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Major thrombotic complications with lower limb PICCs in surgical neonates

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ABSTRACT

Background: PICC lines are now used routinely to provide central access for neonatal intensive care unit (NICU) patients. Neonates are known to be at risk for venous thromboembolism (VTE) related to central catheters. No literature exists about VTE PICC-related morbidity in the NICU abdominal surgery subgroup.
Methods: With REB approval, a retrospective review of a NICU database of PICC insertions performed at a tertiary children's hospital was conducted (January 2010–June 2013). Information about PICCs and complications was recorded. For patients with a major thrombotic complication, charts were reviewed. A major thrombotic complication was defined as a thrombosis which required medical and/or surgical intervention.
Results: 692 PICCs were inserted (485 in the upper extremity, 142 in the lower extremity, and 65 in the scalp). Seventy-four patients had significant intraabdominal pathology, and 5 had a major thrombotic complication. All patients with a major thrombotic complication had a lower extremity PICC which was at or below L1 (L1-S1) running parenteral nutrition.
Conclusions: In the current study, only neonates with abdominal pathology and a lower extremity insertion site suffered major thrombotic complications from PICC lines. Given all patients' PICC tips were below the recommended location, more rigorous surveillance (with repositioning if required) may avoid these complications for future patients.

Peripherally inserted central catheters (PICCs) are now used routinely to provide central access for the neonatal intensive care (NICU) population [1]. The current literature on PICC-related complications describes general complications of PICCs in the entire NICU population [2–6]. Comparison of PICCs in the in upper limbs (UL) vs. lower limbs (LL) has not demonstrated an increased venous thromboembolism (VTE) rate in LL PICCs. However, this increased risk has been described in the neonatal population with the use of central venous lines (CVLs) placed in the LL [7,8]. Noncentral PICC tips have also been associated with increased risk of complication (including VTE and extravasation) [3–6]. The incidence of VTE related to CVLs also increased with catheter days and severity of prematurity [9,10]. Although most NICU patients with VTE do not have any serious sequelae, major morbidity [3–5] has been noted. Roberts et al reported on newborn surgical patients with CVLs, the main complication described was catheter sepsis and its incidence increased with the number of catheter days [11]. No literature currently exists which documents PICC-related morbidity in neonates who have undergone abdominal surgery.

Newborns with abdominal surgical conditions may be especially predisposed to PICC-related VTE, especially if it is placed in the LL [7,8]. Many of these patients are preterm. In addition, abdominal pathology and/or subsequent surgery may put them at risk for intraabdominal hypertension and abdominal compartment syndrome. Schierz et al found that abdominal compartment syndrome was seen more in newborns (57%) that had had repair of abdominal wall defects [12]. By inducing venous stasis, intraabdominal hypertension puts the patient at risk for venous thromboembolism. Furthermore, many require prolonged parental nutrition which is an independent risk factor for VTE [13]. Our hypothesis was that major PICC-related VTE morbidity would be increased in neonates with a PICC and abdominal pathology. A secondary aim was to determine if LL PICC placement (vs. UL) was associated with increased VTE in this group of infants.

1. Methods

With research ethics board approval (#H13-03423), a retrospective review of the NICU database of PICC insertions performed at a tertiary children's hospital was conducted (January 2010–June 2013). Patients with PICC lines placed while admitted to the NICU were identified; central lines placed surgically or in the pediatric intensive care unit were excluded (as the data for these was not collected in the NICU PICC database). Gestational age, weight, site (UL, LL or scalp) and the presence of significant abdominal surgical pathology were documented. Significant abdominal pathology was defined as any abdominal condition requiring

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Table 1
PICC insertion site and patient characteristics.

