ORIGINAL RESEARCH

Risk of Venous Thromboembolism in Hospitalized Patients with Peripherally Inserted Central Catheters

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All data were collected at Methodist University Hospital, Memphis, TN. Author contributions are as follows: B.L.L. and G.V. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis; study concept and design: B.L.L., G.V., R.S.; acquisition of data: B.L.L., J.B.; analysis and interpretation of data: G.V., B.L.L., J.B.; drafting of the manuscript: B.L.L., G.V., A.B.R.; statistical analysis: G.V.; obtained funding: B.L.L.; administrative, technical, or material support: B.L.L., J.B.; study supervision: B.L.L., G.V. Methodist Healthcare Foundation funded this study for data collection and management. Methodist Healthcare Foundation was not involved in the management, analysis, or interpretation of data or the preparation of the manuscript. Methodist Healthcare Foundation reviewed the manuscript prior to submission for publication.

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BACKGROUND: Peripherally inserted central catheters (PICC) are increasingly used in hospitalized patients. The benefit can be offset by complications such as upper extremity deep vein thrombosis (UEDVT).

METHODS: Retrospective study of patients who received a PICC while hospitalized at the Methodist University Hospital (MUH) in Memphis, TN. All adult consecutive patients who had PICCs inserted during the study period and who did not have a UEDVT at the time of PICC insertion were included in the study. A UEDVT was defined as a symptomatic event in the ipsilateral extremity, leading to the performance of duplex ultrasonography, which confirmed the diagnosis of UEDVT. Pulmonary embolism (PE) was defined as a symptomatic event prompting the performance of ventilation-perfusion lung scan or spiral computed tomography (CT).

RESULTS: Among 777 patients, 38 patients experienced 1 or more venous thromboembolisms (VTEs), yielding an incidence of 4.89%. A total of 7444 PICC-days were recorded for 777 patients. This yields a rate of 5.10 VTEs/1000 PICC-days. Compared to patients whose PICC was inserted in the SVC, patients whose PICC was in another location had an increased risk (odds ratio = 2.61 [95% CI = 1.28-5.35]) of VTE. PICC related VTE was significantly more common among patients with a past history of VTE (odds ratio = 10.83 [95% CI = 4.89-23.95]).

CONCLUSIONS: About 5% of patients undergoing PICC placement in acute care hospitals will develop thromboembolic complications. Thromboembolic complications were especially common among persons with a past history of VTE. Catheter tip location at the time of insertion may be an important modifiable risk factor. ***Journal of Hospital Medicine*** **2009;4:417–422.** © *2009 Society of Hospital Medicine.*

KEYWORDS: anticoagulation, deep vein thrombosis, embolism, intravenous, PICC, pulmonary embolism, thrombosis.

The use of peripherally inserted central catheters (PICCs) to facilitate the administration of intravenous medications and fluids has become commonplace in hospitalized patients. Clinicians often prefer PICCs over other central venous catheters due to their ease of insertion and the perception that PICCs may have lower risks than other central venous catheters. However, recent studies[1,2] have begun to suggest that the benefit derived from these devices can be offset by the development of complications such as upper extremity deep vein thrombosis (UEDVT). Since venous thromboembolism (VTE) in hospitalized patients is associated with increased morbidity, mortality, length of stay, and costs, we sought to determine the rate of VTE in a population of patients who received a PICC solely during their hospital stay.

Methods

Data Collection

This study was a retrospective, electronic chart review of patients who received a PICC while hospitalized between August 1, 2005 and November 1, 2005 at the Methodist University Hospital (MUH), a 652-bed, urban, university-

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affiliated, community hospital in Memphis, TN. Patients were identified through the use of a PICC database that is maintained by the nurses who routinely place the PICCs. The data collected included the date of insertion, the diameter of the catheter, the vein accessed, the position of the catheter tip, and the reason for PICC insertion. These factors as well as demographics were examined to determine whether they were associated with thrombosis. These data were linked with data from the ultrasound laboratory and nuclear medicine/radiology laboratory and with hospital discharge data. Data were recorded by trained research assistants and verified for accuracy by the study investigators. The institutional review board approved the study protocol prior to data collection.

Patients and Outcomes

All adult consecutive patients who had a PICC inserted during the study period and who did not have a UEDVT or pulmonary embolism (PE) at the time of PICC insertion were included in the study.

