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Deep Venous Thrombosis Screening in Patients with Inherited Bleeding Disorders and Central Venous Catheters

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Abstract

Introduction—Children with inherited bleeding disorders often require central venous catheters (CVC). Although CVCs are known to be complicated by deep venous thrombosis (DVT), little is known about the timeline of DVT development or risk of post-thrombotic syndrome (PTS).

Aim—To determine the timeline and confirm the incidence of thrombosis in patients with bleeding disorders who have CVCs.

Methods—In 2002 we instituted a screening program to monitor for CVC-related complications in children with hemophilia and von Willebrand disease. This is a retrospective review of this cohort. All children with CVC followed between January 1, 2000 and June 1, 2009 were evaluated for DVT every 24 months with contrast venography and Doppler sonography. An institutional PTS severity scale was utilized at each visit.

Results—Thirty-six patients had 37 CVCs placed. Thirty patients had imaging studies, with DVT observed in 14 (47%). Most DVT were diagnosed at the first venogram (median CVC duration 26 months). There were no abnormal ultrasound results. Sixteen patients (44%) had clinical findings consistent with PTS, including 10 (71%) with an abnormal venogram. Dilated chest wall veins appeared to be more strongly associated with underlying DVT (positive predictive value of 0.8) than arm circumference discrepancy. Successful transition to use of peripheral veins occurred at a median of 11 months after abnormal venograms.

Conclusions—CVC-related DVT is common in children with inherited bleeding disorders, and likely occurs earlier than previously thought. Clinical signs of PTS are also common, but long-term sequelae and severity of PTS are not known.

Keywords

Catheter; hemophilia; post-thrombotic syndrome; thrombosis; venogram

Introduction

Patients with inherited bleeding disorders often require frequent venous access for infusion of coagulation factors for prophylaxis, immune tolerance induction (ITI), or on demand

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therapy.[1] While peripheral vein infusion is preferred, it is sometimes not feasible in younger patients. Thus children often require surgically inserted catheters (e.g. Port-a Cath®, Bard Access Systems, Salt Lake City) to facilitate treatment.[2] Unfortunately, these devices are associated with infection, mechanical failure and thrombosis.[3] In 2001, we reported a thrombosis rate of 50% in hemophilia patients utilizing screening contrast venography. These deep vein thrombi (DVT) were most commonly identified ≥ 48 months following insertion.[4] Similar results were reported by others.[5, 6] The challenge with central venous catheter (CVC)-thrombosis has been lack of clarity about the long-term implications of thrombosis in patients with bleeding disorders and the associated late effects, particularly post-thrombotic syndrome (PTS). In 2002, we began screening our patients for thrombotic complications and their sequelae.

The main objective of this study was to determine the timeline of development and confirm the incidence of CVC-thrombosis in patients with inherited bleeding disorders. Secondary objectives were 1) to determine if transition to peripheral veins infusion could be accomplished within 12 months of diagnosis of DVT and/or within 5 years after CVC insertion and 2) to evaluate for PTS.

Materials and Methods

All children with congenital bleeding disorders who had an indwelling CVC and were followed at Children's Medical Center between January 1, 2000 and June 1, 2009 were included in this retrospective cohort. The following information was collected: type of bleeding disorder, date of CVC insertion, anatomical location of the CVC, CVC-related complications, results of imaging studies, PTS evaluation, and the date of CVC removal. We also documented time to transition to peripheral veins. The duration of CVC insertion was calculated from date of insertion until date of CVC removal, date of transfer from our center, or July 1, 2009 for children whose CVC remained in place.

This study was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center at Dallas.