	Insertion site			
	Upper extremity	Lower extremity	Scalp	p-value
Total number	485	142	65	
Gestational age, weeks [median, IQR*]	28 [26, 32]	31 [27, 35]	37 [34, 38]	<0.001
Birth weight, grams [median, IQR]	1008 [800, 1505]	1320 [903, 2094]	2674 [2253, 3073]	<0.001
Male:female (%)	60:40	52:48	53:47	0.783
Line days [median, IQR]	15 [9, 24]	13 [8,23]	13 [8,22]	0.258

* IQR: interquartile ranges [25th, 75th percentiles].

intestinal resection, intestinal repair/anastomosis, closure of abdominal wall defect, repair congenital diaphragmatic hernia, evidence of intestinal perforation, ischemia and/or obstruction or tumor resection. Infants undergoing gastrostomy tube placement alone or inguinal hernia repair were excluded. For all patients with significant intraabdominal pathology and an LL PICC, abdominal radiographs were reviewed to determine the most peripheral extent of the tip. For all the patients with a major PICC-related VTE morbidity, charts were reviewed. A major VTE morbidity was defined as a complication related to VTE which required intervention (medication or procedure) [14]. Significant VTEs were suspected by development of symptoms or PICC malfunction (thrombophlebitis, extremity swelling, persistently positive blood cultures despite appropriate antibiotic treatment), inability to remove PICC and poor flow of PICC and were subsequently confirmed with Duplex Doppler ultrasound. Details about the PICC position (initial and subsequent at the time of the VTE), weight, diagnosis, use of parenteral nutrition, surgical procedures, presence of intraabdominal hypertension and/or abdominal compartment syndrome, interventions related to the VTE and final patient outcomes were tabulated. Intraabdominal hypertension was defined either by a clinical diagnosis in the chart or with documentation of bladder pressures $\geq$10 mmHg [15]. Abdominal compartment syndrome was defined as intraabdominal hypertension in addition to evidence of new or worsening organ compromise (including renal, pulmonary and cardiac); need for decompressive laparotomy was also included in the definition [15]. Descriptive statistics were used to characterize the group of patients with a major VTE-related PICC morbidity. The Wallis test was used to compare the parameters of the three PICC insertion site groups, $p < 0.05$ was considered significant.

2. Results

There were 692 PICCs inserted in 578 infants admitted into neonatal intensive care unit during Jan 2010 and Jul 2013 inclusively. There were 485, 142 and 65 inserted in the upper extremity, lower extremity and scalp respectively (Table 1). Patients with UL PICC insertion sites were significantly younger and had a lower birth weight than those with LL and scalp insertion sites. Those receiving LL PICCs were significantly lower birth weight and gestational age compared to those with scalp sites, but larger and older than the UL PICC infants. PICCs ranged in size from 1 Fr (if infant <1 kg) to 1.9 Fr or 3 Fr ($\geq$1 kg).

There were 74 patients with significant intraabdominal pathology who received 158 PICCs. Diagnoses for these 74 patients were: gastroschisis, necrotizing entercolitis (NEC), malrotation, spontaneous intestinal perforation, intestinal atresia, complicated meconium ileus, intestinal ischemia, congenital diaphragmatic hernia, omphalocele, abdominal and retroperitoneal tumors, intestinal stricture (post NEC) and cloacal extrophy. There were thirty two lower extremity PICCs in the 74 patients; for these 32 PICCs the lowest tip location was at or below L1 in 16. There were no documented PICC related major VTE complications for patients with either scalp or upper extremity PICCs during the study period. Of the NICU population receiving PICCs, 12% had significant intraabdominal pathology and no significant PICC related VTE.

Five patients had a major thrombotic complication related to their PICC and all had significant abdominal pathology (Table 2). PICCs were either 1 Fr or 1.9 Fr and all were single lumen. Two patients required 6 weeks of antimicrobial therapy because of infected thrombophebilitis and 3 patients were anticoagulated. Patient 4 underwent TIPSS and subsequent anticoagulation after development of posthepatic liver failure related to the complete occlusion of all 3 hepatic veins (in addition to an occlusive IVC thrombosis). Patients 2 and 5 did not receive anticoagulation because the VTE was confined to the femoral vein and owing to preexisting grade 4 intraventricular hemorrhage respectively. All patients were evaluated by hematology and had a thrombotic workup. None of the five patients were found to have other hematologic risk factors for an increased risk of thrombosis.