PICCs were placed using a modified Seldinger technique at the bedside with portable ultrasound guidance. The vessel of choice for insertion was the basilic vein. Confirmation of catheter tip placement in the lower third of the superior vena cava (SVC) was done with chest x-ray prior to use of the PICC. The PICC manufacturer was Boston Scientific (Vaxcel with PASV; Natick, MA) and normal saline was used for routine flushing of the PICC.

Study Outcomes

Symptomatic UEDVT

A UEDVT was defined as a symptomatic event in the ipsilateral extremity leading to the performance of duplex ultrasonography, which confirmed the diagnosis of UEDVT. Systematic screening for UEDVT was not performed on any patients during the study period. Sonographic diagnosis of UEDVT was based on noncompressibility of a venous segment of the upper arm or the internal jugular vein; absent or reduced flow on Doppler imaging with failure to augment on compression of the arm; or the presence of echogenic material compatible with thrombus in the arm or central venous vasculature on real-time imaging. Superficial thrombosis was not counted as a UEDVT event.

Symptomatic PE

PE was defined as a symptomatic event prompting the performance of ventilation-perfusion lung scan or spiral computed tomography (CT). Systematic screening for PE was not done on any patients during the study period. Radiologic diagnosis of PE was not standardized, but intraluminal filling defect of a lobar artery or more proximal pulmonary arterial vasculature on spiral CT, or an abnormal ventilation-perfusion (V2) scan with a high clinical suspicion for PE must have been noted on the radiology report along with the physician's clinical diagnosis of PE.

TABLE 1. Baseline Characteristics

Patient Characteristics	Study Population
Age (years), mean (SD); range	60.8 (17.8); range, 19–99
Gender, n (%)	
Women	465 (59.8)
Ethnicity, n (%)	
White	223 (28.6)
African American	543 (69.9)
Hispanic	4 (0.5)
Weight (kg), mean (SD); range	81.0 (25.8); range, 30–207
History of cancer, n (%)	157 (20.21)
History of venous thromboembolism, n (%)	55 (7.07)
PICC location, n (%)	
Right vein	538 (69.2)
Vein accessed, n (%)	
Basilic	695 (90.0)
Cephalic	39 (5.1)
Median	38 (4.9)
PICC reason, n (%)*	
Poor access	704 (90.6)
Antibiotic iv.	377 (69.2)
Hydration iv.	389 (50.1)
Irritant drug	19 (2.5)
TPN	47 (6.1)
Chemotherapy	23 (3.0)
Pain medication	22 (2.8)
Blood and blood products	16 (2.1)
Other nonblood	30 (3.9)
PICC tip location, n (%)	
Central location†	643 (85.3)
Noncentral location	111 (14.7)
Catheter lumen, n (%)	
4–Fr	10 (1.3)
5–Fr	758 (97.5)
Other	9 (1.1)
Length of stay (days), mean (SD); range	16.3 (17.2); range, 1–224
PICC days; range	9.6 (9.0); range, 1–64

NOTE: Number of patients (n) = 777.

Abbreviation: iv, intravenous; PICC, peripherally-inserted central catheter; SD, standard deviation; TPN, total parenteral nutrition.

*Most patients had multiple indications for PICC.

†Central location was defined as tip placement in superior vena cava or right atrium.

Statistical Analyses

The incidence of VTE was reported as the proportion of patients who had a documented event during hospitalization, and also as the number of events per 1000 PICC-days. Baseline characteristics were assessed as potential risk factors. Differences in proportions were tested with the chi square or Fisher exact test, and differences in means of the continuous variables were tested using the *t*-test. Univariate analysis of symptomatic VTE by each potential risk factor was performed using logistic regression. Logistic regression models were used to simultaneously assess the relationship between the baseline factors and the probability of developing a thrombotic event. Using a backward elimination modeling strategy, only factors that maintained a P value of <0.05 were retained in the final model. Odds ratios (ORs) and corresponding 95% confidence

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TABLE 2. VTE Incidence

Outcome	n	%
Total VTE	38*	4.89
Upper extremity thromboses	31	3.99
UEDVT	27	3.47
Superficial upper extremity thrombosis	4	0.51
PE	8	1.03

*One patient with a PE and UEDVT was counted as a single event.