Education of Patients and Families

The parents of children with bleeding disorders were informed that CVCs were designed to be in place only temporarily. Since previous studies have demonstrated thrombosis risk ≥ 48 months following insertion, our standard of care is to remove the lines by 5 years after insertion.[4, 5] If thrombosis was identified, earlier transition to peripheral veins was attempted within 1 year. Children were managed using the institutional protocol. [7]

Radiographic Screening for CVC-related DVT

Screening imaging for evidence of CVC-related DVT was performed every two years. Venograms were performed by injection of contrast in the antecubital vein ipsilateral to the CVC. [8] Bilateral antecubital injections were not performed because families were reluctant to have two peripheral intravenous lines. In 2004, the jugular vein became the preferred site for catheter insertion for our surgeons. Doppler ultrasonography, which is more sensitive for jugular vein DVT, and contrast venography were used to screen after 2004 [7].

Definition of thrombosis or vascular occlusion identified by screening imaging included: (1) thrombus in the superior vena cava and/or the subclavian, jugular, brachiocephalic veins; (2) stenosis; (3) post-stenotic dilation; and/or (4) multiple prominent collateral veins.

Evaluation for Post-thrombotic Syndrome

Families were questioned about CVC complications. Our PTS scale, modified from a published pediatric tool by Kuhle et al, included evaluation of arm pain, dilated chest wall veins, and arm circumference discrepancy. [9] Arm circumference was determined using a paper measuring tape with bilateral arm circumference measured from the same distance from the antecubital fossa. We utilized the percentage arm circumference difference calculated as the absolute difference divided by the average of the two arm measurements. Results were considered abnormal if >2%. [10]

Statistical Analysis

Descriptive analysis was used where appropriate. The incidence rate of thrombosis at 24 and approximately 5 years after CVC insertion was calculated. Wilcoxan-Mann-Whitney two-tailed test was used to determine the significance of age, catheter duration, and location between the patients with positive and negative imaging studies. We conducted analyses using SAS software, version 9.2 (SAS Institute Inc, Cary, NC). The sensitivity and specificity of physical examination findings corresponding to catheter-related thrombosis and PTS were also calculated.

Results

Patients

Thirty-six patients had 37 CVCs inserted. Table 1 describes the study population. One child with factor VIII deficiency and an inhibitor had two catheters placed. The majority of children had CVC inserted for prophylaxis (n=30, 83%). The median age at CVC insertion was 25 months (range 3 – 189 months).

Catheters

All but 5 catheters were inserted at Children’s Medical Center. The catheters were placed in the subclavian, external jugular, internal jugular, or facial vein. Placement could not be verified in one patient since the CVC was inserted at another institution and he has not had imaging performed. All patients had a single lumen Port-A-Cath®. Five patients have transferred out of our program with their CVC still in place.

Results of Imaging Tests

An initial venogram was performed on 30 patients at a median time of 26 months (range 21–38 months) after CVC insertion. No patients had complications with venography. Of the 6 patients (with total of 7 catheters) who did not have imaging, 3 had their CVC in place for ≤ 25 months, 1 CVC was removed without imaging, 1 transferred to another program, 1 transferred to our center with a line in place >24 months, and one had his CVC removed because of an infected hematoma. Eight patients had a second venogram performed at

approximately 4 years after CVC insertion, and 3 boys underwent a third procedure at approximately 6 years.

DVT was observed in 14 of the 30 (47%) patients. (Figure 1) The incidence of DVT on the first venogram was 37% (n= 11). The median time of the first abnormal venogram was 26 months after CVC insertion (range 24–82 months). Three additional patients were diagnosed with DVT after the third image (54, 58, and 82 months respectively). Nine patients had collateral vessel formation and 4 patients had stenosis. There was no statistical difference in number of DVT based on location of CVC placement (p=0.5). DVT was identified in 13 patients on prophylaxis, and in 1 on ITI, p= 0.2. (Table 2)

Of the 21 patients with CVCs placed in the jugular or facial veins, 11 also had normal Doppler ultrasound examinations performed. The other 10 patients did not have sonography because their CVCs had been in place ≤ 24 months (n=5), they transferred to another program (n=1), or they had venogram screening performed before routine ultrasonography was instituted (n=4).

