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ORIGINAL ARTICLE

Venous thrombosis and stenosis after peripherally inserted central catheter placement in children

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Abstract
Background Peripherally inserted central catheters (PICCs) can lead to development of venous thrombosis and/or stenosis. The presence of venous thrombosis and/or stenosis may preclude children with chronic medical conditions from receiving lifesaving therapies, from hemodialysis in end-stage renal disease to total parenteral nutrition in short bowel syndrome. Several adult studies have found an association between PICCs and venous thrombosis and/or stenosis, but none has evaluated for this association in children.
Objective To determine the incidence of venous thrombosis and/or stenosis after PICC placement and identify factors that increase the risk of venous thrombosis and/or stenosis after PICC placement in children.
Materials and methods We conducted a retrospective review of children ages 1–18 years with a PICC placed between January 2010 and July 2013 at our center, and included those who had at least one vascular imaging study of the ipsilateral extremity (Doppler ultrasound, venogram or MR angiogram) after PICC placement. Logistic regression was applied to determine risk factors for development of venous thrombosis and/or stenosis.
Results One thousand, one hundred and ten upper extremity PICCs were placed, with 703 PICCs in the right and 407 PICCs in the left. Eight hundred fifty-one imaging studies (609 Doppler ultrasounds, 193 contrast venograms and 49 MR angiograms) were performed in 376 patients. The incidence of venous thrombosis and/or stenosis in the imaged cohort was 26.3%. PICC laterality, insertion site, duration, patient height to PICC diameter ratio, and number of PICCs per patient were not associated with development of venous thrombosis and/or stenosis. Additionally, primary diagnosis and symptoms at the time of imaging did not predict findings of venous thrombosis and/or stenosis. However, patients exposed to non-PICC central venous catheters (CVC) were more likely to develop venous thrombosis and/or stenosis (odds ratio 1.95, 1.10–3.45).
Conclusion More than a quarter of the vascular imaging studies performed in this study cohort showed previously unknown venous thrombosis and/or stenosis, irrespective of PICC laterality, insertion site, duration and size and the number of PICCs. A history of CVC was associated with a nearly two-fold increase in risk of venous thrombosis and/or stenosis after PICC placement. We suggest that PICCs and CVCs should be placed judiciously in all children, but especially in those with lifelong medical conditions who are more likely to incur direct consequences from limited vascular access.

Keywords Children · Chronic kidney disease · Peripherally inserted central catheter · Stenosis · Thrombosis · Vascular access

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Introduction

Peripherally inserted central catheters (PICCs) are catheters that are inserted percutaneously into a peripheral vein, with the tip ideally positioned at the junction of the superior vena cava and right atrium [1, 2]. They provide reliable venous access for a multitude of uses, including long-term antibiotic therapy, total parenteral nutrition, chemotherapeutic agents and frequent blood draws [1]. PICCs have a significant advantage over peripheral intravenous catheters (PIVs) in children, where cannulation can be difficult due to small vessel diameter and poor visualization of the veins [3]. PICCs also reduce psychological stress for patients by decreasing the number of repeated PIV placement attempts [4]. As a result, the use of PICCs has become increasingly more popular in the pediatric population. Experiences at two different pediatric centers have shown that the number of PICC insertions nearly doubled between 2005 and 2012 [5, 6]. Despite the advantages that PICCs provide, they also pose significant associated risks, including accidental dislodgement, line fracture, infection, thrombosis and vessel stenosis [1, 7–9]. More than a third of children receiving PICCs experience a catheter-associated complication [8, 10].

In children with chronic medical conditions, venous thrombosis and/or stenosis is of particular concern, as their development may preclude these children from receiving lifesaving therapies. One such situation is in chronic kidney disease, where venous thrombosis and/or stenosis can limit the placement of permanent hemodialysis access, such as an arteriovenous fistula or graft, related to subclavian vein occlusion, or render a patient ineligible for kidney transplantation due to iliac vein occlusion [9]. Other examples include the inability to provide total parenteral nutrition in patients with short bowel syndrome and the preclusion of children with congenital heart disease from cardiac catheterization. Therefore, preserving vessels is especially critical in children with chronic medical conditions who may require reliable vascular access for a significant proportion of their life span. Thus, determining the risk of venous thrombosis and/or stenosis with PICC placement is important in the pediatric population.

