac catheterization or placement of an indwelling arterial catheter. Incidentally identified catheter-related arterial thrombosis were excluded from this study. Laboratory investigations such as platelet count, D-dimer, fibrinogen, prothrombin time (PT), and partial thromboplastin time (PTT) were done in all patients prior to initiation of anticoagulation.

Patients with radiologic evidence of catheter-related arterial thrombosis were treated with therapeutic doses of UFH to attain anti-FXa levels of 0.3 to 0.7 or PTT of 70 to 110 seconds, or LMWH to attain anti-Xa levels 0.5 to 1, unless anticoagulation was contraindicated. Though it is not standard of practice at our institution, antithrombin concentrate was administered to patients at the clinician's discretion at doses of 40-50 units/kg. Addition of systemic or catheter-directed thrombolysis and/or thrombectomy was suggested for patients with limb-threatening thrombosis. Ultrasounds were performed at approximately 7, 14, 21, and 28 days following diagnosis and as needed if there was a clinical concern. For indwelling arterial catheter-related thrombosis, catheter removal was performed following diagnosis.[11] A subset of patients received aspirin at a dose of 5 mg/kg for cardiac shunt prophylaxis. Ethical approval for the study was obtained from the research ethics board of Texas Children's Hospital. The requirement for informed consent was not deemed necessary by the research ethics board given the retrospective nature of the study.

Study Procedures

Infants with symptomatic catheter-related arterial thrombosis were identified through electronic medical records using International Classification of Diseases (ICD)-9 and ICD-10 codes for arterial thrombosis (including ICD-9 codes starting with 444 such as 444.0, 444.01, 444.09, 444.1, 444.2, 444.21, 444.22, 444.8, 444.81, 444.89, 444.9; and ICD-10 codes starting with I74 such as I74.01, I74.09, I74.10, I74.11, I74.19, I74.2, I74.3, I74.4, I74.5, I74.8, I74.9). This resulted in 502 patients. Individual patient charts were manually reviewed and selected to include infants with symptomatic catheter-related arterial thrombosis confirmed via imaging. Exclusion criteria were age ≥365 day at the time of diagnosis with catheter-related arterial thrombosis, arterial thrombosis not clearly catheter-related, no anticoagulation administered because of bleeding concerns, no available follow-up ultrasound to assess response to therapy, and nonsymptomatic, incidentally diagnosed arterial thrombosis. A dysfunctional arterial line was not a criterion for symptomatic thrombosis in this study. All charts were manually reviewed to confirm eligibility criteria. Arterial thromboses secondary to umbilical arterial catheter placement were not included in this study. We included medical and radiologic information limited to 33 days postcatheter-related arterial thrombosis diagnosis, to include patient follow-up imaging and data that was collected within 5 days of the maximum intended treatment period, 28 days.

Participant charts were reviewed by at least 1 of the investigators. Demographic data, clinical features at presentation, diagnostic studies, treatment modalities, and outcomes were extracted and placed into an anonymized database. Ten percent of reviewed charts were randomly selected and double-checked by a second investigator to ensure accuracy of the data; no discrepancies in recorded data were identified.

Outcomes

As suggested by the International Society of Thrombosis and Haemostasis,[12] our primary outcomes were the percent of catheter-related arterial thrombosis with progression, which was defined as radiologically proven noncontiguous new thrombus or a contiguous progression of a previously defined thrombus; and the rate of major bleeding events, defined as fatal bleeding, bleeding with decrease in hemoglobin ≥2 g/dL in a 24-hour period, retroperitoneal bleeding, intracerebral bleeding, or bleeding requiring surgical intervention in the operating room.

Our secondary outcomes were the percent of complete radiologic clot resolution within 33 days of catheter-related arterial thrombosis diagnosis, defined as complete if the thrombus was no longer detected on Doppler ultrasonography and/or blood flow had returned to normal, and noncomplete if there was partial (defined as a reduction of the thrombus and/or still reduced blood flow) or unchanged (defined as no change in size or volume of thrombus and/or no change in blood flow) thrombus; catheter-related arterial thrombosis-specific and all-cause mortalities; and the rate of clinically relevant, nonmajor and minor bleeding, defined as overt bleeding

requiring blood product transfusion (not directly attributable to the patient's underlying condition), bleeding requiring medical or surgical intervention to restore hemostasis other than in the operating room, other bleeding for which medical attention has been sought and/or any overt macroscopic evidence of bleeding not fulfilling above criteria for major bleeding.