Post-Thrombotic Syndrome

Sixteen of the 36 children with CVCs (44%) had clinical findings consistent with PTS. [9] These patients had dilated chest wall veins and/or significant ipsilateral arm circumference difference. Of patients with arm circumference difference, the median was 2.8% (range 2–9%). All lacked complaints of arm pain or dysfunction unrelated to joint disease. PTS exam findings were noted at a median time of 27 months post-CVC insertion, and they were identified in children with and without abnormal venogram results. Ten patients with an abnormal venogram (71%) had PTS findings. PTS findings did not prompt earlier venography. Table 3 illustrates the post-thrombotic exam findings. The presence of dilated chest wall veins had a specificity of 0.94 and a positive predictive value for DVT of 0.8. Larger ipsilateral arm circumference was less predictive with a sensitivity of 0.6 and a specificity of 0.7 for DVT.

Outcome of Central Venous Catheters

Twenty-two patients (61%) have had their CVCs removed. Indications for removal included thrombosis (n=9), peripheral vein transition (n=7), and other complications (n=6). One patient required replacement due to hardware exposure and another required revision due to malfunction. The CVC was removed in one patient whose catheter embolized to the pulmonary artery. Three patients had CVC removal due to infection.

The overall rate of CVC-related infection was 0.059 episodes per 1000 catheter days. The infectious complications included an infected hematoma, bacteremia, and fatal staphylococcal sepsis. [11] None of these patients had radiographic evidence of DVT.

Ten (71%) of fourteen patients with a positive venogram had a CVC removed within 12 months after evidence of DVT (median time of 11 months). Delay in removal of CVC was secondary to parental resistance and/or difficult peripheral venous access (n=2) or transfer to other programs (n= 2).

Discussion

In 2001, we reported a 50% prevalence of thrombosis in children with hemophilia. [4] However, the time at which this risk and its associated complications are greatest is not known. Since implementing our screening program, we have identified that up to a third of patients will develop CVC thrombosis within the first 2 years. However, no one suffered from pulmonary embolism or arm pain that required anticoagulation treatment.

The screening program also provided a cohort of patients with bleeding disorders and CVC thrombosis that can be followed prospectively for PTS. PTS is a known complication of deep vein thrombosis. [9, 12] However, the prevalence and long-term outcome in childhood, particularly in upper extremities, is not well-defined. Over two-thirds of our patients with DVT also had signs or symptoms of PTS; however, they need longer follow-up to understand the long-term implications of DVT and degree of severity of PTS in bleeding disorder patients.

We determined that 44% of the entire cohort had exam findings consistent with mild PTS. Abnormal arm circumference measurements were noted in 14 of our patients including 8 of the 14 (57%) patients with DVT. The findings were accentuated when the CVC was also on the dominant hand side. It was hypothesized that the increased ipsilateral size was due to either thrombosis or relative catheter size to the vein size. [13] In our current study, 6 patients without DVT also had a significant arm circumference differences. Therefore, we questioned if patients can develop symptoms of PTS in the absence of a DVT. We hypothesize that these children may have had transient catheter-related thrombosis after the insertion.

The arm circumference measurements in our patients were not performed by a single practitioner, but rather several in the clinical setting. This, admittedly, complicates interpretation of the results since there could be measurement error. Additionally, arm circumference measurements may not be the most reliable indicator of DVT. Furthermore, PTS evaluations were not performed prior to CVC insertion; therefore, baseline exam findings were not available for comparison. More patients with CVCs in the chest and arm veins need to be followed prospectively to determine how much arm circumference difference will correlate with more severe PTS.

Since 80% of patients with dilated chest wall veins had positive venograms, the presence of dilated chest wall veins may be more reliable in determining which patients are at higher risk of having DVT. Patients exhibiting this clinical finding may require screening earlier than 24 and 48 months. However, due to our small sample size, more patients should be evaluated to determine if the predictive value of dilated chest wall veins for DVT is upheld.