The rates of venous thrombosis and venous stenosis after PICC in adults have been shown to be 3–23% and 7%, respectively [11–15]. In children, while the incidence of thrombosis after PICC is known to be 0.3–9%, the rate of stenosis is unknown [2, 8, 16, 17]. No published studies have evaluated the rate of both venous thrombosis and stenosis in children. Additionally, the rates of PICC placement in children specifically with chronic kidney disease and other chronic medical conditions and the incidence of venous thrombosis and/or stenosis in these children are also unknown. Therefore, we aimed to determine the rate of both venous thrombosis and stenosis associated with PICCs and to characterize risk factors for these conditions in children, with a particular focus on those with chronic illness.

Materials and methods

Medical records of all patients with PICCs placed between Jan. 1, 2010, and July 31, 2013, at Cincinnati Children's Hospital Medical Center were reviewed. The Institutional Review Board approved this study as minimal risk with a waiver of the need for parental or patient informed consent. Patients were identified using radiology billing codes for PICCs. All PICCs were placed by specially trained registered nurses at the bedside or by interventional radiologists. The radiology department database software (Illuminate, Prairie Village, KS), which searched the electronic medical records for keywords, was then used to generate a list of patients who had one or more vascular imaging studies of interest during the study period, which included Doppler ultrasounds (US), contrast venograms and magnetic resonance angiograms. Illuminate search terms included ultrasound, upper extremity, DVT (deep venous thrombosis), Doppler, IR (interventional radiology) line placement with contrast, MRI venogram and MRI chest. The two queries were merged to identify patients who had both PICC placement and vascular imaging studies. We then determined if both the PICCs and vascular imaging studies were in the same extremity by chart review, and only those patients with one or more vascular imaging studies of the same extremity as the PICC, performed after PICC placement, were included.

Patients younger than 1 year of age were excluded, as vascular access is especially challenging in infants and often limited to PICCs with no other suitable alternative. Patients older than 18 years of age and patients with documented thrombophilia (increased tendency to form clots) by ICD-9 codes were also excluded.

Once the cohort was identified, pertinent clinical data were extracted from the electronic medical records (Epic®, Verona, WI), including demographic information (age, sex, height), primary chronic clinical diagnosis and the presence of the diagnosis of chronic kidney disease by ICD-9 codes, PICC characteristics (French size, location, duration) for all PICCs placed in the same extremity for each patient, baseline serum creatinine (defined as the lowest serum creatinine value in the 6 months preceding PICC placement), radiology reports of vascular imaging studies, the presence or absence of symptoms of PICC-related complications at the time of vascular imaging study as defined by the reason for imaging study documented on the vascular imaging study order (swelling, pain, erythema, PICC malfunction), and positive or negative history of non-PICC central venous catheters (CVC) in the

same extremity prior to PICC placement. The primary clinical diagnosis was categorized into kidney disease, cystic fibrosis, hematological/oncological disease, gastrointestinal/liver disease, cardiac disease and infection, with infection representing previously healthy patients who underwent PICC placement for the sole purpose of long-term antibiotic therapy. PICC and CVC data were obtained from a standardized central line report within the emergency medical records and cross-referenced with the procedure note in instances where data were missing from the report. The presence of venous thrombosis and/or stenosis was defined as documentation of venous thrombosis and/or stenosis or collateral vessels on vascular imaging study reports. Venous thrombosis and/or stenosis was reviewed collectively, as it was difficult to delineate thrombosis versus stenosis retrospectively on Doppler US, which was the primary imaging modality. In the case of ambiguous radiology reports, the images were reviewed by a single radiologist (A.J.T., with 8 years of experience) to determine whether venous thrombosis and/or stenosis was present or absent. Incident venous thrombosis and/or stenosis was defined as either venous thrombosis and/or stenosis found on the first vascular imaging study after PICC placement or venous thrombosis and/or stenosis found on subsequent vascular imaging study that was not described on previous imaging. Incident venous thrombosis and/or stenosis was ascribed to all previous PICCs by examining PICC duration prior to the vascular event. Primary kidney disease was defined as any disease process intrinsic to the kidneys, as well as kidney disease due to abnormalities of the genitourinary tract. Secondary kidney disease was defined as renal insufficiency related to treatment of the primary diagnosis (such as nephrotoxin-associated chronic kidney disease after bone marrow transplant), as evidenced by an estimated glomerular filtration rate of <90 ml/min/1.73 m2, calculated using the modified pediatric Schwartz equation. PICC duration was analyzed as cumulative dwell time of all PICCs placed in the same extremity as the vascular imaging study for each patient.