Of the patients who sustained a major VTE, all were premature (gestational age averaged 31 weeks), all were receiving parenteral nutrition and had evidence of intraabdominal hypertension (Table 3). Two of the patients had intraabdominal (bladder) pressure measurements (with maximums >20 mmHg). Three of the 5 patients required decompressive laparotomy at the time the PICC associated with the VTE was indwelling. All PICCs were placed within days of birth in the lower extremity (resulting in a 16% major VTE complication for lower extremity PICCs in patients with significant intraabdominal pathology). All PICC tips were at or below L1 at the time of VTE diagnosis. Rate of flow through the PICCs was highly variable as the course for all these infants was marked by significant changes in fluid and support required while the PICC related to the VTE was in situ. The length of time from the PICC insertion to the VTE ranged from 30 to 210 days (averaged >98 days).

3. Discussion

Central lines are used in neonates and infants for administration of intravenous therapy, such as fluids, medications, parenteral nutrition (PN) and blood products. Thrombotic complications are thought to arise by several mechanisms: damage to the vessel wall by the catheter, or by substances infused through the catheter, such as PN, disrupted

Table 2
Clinical characteristics of patients with major PICC-related VTE morbidity.

Patient	Diagnosis	Extent of thrombosis	Intervention	Outcome
1	Complicated gastroschisis	Suprarenal IVC, infrarenal IVC to right femoral vein, infected thrombophlebitis	IV antibiotics (6 weeks) Anticoagulation	Right leg venous stasis Survival
2	Perforated NEC	Right femoral vein thrombosis	Cut down ×3 (retained PICC)	Survival
3	Perforated meconium ileus	IVC clot to level of renal veins and right iliac	Anticoagulation	Survival
4	Complicated jejunal atresia	Budd Chiari (×3) and IVC	Anticoagulation TIPSS	Retained PICC Mortality
5	Perforated NEC	Suprarenal IVC thrombus Infected thrombophlebitis	IV antibiotics and antifungals (6 weeks)	Survival

Table 3
Clinical and catheter characteristics in patients with PICC-associated VTE.

Patient	1	2	3	4	5
Gestational age (weeks)	34 + 2	25 + 3	35	36	25 + 4
Birth weight (grams)	2150	770	3000	2190	905
Intra-abdominal hypertension	Yes	Yes	Yes	Yes	Yes
Bladder pressure (mmHg)	>20	n/a	n/a	>20	n/a
Surgical procedure*	Decompressive laparotomy	Laparotomy	Decompressive laparotomy	Decompressive laparotomy	Penrose drain
PICC insertion site	R saphenous	R saphenous	R saphenous	L saphenous	L saphenous
Catheter duration (days)	210	72	60	120	30
Catheter tip site†	L5	R femoral vein	L1	L4/L5	L2
PN‡	Yes	Yes	Yes	Yes	Yes
Duration of PN‡ (days)	>240	129	>240	>120	94
Blood culture	Positive	Positive	Positive	Positive	Positive

* Surgical procedures at the time of intraabdominal hypertension. All patients undergoing laparotomy (decompressive and not) underwent bowel resection and stoma creation.
† Location at the time of VTE diagnosis.
‡ Parenteral nutrition.

blood flow and thrombogenic catheter materials [9,10,13]. The use of central lines is the most common cause for thrombosis in neonates and infants preterm babies [7,9,10]. Most of the NICU population is preterm and many are of low birth weight and require PN to meet their calorific needs. However, the 5 with major VTEs ranged in gestational age from 25 to 36 weeks and weights of 770–3000 g, suggesting the severity of prematurity or low birth weight per se was not the most influential of factors. All premature infants have small vessels that are easily injured by the relatively larger catheters and are also prone to sepsis and this increases the thrombotic risk [9]; all the subjects in the current series had sepsis confirmed on blood cultures. Other hematologic conditions can increase risk for thrombosis, however all 5 patients who developed a major VTE had a thrombotic workup and none had disorders identified.