This is the first study to describe the utility of a CVC screening program and to prospectively determine the incidence of CVC-related DVT. In addition, it is the first to assess the prevalence of PTS in children with bleeding disorders and CVCs. Our primary goal of the screening program was to ensure that patients with bleeding disorders are transitioned to peripheral veins within 5 years and this has occurred in all but 2 eligible patients. We wanted to remove catheters earlier if there were any signs of DVT. We were

able to use peripheral veins within 12 months in 50% of the patients with DVT. For earlier transition to peripheral veins, we found that it may be necessary to demonstrate thrombosis on imaging to encourage the transition. Overall, we believe our screening program has been successful.

It is important to carefully consider which children require CVCs. The ones who do need to utilize these devices should be monitored closely for CVC complications and the families need to understand the importance of removing the CVCs as soon as PV infusion becomes feasible. . Finally, since mild PTS can be seen within a couple of years of CVC removal, long-term observation of the children diagnosed with DVT is necessary in order to determine if they develop more severe symptoms of the syndrome.

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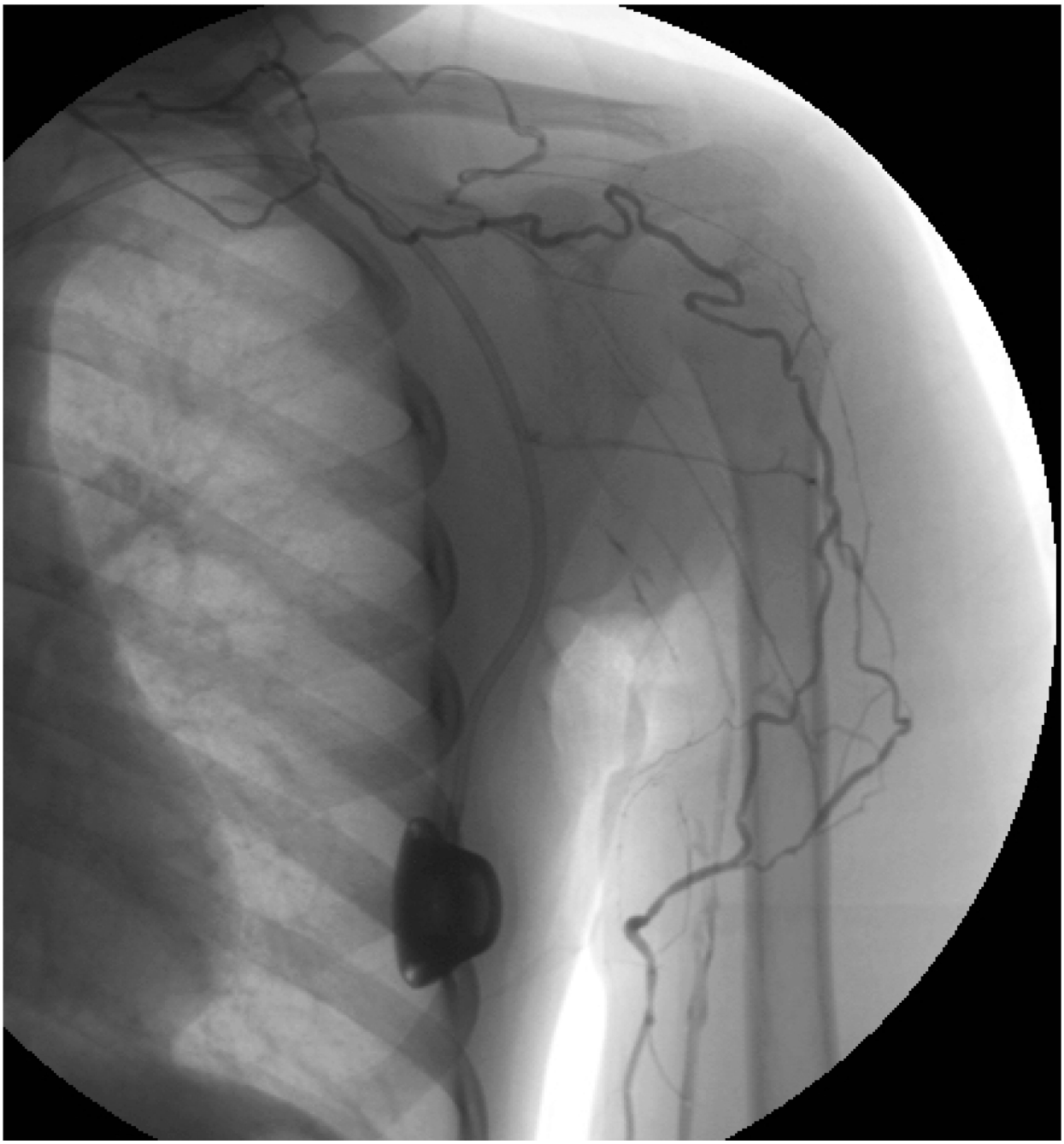