Statistical Analyses

Patient characteristics are summarized using median with 25th and 75th percentile, or frequency with percentage. Between-group comparisons were performed using Mann-Whitney for variables that were ordinal and not normally distributed. Contingency tables and Fisher exact or χ^2 tests were used to discern difference in the patient characteristics or outcomes as appropriate. Statistical analyses were performed using GraphPad Prism v 8.4.3 for Windows (GraphPad Software; www.graphpad.com).

Results

Study Participants and Baseline Characteristics

A total of 99 met eligibility criteria and were included in the analysis. Patient characteristics and detailed summary statistics stratified by catheter type are shown in **Table I**. Radiologically proven catheter-related arterial thrombosis was related to indwelling arterial catheter in 51 (51.5%) and cardiac catheterization in 48 (48.5%). The median age at diagnosis of catheter-related arterial thrombosis was 52 days (IQR 19-122 days) without a significant difference between the 2 groups. The patient weights, underlying comorbidities, and presence of infection were similar between the 2 groups. The cardiac catheterization group contained fewer Hispanic patients (22.9%, n = 11) compared with the indwelling arterial catheter group (49%, n = 25, $P = .012$). The overall median time from indwelling arterial catheter placement or cardiac catheterization to diagnosis of catheter-related arterial thrombosis was 2 days (IQR 1-6 days), patients in the cardiac catheterization cohort had shorter time to catheter-related arterial thrombosis diagnosis compared with the indwelling arterial catheter cohort, 1 vs 5 days, respectively ($P < .01$).

Thrombus Characteristics

The majority of the thrombi affected arteries of the trunk and lower extremities, most commonly affecting the femoral (85.8%, n = 85) and iliac (74.7%, n = 74) arteries. Complete breakdown of thrombosis location is in **Table I**. The thrombus was occlusive in 84.8% (n = 84) at the time of diagnosis, with a higher frequency of occlusive thrombi in the cardiac catheterization group (97.9%, n = 47) compared with the indwelling arterial catheter group (72.5%, n = 37, $P < .01$). A total of 31 (31.3%) had undetectable pulses via bedside Doppler at presentation, with no difference noted between the indwelling arterial catheter and cardiac catheterization groups. No patients had skin necrosis or ulceration at presentation.

Treatment Characteristics and Bleeding Events

LMWH was administered as initial therapy in 53 (53.3%) patients and UFH in 46 (46.5%), with more patients in the indwelling arterial catheter group receiving UFH compared with the cardiac catheterization group, 56.9% (n = 29) vs 35.4% (n = 17, $P = .044$), respectively. This likely reflects that all patients with indwelling arterial catheter-associated catheter-related arterial thrombosis were critically ill requiring arterial catheter placement for invasive blood pressure monitoring and frequent arterial laboratory assessment. Cardiac catheterization is often performed as an elective procedure to monitor the patient's underlying cardiac disease in the absence of an acute illness. As is the case, patients in the cardiac catheterization group overall had a lower risk of bleeding making LMWH a more appropriate initial anticoagulant compared with the indwelling arterial catheter group. A total of 38 (38.3%) and 71 (71.7%) patients had anticoagulation levels (heparin level for those receiving UFH and anti-Xa level for those on LMWH, with UFH and LMWH standards, respectively) within therapeutic range at 24 and 72 hours. Those in the indwelling arterial catheter group had a lower rate of achieving therapeutic coagulation levels within 24 hours (21.6%, n = 11) compared with the cardiac catheterization group (56.3%, n = 27, $P < .01$), though this was not associated with thrombus resolution at the end of the treatment period. The higher 24-hour therapeutic level rate in the cardiac catheterization group also likely reflects that more patients in that group were started on LMWH compared with the indwelling arterial catheter group. The median duration of anticoagulation received was 24 days (range 6-28), with 40 (40.4%) receiving 28 days of anticoagulation.