Descriptive statistics were used to describe the cohort. Chi-square test or Fisher exact test was used to assess a potential association between categorical risk factors and the presence of venous thrombosis and/or stenosis. T-test or Wilcoxon sum rank tests were used to detect the association between continuous risk factors and the presence of venous thrombosis and/or stenosis. Logistic regression was applied to determine risk factors for development of venous thrombosis and/or stenosis. All analyses were performed by SAS (Cary, NC) version 9.3. A P-value of <0.05 was considered statistically significant.

Results

The selection process for the study is represented in Fig. 1. Four thousand one hundred fifty upper and lower extremity

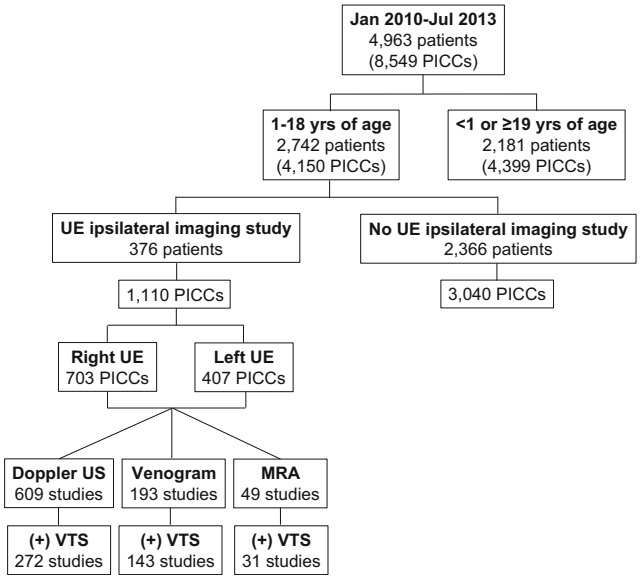

Fig. 1 Study flowchart. *PICC* peripherally inserted central catheter, *UE* upper extremity, *US* ultrasound, *MRA* magnetic resonance angiogram, *VTS* venous thrombosis and/or stenosis

PICCs were placed in 2742 patients between 1 and 19 years of age, for an overall exposure rate of 1.5 PICCs per patient. After exclusion criteria were applied, 376 patients remained with at least one imaging study of the ipsilateral side after upper extremity PICC placement. No patients with lower extremity PICC placement underwent ipsilateral lower extremity vascular imaging study. Two patients were excluded due to a documented diagnosis of thrombophilia.

The study cohort was comprised of1110 upper extremity PICCs (Fig. 1) and included 851 imaging studies (609 Doppler ultrasounds, 193 contrast venograms and 49 MR angiograms). The discrepant number of PICCs and vascular imaging studies was due to patients who received multiple PICCs but did not have a vascular imaging study after every PICC. PICC exposure rate of the study cohort was 2.95 per patient, while the PICC exposure rate of the subgroup of patients who did not undergo vascular imaging studies was 1.28 per patient ($P < 0.001$). Mean patient age of the cohort at time of PICC placement was 7.2 ± 5.9 years, with a median of 6 years (interquartile range [IQR] 2–12.4). Median PICC size was 3.0 French (range: 1.9–6.0 French), and mean patient height was 113.9 ± 37.9 cm. Mean cumulative PICC dwell time was 34.6 ± 64 days, with a median of 17 days (IQR 9–37) (Table 1).

The largest proportion of PICCs was placed in children with primary hematological or oncological conditions, followed by those with gastrointestinal diseases. Seventy four (6.7%) and 81 (7.3%) PICCs were placed in patients with primary and secondary kidney disease, respectively, for a total of 14% of PICCs being inserted in patients with any diagnosis of kidney disease (Table 1). However, only 45 (4.1%) of the PICCs inserted were in patients with documentation of an ICD-9

Table 1 Clinical characteristics

Patients, *n*	376	
Male, *n* (%)	210	(55.9)
Mean age, years ± SD	7.2	± 5.9
PICCs, *n*	1110	
PICC insertion site, *n* (%)		
Basilic	574	(51.7)
Brachial	272	(24.5)
Cephalic	196	(17.7)
Axillary	3	(0.3)
Medial	1	(0.1)
Unknown	61	(5.5)
Mean cumulative PICC dwell time, days ± SD	34.6	± 64
Primary diagnosis at PICC insertion, *n* (%)		
Heme/onc disease	257	(23.2)
GI/liver disease	243	(21.9)
Cardiac disease	119	(10.7)
Cystic fibrosis	136	(12.3)
Kidney disease	74	(6.7)
Infection	41	(3.7)
Other	240	(21.6)
Secondary CKD at PICC insertion, *n* (%)*	81	(7.3)
Imaging studies, *n* (%)	851	
Doppler US	609	(71.6)
Contrast venogram	193	(22.7)
MR angiogram	49	(5.8)
Imaging studies with any VTS, *n* (%)	445	(52.3)
Imaging studies with new VTS following PICC, *n* (%)	292	(26.3)

CKD chronic kidney disease, *GI* gastrointestinal, *Heme/Onc* hematological/oncological, *PICC* peripherally inserted central catheter, *SD* standard deviation, *VTS* venous thrombosis and/or stenosis

*Estimated glomerular filtration rate <90 mL/min/1.73m^2 without primary kidney disease

code for chronic kidney disease (primary or secondary) in the medical record at the time of PICC placement.