Figure 1.
Venogram in a 7 year old male with severe Factor VII deficiency with a left subclavian CVC placed for factor prophylaxis. The venogram demonstrates left axillary vein occlusion and marked collaterals.

Table 1

Demographic Data

	Total (%)	Positive Venogram (%)	Negative Venogram (%)
Number of Patients	36	14 (39%)	16 (44%)
Bleeding Disorder			
Factor VIII Deficiency	28 (78%)	10 (71%)	12 (75%)
Factor IX Deficiency	6 (17%)	3 (21%)	3 (19%)
VWD	2 (6%)	1(7%)	1 (6%)
Reason for CVC placement			
Prophylaxis	30 (82%)	13(93%)	13 (81%)
ITI	7 (19%)	1 (7%)	3 (19%)
Location			
Subclavian	15 (42%)	6 (43%)	7 (44%)
External Jugular	17 (47%)	8 (57%)	7 (44%)
Internal Jugular	3 (8%)	0	0
Facial	1 (3%)	0	1 (6%)
Not known	1 (3%)	0	1 (6%)
Median Age at CVC placement (months) [25%, 75%]	25 [13, 38]	17.5 [12, 27]	33.5 [21, 51.5] (p= 0.02)
Median CVC duration (months) [25%, 75%]	46 [31, 64]	61 [45, 67]	52 [38, 60] (p= 0.5)

Table 2

Patients with DVT confirmed by Venography

Patient	Bleeding Disorder	Age at CVC placement (months)	Location of CVC	Time to Confirmation of DVT (months)	Venogram number at time of DVT detection	Time to CVC removal transfer, or study analysis (months)
1	VIII	28	Left SCL	36	1	10 Removal
2	VIII	28	Left SCL	54	2	0 Removal
3	IX	25	Left EJ	82	3	0 Removal
4	VIII	27	Left EJ	25	1	11 Removal
5	VIII	19	Left SCL	58	2	10 Removal
6	VIII	12	Left SCL	25	1	54 Transfer
7	IX	13	Left SCL	28	1	4 Removal
8	VII	12	Left EJ	25	1	34 Still in place
9	VWD 2B	49	Right SCL	24	1	10 Removal
10	IX	8	Left EJ	26	1	23 Still in place
11	VIII	23	Left EJ	26	1	20 Still in place
12	VIII	16	Left EJ	24	1	21 Still in place
13	VIII	10	Left EJ	37	1	21 Transfer
14	VIII	14	Left EJ	26	1	1 Still in place[+]

[+]This patient had DVT identified one month prior analysis of results

SCL= Subclavian Vein, EJ= External Jugular Vein

Table 3

Assessment for Post-thrombotic Syndrome

	Total	Positive Venogram	Negative Venogram
Dilated Chest Wall Veins only	2	2	0
Significant Ipsilateral Arm Circumference >2% only	11	6	5
Dilated Chest Wall Veins and Significant Ipsilateral Arm Circ	3	2	1