Antithrombin concentrate was administered in 32.3% (n = 32) of all patients; 28 of these received antithrombin because of a difficulty achieving therapeutic UFH levels (the other 4 patients were given replacement because of low antithrombin levels alone in the setting of therapeutic anticoagulation). Only 5 (17.9%) of the 28 patients achieved therapeutic heparin levels within 24 hours of antithrombin administration. A minority of patients received interventional therapy, including thrombolysis in 1 (1%) and thrombectomy in 4 (4%). Patients were taking aspirin at the time of catheter-related arterial thrombosis diagnosis 13.1% (n = 13) of cases, with no difference noted between the cardiac catheterization and indwelling arterial catheter groups. A single major bleeding event and 3 nonmajor bleeding events occurred. The major bleeding occurred in a premature 2-month-old (adjusted to 38 postmenstrual age) who was admitted with group B Streptococcus meningitis, sepsis, and ulcerative adenitis. He required extensive resuscitation (including high frequency oscillator ventilation) for cardiopulmonary compromise and developed bilateral grade 1 germinal matrix hemorrhages shortly after his admission. He subsequently developed a line-associated femoral artery thrombosis and was treated with UFH. One week later, he was noted to have expansion of the intracranial hemorrhage, in addition to the development of a large dural venous sinus

Table I. Patient characteristics stratified by type of catheter

Variables	Overall n = 99	Indwelling arterial catheter n = 51	Cardiac catheterization n = 48	*P* value
Age at diagnosis of thrombosis, d				.076
Median (IQR)	52 (19-122)	77 (21.5-146)	28 (14.5-109.2)	
Range (min-max)	0 to 330	4 to 330	0 to 326	
Sex, n (%)				1.0
Male	53 (53.5)	27 (52.9)	26 (54.2)	
Female	46 (46.5)	24 (47.1)	22 (45.8)	
Ethnicity, n (%)				.012
Hispanic	36 (36.4)	25 (49)	11 (22.9)	
Non-Hispanic	63 (63.6)	26 (51)	37 (77.1)	
Weight, kg				.53
Median (IQR)	3.82 (2.95-5.1)	3.9 (3.1-5.4)	3.66 (2.9-4.9)	
Range (min-max)	1.72 to 8.5	2.2 to 8.5	1.7 to 8	
Infection at the time of diagnosis, n (%)				.060
Yes	23 (23.2)	17 (33.3)	7 (14.6)	
No	76 (76.8)	34 (66.7)	41 (85.4)	
Comorbidities,*n (%)				.25
Prematurity	27 (27.3)	16 (31.4)	11 (22.9)	
Cyanotic heart disease	35 (35.4)	17 (33.3)	18 (37.5)	
Noncyanotic heart disease	48 (48.5)	21 (41.2)	27 (56.3)	
Other	14 (14.1)	10 (19.6)	4 (8.3)	
Pulses undetectable via Doppler, n (%)				.37
Yes	31 (31.3)	13 (25.5)	18 (37.5)	
No	50 (50.5)	29 (56.9)	21 (43.8)	
Unknown	18 (18.2)	9 (17.6)	9 (18.8)	
Time (d) from indwelling arterial catheter or cardiac catheterization to catheter-related arterial thrombosis, n (%)				.0003
Median (IQR)	2 (1-6)	5 (1.25-8)	1 (1-2)	
Range (min-max)	0 to 30	0 to 20	0 to 30	
Location of thrombosis,†n (%)				
Head and neck				
Common carotid	1 (1)	0	1 (2.1)	
External carotid	1 (1)	0	1 (2.1)	
Internal carotid	1 (1)	0	1 (2.1)	
Upper extremity				
Axillary	1 (1)	0	1 (2.1)	
Brachial	1 (1)	0	1 (2.1)	
Radial	2 (2)	2 (3.9)	0	
Trunk/lower extremity				
Descending aorta	7 (7.1)	7 (13.7)	2 (4.2)	
Renal	1 (1)	1 (2)	0	
Iliac	74 (74.7)	44 (86.3)	30 (62.5)	
Femoral	85 (85.8)	43 (84.3)	42 (87.5)	
Popliteal	5 (5.1)	4 (7.8)	1 (2.1)	
Degree of occlusion, n (%)				.0004
Occlusive	84 (84.8)	37 (72.5),	47 (97.9)	
Nonocclusive	15 (15.2)	14 (27.5)	1 (2.1)	
Initial anticoagulation, n (%)				.044
LMWH	53 (53.3)	22 (43.1)	31 (64.6)	
UFH	46 (46.5)	29 (56.9)	17 (35.4)	
On aspirin at catheter-related arterial thrombosis diagnosis, n (%)				.77
Yes	13 (13.1%)	6 (11.8%)	7 (14.6%)	
No	86 (86.9%)	45 (88.2%)	41 (85.4%)	
Therapeutic within 24 h, n (%)				.0005
Yes	38 (38.4)	11 (21.6)	27 (56.3)	
No	61 (61.6)	40 (78.4)	21 (43.8)	