Eighty-five (22.6%) patients had CVC exposure prior to PICC placement. A greater number of PICCs was placed in these patients when compared to those without a history of exposure to CVC. Patients with a history of CVC exposure were also younger and had longer PICC duration (Table 2).

Two hundred and ninety-two venous thrombosis and/or stenosis events were analyzed. The prevalence of venous thrombosis and/or stenosis among all PICCs preceding vascular imaging study evaluation was 40.1%. The incidence rate of venous thrombosis and/or stenosis in the study cohort was 26.3%. The mean cumulative PICC dwell time prior to incident venous thrombosis and/or stenosis events was 35.2 ± 16 days. The median time to venous thrombosis and/or stenosis after PICC placement was 14 days when only the PICCs placed immediately prior to the vascular imaging study were analyzed. Additionally, the incidence of venous

Table 2 Comparison of characteristics in patients with and without history of CVC exposure preceding PICC insertion

	CVC exposure		No CVC exposure		*P*-value
Patients, *n* (%)	85	(22.6)	291	(77.4)	<0.001
PICCs, *n* (%)	705	(63.5)	405	(36.5)	<0.001
Mean cumulative PICC dwell time, days ± SD	36.3	± 59.5	31.8	± 103	<0.01
Imaging studies, *n* (%)	575	(67.6)	276	(32.4)	<0.001
Doppler US	394	(64.7)	215	(35.3)	<0.001
Contrast venogram	132	(68.4)	61	(31.6)	<0.001
MR angiogram	49	(100)	0	(0)	<0.001
Imaging studies with any VTS, *n* (%)	329	(57.2)	116	(42.0)	<0.01
Imaging studies with new VTS following PICC, *n* (%)	203	(28.8)	89	(22.0)	0.029

CVC non-PICC central venous catheter, *PICC* peripherally inserted central catheter, *SD* standard deviation, *VTS* venous thrombosis and/or stenosis

thrombosis and/or stenosis was significantly higher in patients with a history of exposure to CVC (Table 2). Among the vascular imaging studies performed due to clinical symptoms concerning for PICC complication, 44.6% were found to have venous thrombosis and/or stenosis, and there was no statistically significant difference in venous thrombosis and/or stenosis rate on imaging when compared to those without symptoms (Table 3). Patients without symptoms underwent imaging evaluation for routine follow-up of a previously known venous thrombosis and/or stenosis or for other clinical reasons unrelated to the PICC. PICC laterality, PICC insertion site, patient height to PICC diameter ratio and the number of

Table 3 Risk factors for venous thrombosis and/or stenosis after PICC

	(+) VTS		(−) VTS		*P*-value
Symptoms at time of imaging, *n* (%)	144	(44.6)	179	(55.4)	0.85
PICC insertion site, *n* (%)					0.56
Cephalic	26	(44.1)	33	(55.9)	
Brachial	28	(49.1)	29	(50.9)	
Basilic	66	(52.8)	59	(47.2)	
Axillary	0		1		
Unknown/other	7	(38.9)	11	(61.1)	
PICC laterality, *n* (%)					0.76
Right upper extremity	186	(26.5)	517	(73.4)	
Left upper extremity	106	(26.0)	301	(74.0)	
Height to PICC diameter ratio (cm/Fr), mean	36.6		37.2		0.64
Number of PICCs per subject, mean	2.8		3.4		0.41

PICC peripherally inserted central catheter, *VTS* venous thrombosis and/or stenosis

PICCs per subject were also not associated with presence of venous thrombosis and/or stenosis (Table 3). Additionally, primary diagnosis and PICC duration were not associated with venous thrombosis and/or stenosis (Table 4). However, patients with exposure to CVC were more likely to develop venous thrombosis and/or stenosis, with an odds ratio of 1.95 (Table 4).

Discussion

The dramatic increase in the use of PICCs in pediatric patients over the past several years correlates with a significant rise in the rate of venous occlusion at pediatric hospitals across the United States [5, 6, 18]. This poses a considerable problem for children with chronic illness, who depend on reliable vascular access for life-saving or life-sustaining treatments. For this reason, we examined the rates and risk factors for venous thrombosis and/or stenosis after PICC in children, especially in those with chronic illness.