Abbreviations: PE, pulmonary embolism; UEDVT, upper extremity deep vein thrombosis; VTE, venous thromboembolism.

intervals (CIs) were calculated. SAS version 8.2 (SAS Institute, Inc., Cary, NC) was used for data analysis.

Results

Patient Demographics and Baseline Characteristics

From August 1, 2005 to November 1, 2005, 954 PICCs were inserted in 777 patients. The demographics and baseline characteristics of the 777 patients are outlined in Table 1. History of cancer was present in 20.21% of the patients. History of VTE was present in 7.02% of the patients. The most common reason for PICC insertion was poor access in 90.6% of the PICCs. The most common medication infused through the PICC was antibiotics in 69.2% and intravenous hydration in 50.1%. The basilic vein was accessed in 90%. The tip location, as determined by chest X-ray at the time of insertion, was the SVC in 85.3%. PICCs were in situ for an average of 9 days and most were 5-French (Fr) catheters. The average duration of PICC placement was over 9 days, and the average length of stay slightly exceeded 16 days.

Outcomes: VTE

During their hospital stay, 38 patients experienced 1 or more VTEs, yielding an incidence of 4.89% (Table 2). A total of 7444 PICC-days were recorded for 777 patients. This yields a rate of 5.10 VTEs/1000 PICC-days. There were 27 patients who had a UEDVT over the 7444 PICC days yielding a rate of 3.65 UEDVT/1000 PICC days. The mean length of stay was 26 days in those with VTE versus 15.8 days in those who did not develop VTE ($P < 0.001$). Average PICC-days were also longer in those who developed VTE compared to those who did not (13 days vs. 9; $P < 0.001$).

VTE prophylaxis (using enoxaparin or heparin) was administered to 26% of patients from the time of PICC insertion until UEDVT occurred. Only 12.5% of those who developed PE were given VTE prophylaxis. All patients who developed a UEDVT or PE were treated with full anticoagulation except those with contraindications and patients with superficial upper extremity thrombosis. Five of the patients with UEDVT and 2 of the patients with PE died during their hospitalization.

Four of the 8 patients with PICC-associated PE had bilateral lower extremity ultrasounds performed, and 3 of these were negative. The other 4 patients did not have ultrasounds performed.

TABLE 3. Univariate Analysis of Risk Factors Predicting VTE

Characteristic	Univariate Model OR (95% CI)
Age	1.01 (0.99–1.03)
Gender (male versus female)	1.06 (0.56–2.01)
Race (nonwhite versus white)	1.07 (0.53–2.18)
History of cancer	1.72 (0.82–3.61)
History of VTE	10.36 (4.81–22.34)
PICC location: right versus left vein	1.62 (0.76–3.44)
PICC location	
Cephalic	Referent
Basilic	2.29 (0.31–17.07)
Median	4.91 (0.53–45.97)
PICC tip location: (noncentral versus central)*	2.43 (1.15–4.75)
PICC days (10 days unit)	1.40 (1.07–1.84)
Length of stay (10 days unit)	1.18 (1.05–1.33)

*Central location was defined as tip location at the time of placement in superior vena cava or right atrium.

Risk Factors

History of VTE was the strongest risk factor for VTE in univariate analysis, patients with a history of VTE being 10 times more likely to develop a PICC-related VTE event (Table 3). PICC tip location was strongly associated with VTE. A noncentral location of the tip at the time of insertion was associated with a 2.34 (95% CI, 1.15-4.75) higher risk of developing VTE during the hospitalization stay, compared to a central location (SVC or RA). The duration of PICC use was also associated with an increased risk of developing VTE (OR for a 10-day increase in duration, 1.40 (95% CI, 1.07-1.84), as it was the length of hospital stay (OR for a 10-day increase in duration, 1.18 (95% CI, 1.05-1.33). The duration of hospital stay was correlated with the duration of PICC use; however, its temporal relationship with a VTE was uncertain, as a prolonged hospital stay could be the consequence of a VTE event in some cases. In the multivariate analysis, history of VTE, PICC tip location, and length of stay retained statistical significance (Table 4); while our data are suggestive for an association with VTE events, the duration of PICC use did not maintain statistical significance, in the presence of PICC tip location. History of VTE remained the strongest risk factor for subsequent VTE (OR, 10.83; 95% CI, 4.89-23.95); the location of the PICC tip was location highly associated with subsequent VTE (OR, 2.61; 95% CI, 1.28-5.35).