*Individual comorbidities listed; subsets of patients had more than 1 listed comorbidity.
†Listed thrombi include patients with multiple levels or sites of thrombosis.

thrombosis. The 3 nonmajor bleeding events were all self-limiting episodes of lower gastrointestinal bleeding.

Overall Outcomes by Catheter Type

Progression of catheter-related arterial thrombosis was seen in 8 (8.1%) patients. The total number of patients with complete clot resolution was 6 (6%), 27 (27%), and 60 (60.6%) within 10 days, 20 days, and 28 days from diagnosis, respectively. Although our general practice is that patients get weekly Doppler ultrasonography until clot resolution, not all patients had Doppler ultrasonography done with this frequency and it is possible that some clots resolved sooner. At the end of the study period, 28 days from diagnosis, partial resolution (representing persistent partial occlusion) thrombus occurred in 33 (33.3%) and no resolution (persistent occlusive

thrombosis) in 6 (6.1%). For indwelling arterial catheter-related catheter-related arterial thrombosis (n = 51), clot progression occurred in 3 (5.9%) and complete resolution in 31 (60.7%). For cardiac catheterization-related catheter-related arterial thrombosis (n = 48), clot progression occurred in 5 (10.4%) and complete resolution in 29 (60.4%). There were 4 patients (4%) who died during the treatment course for their catheter-related arterial thrombosis, though none of the deaths were directly related to the thrombus or anticoagulation.

Predictors of Radiologic Complete Clot Resolution

Patient, thrombus, and treatment characteristics in relation to thrombus resolution are demonstrated in Table II. Both partial and no thrombus resolution are included in the noncomplete thrombus resolution group. A shorter time from intervention (either indwelling catheter placement or catheterization) to catheter-related arterial thrombosis diagnosis was associated with thrombus resolution, as patients who experienced thrombus resolution had a median time to diagnosis of 1 day, while those who did not

Table II. Variables associated with complete and noncomplete arterial thrombosis resolution