Our results show that PICCs are placed frequently, with an average rate of 2443 PICCs per year at our institution. Even more concerning is that more than half of the 1110 PICCs in our cohort were placed in children with chronic medical conditions who are not only more likely to require intravenous therapies in the future, but are also at increased risk of developing chronic kidney disease related to their underlying illness. The relatively high rate of PICC placement in these patients may be attributed to a lack of physician knowledge regarding the gravity of potential consequences of PICC placement in these special populations.

More than a quarter of patients receiving PICCs who had imaging evaluation were found to have evidence for new venous thrombosis and/or stenosis on imaging after PICC placement. The rate of venous thrombosis and/or stenosis may be an overestimation, as patients with symptoms of PICC complication are more likely to receive imaging evaluation. However, only about half of patients with venous thrombosis and/or stenosis had signs or symptoms of PICC complication at the time of vascular imaging study, suggesting otherwise.

The risk of developing venous thrombosis and/or stenosis after PICC was not affected by PICC duration, insertion site, PICC size or the total number of PICCs per patient. Thus, placement of even just one PICC for a minimal period of time can result in venous thrombosis and/or stenosis. Additionally, exposure to CVC was associated with a nearly two-fold increase in risk of venous thrombosis and/or stenosis after PICC placement. This is particularly pertinent to the pediatric chronic kidney disease population, where there is a higher rate of hemodialysis catheter use (as opposed to arteriovenous fistula or graft) and therefore, higher risk of developing venous thrombosis and/or stenosis with PICCs.

There are several limitations to this study. Due to its retrospective nature, the documented clinical data may be inaccurate or biased toward examination of patients who had a vascular imaging study. In addition, not all placed PICCs were followed up with imaging and patients with known venous thrombosis and/or stenosis often received subsequent surveillance imaging, both of which lead to the potential for either under- or overestimation of venous thrombosis and/or stenosis rates. Inter-rater reliability of venous thrombosis and/or stenosis diagnosis also cannot be assured, as the presence of venous thrombosis and/or stenosis was determined by historical radiology reports. Transient venous spasm or presence of the PICC during vascular imaging, both of which can result in narrowed appearance of the vein lumen, could also have been interpreted as venous thrombosis and/or stenosis. Furthermore, the development of venous thrombosis and/or stenosis after PICC was presumed when new findings of venous thrombosis and/or stenosis were found on vascular imaging studies of the same extremity at any time point after PICC placement, which may have led to inaccurate assumptions regarding the association between PICC and venous thrombosis and/or stenosis.

The major strength of this study is the sample size. To our knowledge, it is the largest cohort of PICCs that has been reviewed with a primary focus on venous thrombosis and/or stenosis. It is also the first study to examine PICC placement and subsequent development of venous thrombosis and/or stenosis specifically in children with chronic kidney disease. Additionally, because this study was conducted at a large tertiary care pediatric institution, our results are applicable to the rising number of children in whom avoidance of PICCs is critical - those who are at highest risk of developing secondary chronic kidney disease.

Table 4 Logistic regression analysis of risk factors for venous thrombosis and/or stenosis after PICC

	P-value	OR (95% CI)
Primary diagnosis		
Heme/onc disease	0.46	0.86 (0.58–1.28)
GI/liver disease	0.05	1.56 (1.00–2.43)
Cardiac disease	0.08	0.57 (0.30–1.06)
Cystic fibrosis	0.60	1.21 (0.59–2.50)
Kidney disease	0.81	0.93 (0.49–1.74)
Infection	0.96	0.98 (0.43–2.24)
Other	1.00	1.00 (0.65–1.54)
PICC duration	0.56	1.00 (1.00–1.00)
Exposure to CVC	0.02	1.95 (1.10–3.45)

CI confidence interval, *CVC* non-PICC central venous catheter, *GI* gastrointestinal, *Heme/Onc* hematological/oncological, *OR* odds ratio, *PICC* peripherally inserted central catheter

Conclusion

There are unique challenges to vascular access in the pediatric patient that often necessitate the use of PICCs. Yet, PICCs are also known to cause venous thrombosis and stenosis, which pose considerable challenges for future vascular access. Given this implication, we suggest that PICCs and CVCs should be placed judiciously in all children, but especially in those with lifelong medical conditions who are more likely to suffer direct consequences from limited vascular access.

Compliance with ethical standards

Conflicts of interest None

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