Intraabdominal hypertension and compartment syndrome lead to venous stasis, completing the thrombogenic triad [16]. Internationally accepted consensus definitions and grades for pediatric intraabdominal hypertension (IAH) exist: Grade I, 10–12 mmHg; Grade II, 13–15 mmHg; Grade III, 16–18 mmHg; Grade IV, >18 mmHg; abdominal compartment syndrome (ACS) as IAP in excess of 18 mmHg (Grade IV IAH) that is associated with new organ dysfunction or failure [15]. In neonates undergoing abdominal surgeries, 85% had intraabdominal hypertension [17] and for those with an abdominal wall defect (like some of the patients in the current study), the majority develop abdominal compartment syndrome [12]. Animal studies (adult animals) have demonstrated marked decrease in femoral blood flow when intraabdominal pressure is ≥10 mmHg [18,19]. Thus, it is likely that many patients with significant intraabdominal pathology had elevated intraabdominal pressures, unfortunately, measurement was not routine in postsurgical patients.

Catheter-related venous TE can be asymptomatic or can result in severe complications such as deep vein thrombosis, portal vein thrombosis, Budd Chiari, superior vena cava syndrome, intracardiac thrombosis, or pulmonary embolism [20]. Clinical manifestations of symptomatic catheter-related thrombosis in neonates depend on the site of the thrombosis. Catheter dysfunction, thrombocytopenia or persistent bacteremia/fungemia may be associated with vascular thrombosis at any site [8,21]. Apart from the loss of venous access owing to catheter-related thrombosis, there is potential danger of injury to vital organs secondary to thrombus propagation, embolization, or infection.

There are accepted guidelines to ensure safe placement and positioning of PICCs [22]. Increased complication rates have been documented with noncentral PICC tips; factors such as small vessel size, decreased blood flow rate, turbulent flow, and endothelial injury are thought to be causative [3–6]. Ideal procedure to place a PICC involves manipulating the catheter centrally, with the goal being a final tip position in the superior vena cava (SVC) if placed from the head, neck or upper extremity and at junction of the inferior vena cava (IVC) and right atrium when placed from the lower extremity [22]. Thus, the tip of an LL catheter should be at or above the level of the diaphragm. Importantly however, initial thrombus formation has been documented to occur within days of catheter insertion, therefore, even in higher flow areas, thrombosis may develop [8]. For all of our patients with VTE, despite optimal initial tip position, all tips were substantially below this recommended level at the time of VTE. For the 16 noncentral LL PICCs in the 74 patients with abdominal pathology, 31% developed a major VTE. The PICCs were all placed near at the time of NICU admission and increase in length of the patient was likely substantial during their NICU course.

The incidence of VTE in the newborn depends on the zeal with which surveillance is performed, the timing and frequency of monitoring, and the diagnostic method used [7–10,23]. Assessment for VTE is variable and controversial: use of clinical signs alone, plain XR, ultrasound or venography. Most authors do recommend periodic verification that the PICC tip is central to ensure repositioning occurs prior to the development of complications [8–10,23].

There are several limitations of the current study. This is a retrospective, descriptive study and therefore it is vulnerable to bias. The true incidence of VTE is unknown as there was no routine monitoring in the patient population. Line tip position was also not regularly monitored, so it is difficult to know how much line position contributed to the development of VTE; migration may have occurred gradually or close in time to the identification of the thrombosis. Furthermore, bladder pressure monitoring is not routinely performed on infants at risk for intraabdominal hypertension, making the diagnosis more reliant on the clinical assessment of abdominal pressure and clinical assessment is recognized to not be highly accurate [15].

Infants with abdominal surgical pathology who have LL PICCs placed during their NICU stay were at risk for major complications related to VTE in our study population. No major symptomatic VTEs were identified in any patient without abdominal pathology. Given that all the PICCs associated with a VTE were LL and noncentral, routine monitoring of PICC tip position is recommended in this high risk population. With recognition of the multiple risk factors which predispose this group of complex neonates to major morbidity secondary to venous thromboembolism, even in the context of a well-positioned PICC tip, a vigilant approach is warranted. Further studies are required to more fully understand the risk of PICC-associated VTE in infants with intraabdominal pathology.

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