Variables	Complete n = 60	Noncomplete n = 39	*P* value
Age at diagnosis of thrombosis, d			.32
Median (IQR)	78.5 (17.5-139)	31 (20-112)	
Range (min-max)	0 to 330	2 to 310	
Sex, n (%)			.42
Male	30 (50)	23 (59)	
Female	30 (50)	16 (41)	
Ethnicity, n (%)			.67
Hispanic	23 (38.3)	13 (33.3)	
Non-Hispanic	37 (61.7)	26 (66.7)	
Weight, kg			.26
Median (IQR)	3.89 (3.12-5.63)	3.55 (2.9-4.9)	
Range (min-max)	1.72 to 8.5	2.41 to 7.8	
Infection at the time of diagnosis, n (%)			.47
Yes	12 (20)	11 (28.2)	
No	48 (80)	28 (71.8)	
Comorbidities,*n (%)			.67
Prematurity	18 (30)	9 (23.1)	
Cyanotic heart disease	20 (33.3)	15 (38.5)	
Noncyanotic heart disease	31 (51.7)	17 (43.6)	
Other	7 (11.7)	7 (17.9)	
Pulses undetectable via Doppler, n (%)			.32
Yes	22 (36.7)	9 (23.1)	
No	27 (45)	23 (59)	
Unknown	11 (18.3)	7 (17.9)	
Time from indwelling arterial catheter or cardiac catheterization to catheter-related arterial thrombosis,			.035
Median (IQR)	1 (1-4)	5 (1-13)	
Range (min-max)	0 to 30	0 to 22	
Type of catheter, n (%)			1.0
Indwelling arterial catheter	31 (51.7)	20 (51.3)	
Cardiac catheterization	29 (48.3)	19 (48.7)	
Vessels involved, n (%)			.015
Iliac only	10 (16.7)	8 (20.5)	
Femoral only	30 (50)	7 (17.9)	
Both	14 (23.3)	15 (38.4)	
Degree of occlusion, n (%)			.39
Occlusive	49 (81.7)	35 (89.7)	
Nonocclusive	11 (18.3)	4 (10.3)	
Initial anticoagulation, n (%)			.42
LMWH	30 (50)	23 (59)	
UFH	30 (50)	16 (41)	
On aspirin at catheter-related arterial thrombosis diagnosis, n (%)			.36
Yes	6 (10)	7 (17.9)	
No	54 (90)	32 (82.1)	
Therapeutic level within 24 h, n (%)			.29
Yes	21 (35)	17 (43.6)	
No	39 (65)	22 (56.4)	
Received antithrombin III concentrate, n (%)			.83
Yes	20 (33.3)	12 (30.8)	
No	40 (66.7)	27 (69.2)	

*Individual comorbidities listed; subsets of patients had more than 1 listed comorbidity.

have thrombus resolution had a median time to diagnosis of 5 days ($P = .035$) following arterial manipulation. Patients experiencing thrombus resolution also had a higher proportion of iliac and/or femoral artery involvement (90%, n = 54) compared with those that did not have thrombus resolution (76.8%, n = 30, $P = .015$).

Discussion

Our institutional practice of treating catheter-related arterial thrombosis with therapeutic anticoagulation for up to 28 days in children under 1 year of age has demonstrated a 60.6% rate of complete thrombus resolution. The rate of complete catheter-related arterial thrombosis resolution in literature varies and has been reported to as high as 91%.[7-10,13] Rizzi et al reported a similar rate of thrombus resolution (67%) though a higher rate of no thrombus resolution, 24%, compared with our rate of 6.1%.[10] They also found a higher rate of thrombus resolution in the indwelling arterial catheter cohort compared with the cardiac catheterization group, and with noncyanotic compared with cyanotic congenital heart disease, neither of which were supported by our findings. Complete resolution in their cohort was associated with lower long-term blood pressure differences between the affected and unaffected leg though no distinctions were made between residual partial and no resolution.[10] We also observed an 8.1% rate of contiguous thrombus progression despite therapeutic anticoagulation.

Overall, our medical approach to catheter-related arterial thrombosis (therapeutic anticoagulation with either LMWH or UFH) for up to 28 days is not associated with frequent bleeding complications. We noted only 1 (1%) patient with a major bleeding event (worsening of an existing intracranial hemorrhage) and 3 (3%) patients with nonmajor clinically relevant bleeding (self-limiting lower gastrointestinal bleeding). Our bleeding rate is lower than was previously reported in children receiving anticoagulation for arterial thrombosis of 24%.[8] Though it is important to note that this increased bleeding rate was largely due to thrombolytic therapy, with the bleeding rate due to anticoagulation (UFH) being just 8%.[8] Considering the long-term sequelae of arterial occlusion include limb growth restriction and claudication in young children,[4,10,14] the importance of providing a full course of therapeutic anticoagulation is clear and, as supported by our findings, not associated with significant bleeding complications.

Shorter time from placement of an indwelling arterial catheter or cardiac catheterization procedure to catheter-related arterial thrombosis diagnosis was associated with thrombus resolution. Specifically, those patients who experienced complete thrombus resolution were diagnosed 1 day following arterial manipulation, while those who did not experience thrombus resolution were diagnosed at 5 days. Although time to catheter-related arterial thrombosis diagnosis was shorter in the cardiac catheterization group, there was no difference noted in thrombus outcomes between the cardiac catheterization and indwelling arterial catheter group, nor between the occlusive and nonocclusive groups. These findings stress the importance of clinical vigilance and having a high index of suspicion for the development of an arterial thrombus after either cardiac catheterization or indwelling arterial catheter in the time period immediately following the intervention. Prompt diagnosis and initiation of anticoagulation may have prognostic significance on the thrombosis outcome.

The association of time from arterial manipulation to diagnosis and thrombus resolution raises the following question: should routine imaging be performed on all infants in the time period following arterial catheterization or indwelling line placement to quickly diagnose acute catheter-related arterial thrombosis? A quality study by Kamyszek et al initiated a routine post procedure femoral arterial ultrasound study on all infants who underwent cardiac catheterization. The result was an increase in arterial thrombus detection from 8.3% to 23.4% of the patients.[15] It is not known, however, if the increased diagnosis is due to identifying asymptomatic, clinically irrelevant arterial lesions whom treating with anticoagulation may offer more of a bleeding risk than benefit to the patient. However, as the long-term prognosis of these clinically asymptomatic lesions is unknown, it may be important to implement a standard of care to identify these lesions in patients following arterial manipulation via either catheterization or indwelling line placement especially in those patients that have a low bleeding risk.

Though there is a lack of data to guide the length of anticoagulation for infant catheter-related arterial thrombosis, our findings suggest that continuing therapeutic anticoagulation beyond 5-7 days[11] results in increasing rates of complete clot resolution. It is possible that extending therapeutic anticoagulation beyond 28 days could have resulted in even higher rates of complete clot resolution, but this remains to be studied. It is unknown if there are any Doppler ultrasonography findings that would help predict if a clot is likely or not to resolve by extending anticoagulation and/or if there is a time point at which if resolution has not occurred it is unlikely that it will occur overall. In addition, the long-term effects of the degree of persistent arterial clots (partial vs complete occlusion) is not known. As our study was retrospective, we were not able to address these questions and we suggest that future studies evaluate these items to better inform our clinical guidelines.

Traditional treatment approaches to infant catheter-related arterial thrombosis involves initial therapy with UFH.[11] Although this remains the preferred choice for patients with increased bleeding risk, recent surgery, and the possible need for thrombolysis or surgical intervention due to the short half-life of UFH, there was no change in the rate of thrombus resolution for those patients that received UFH or LMWH as the initial anticoagulant in our cohort. A previous study by Bontadelli et al demonstrated the safety and effectiveness of upfront LMWH for infant

catheter-related arterial thrombosis, exhibiting a 91% complete resolution rate at a mean of 23 days of treatment.[9] Although we did not see a similar rate of thrombus resolution with exclusive LMWH use, our findings reinforce that in select patients whom there is a low bleeding risk and no plan for surgical intervention, that LMWH is a good initial choice for anticoagulation in infant catheter-related arterial thrombosis.

Although the rate of resolution that was seen in infant catheter-related arterial thrombosis is higher than what has been observed in line-related lower extremity venous thrombosis in both neonates and non-neonates, 30%,[16] there is definite room for improvement with nearly 40% of catheter-related arterial thrombosis having evidence of persistent radiologic arterial occlusion at the end of therapy. As the risk of persistent arterial occlusion is substantial, it is important to identify areas to improve the rate of complete thrombus resolution. One alternative approach would be to extend anticoagulation beyond the 4-week cut-off to 6 weeks or more if continued resolution of the arterial occlusion is being noted on follow-up imaging. Glatz et al evaluated the impact of institution of a clinical pathway on management of pulse loss following cardiac catheterization and noted greater than 80% thrombus resolution after 12 weeks of therapy.[13] In addition to early thrombosis identification (via implementation of a screening protocol) and initiation of anticoagulation (achieving a therapeutic level of anticoagulation within 24 hours of diagnosis was not associated with thrombus resolution), incorporating thrombolysis through a catheter-directed or systemic approach, for those in whom it is safe to do so,[17-19] at diagnosis may increase the resolution rate as well. The use of catheter-directed thrombolysis in our institution has been previously reviewed for venous thrombosis and has demonstrable efficacy and safety profile in our predominantly pediatric population.

In infants, there are some technical challenges to performing invasive therapies. Generally, equipment is not commercially available for this age group, requiring modification of adult catheters, wires, etc. The vascular caliber tends to be small, creating a risk of creating new thrombi in different locations, or occluding a vessel permanently. There is also physical trauma to the vessels because of manipulation, which is not always well tolerated in the infant population. Overall, depending on the severity of the thrombosis/thrombus burden, it is worth collaboration between the care-providing physicians, interventional radiologists, and hematologists. This allows a coherent presentation to the family to allow appropriate decision-making.

Limitations of this study include that it was a retrospective study with a limited number of patients from a single institution. The retrospective nature of the study makes it difficult to directly associate risks and therapies with outcomes. A large proportion of the patients in our study (27.3%) were premature. Developmental hemostasis likely plays an important role in the pathophysiology of thrombosis and response to anticoagulation therapy.[20] The underlying comorbidities such as prematurity and cyanotic congenital heart disease might have an impact on the incidence and response to treatment. Future multicenter prospective studies are needed to adequately answer these questions, given size limitations of the cohort at each individual institution.

Our results further substantiate the need for a large, prospective, randomized trial to answer these questions and determine the most effective method of treatment for infant catheter-related arterial thrombosis. ■

We thank Kristen Staggers of the Baylor College of Medicine Institute for Clinical and Translational Research for assistance with statistical analysis.

Submitted for publication Sep 4, 2020; last revision received Nov 6, 2020; accepted Dec 21, 2020.

Data statement

Data sharing statement available at www.jpeds.com.

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50 Years Ago in *THE JOURNAL OF PEDIATRICS*

Measurement of Urinary Catecholamine Excretion in Patients with Neuroblastoma

Voorhess ML. Neuroblastoma with normal urinary catecholamine excretion. J Pediatr 1971;78(4):680-3.

Neuroblastoma, the most common extracranial solid tumor of childhood, originates from primitive sympathetic ganglion cells. Although primary tumors are typically localized to the adrenal medulla, neuroblastoma may arise from prevertebral sympathetic ganglia and paraganglia in the cervical, thoracic, retroperitoneal, or pelvic regions. As Voorhess observed 50 years ago, tumors that compress the spinal cord can feature suppressed tyrosine metabolism and therefore have normal excretion of catecholamines, including dopamine and norepinephrine, which are further degraded to homovanillic acid (HVA) and vanillylmandelic acid (VMA), respectively. Elevated levels of HVA and VMA, identified in the urine or blood of approximately 90% of patients of neuroblastoma, can confirm a diagnosis, often before the results from tissue biopsy and/or ^{123}I-mIBG nuclear imaging.

Catecholamines associated with neuroblastoma metabolism have been evaluated for applications beyond confirming the diagnosis. In studies from abroad, mass screening programs assessed urinary HVA and VMA in all infants and identified many cases of neuroblastoma that would not otherwise have been clinically evident, in part because some patients have spontaneous resolution of their disease. Such screening has not been associated consistently with a decrease in the death rate owing to neuroblastoma and is, therefore, not used today. However, post-treatment surveillance of urinary HVA and VMA is part of the standard of care for survivors of neuroblastoma and results may provide an early signal of disease recurrence. Further, biologically aggressive tumors generate higher levels of urinary catecholamines, and studies are ongoing to identify how to apply these findings, including absolute values and ratios of catecholamines, as prognostic and therapeutic biomarkers.

The measurement of urine catecholamine degradation products remains integral for the management for patients with neuroblastoma, offering a rapid, noninvasive, and safe approach for diagnosis and monitoring, and novel applications with urine, such as a catecholamine metabolite panel and exosomal molecular profiling, are now being investigated.[1,2] The next decade is sure to reveal further insights into our biologic understanding of this potentially lethal disease.

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