Discussion

Overall Findings

Our study is the first to examine both UEDVT and PE rates in hospitalized adult patients with PICC lines. We found

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TABLE 4. Multivariate Model of Risk Factors for VTE

Characteristic	Multivariate Model OR (95% CI)
History of VTE	10.83 (4.89–23.95)
PICC tip location (noncentral versus central)*	2.61 (1.28–5.35)
Length of stay (10 days unit)	1.21 (1.07–1.37)

*Central location was defined as tip location at the time of placement in superior vena cava or right atrium.

Abbreviations: CI, confidence interval; OR, odds ratio; PICC, peripherally-inserted central catheter; VTE, venous thromboembolism.

that 4.89% of our patients experienced a thromboembolic complication during their hospitalization stay, yielding a rate of 5.1 VTE/1,000 PICC-days and 3.63 UEDVT/1,000 PICC-days. These figures are similar to or higher than those reported by other retrospective studies using symptom-driven ultrasound diagnosis of UEDVT, reporting incidence figures ranging from 2 per 100 patients,[3] to 2.47 per 100 patients,[4] to 3.7 per 100 patients.[5]

There are several factors to consider when comparing our findings to previously published studies. First, our study population differs by being older and by including hospitalized patients with both acute and chronic medical illnesses, and with a wider spectrum of PICC indications. Second, the duration of PICC use is known to be associated with the development of symptomatic UEDVT.[6] Several published studies do not report the duration of PICC use, thus making the comparison of incidence difficult to interpret. Third, the duration of patient follow-up influences the likelihood that a symptomatic UEDVT is diagnosed; patient follow-up time is oftentimes unspecified in some studies, thus making comparisons difficult. In contrast, our study reports the incidence of VTE during a clearly specified time window; ie, hospital stay.

Several studies that reported the incidence per 100 PICCs found incidences ranging from 3.9 per 100 PICCs[7] and 4.66 per 100 PICCs.[8] Similarly, studies of different patient populations and the use of systematic diagnostic and follow-up methods have found very high rates of thrombosis (15.4% in a randomized clinical trial [RCT] of total parenteral nutrition [TPN],[9] 38% with systematic venography to diagnose UEDVT,[10] and 64.52% in an RCT of intensive care unit [ICU] patients[11]).

PE

In the largest study to date of 2063 patients who received a PICC for intravenous antibiotic therapy, it was found that 2.5% developed upper extremity thrombosis; of these, 3.8% also had a positive VQ scan for PE.[4] However, this study did not systematically review records for PE in those without upper extremity thrombosis. Our study showed that approximately 1% of those who received a PICC developed a PE during their hospitalization. In 3 of our 8 patients who developed a PE, bilateral lower extremity ultrasounds were negative for PE. None of the subjects who developed PE received ultrasounds of the upper extremities in order to look for deep vein thrombosis (DVT), possibly due to a lack of awareness of PICC-associated VTE.

Risk Factors

Among the risk factors explored, we found that patients with previous history of a venous thromboembolic event are much more likely to develop a PICC-related VTE. This is not surprising, as previous VTE has been identified a risk factor.[12–14] We also found that patients whose PICC was not confirmed to be in the SVC or at the junction of the SVC and the RA, were twice as likely to experience VTE. An increased risk associated with noncentral tip location was reported in 2 previous studies using venography to assess vein condition among infectious disease patients,[15] and oncology patients.[16] This is biologically plausible, since the smaller diameter vessels may be more conducive to thrombus formation than the SVC or RA. Other factors such as blood flow rate, turbulent flow, and endothelial injury may also play a role. As recognized by the National Association of Vascular Access Networks,[17] tip positioning is influenced by catheter length, anthropometric measurements, and anatomical pathways. Central tip location, whenever possible, may be 1 of the few controllable risk factors for UEDVT. Decreasing the hospital-acquired DVT events has been recognized as an important quality improvement, requiring an increased identification and treatment of high-risk groups. Such hospital-based approaches have been suggested as effective.[18,19] Both tip location and history of VTE are identifiable risk factors that may be readily incorporated into specific strategies to decrease hospital-acquired DVT events.

While previously reported as a risk factor, left-sided catheter location was not significantly associated with VTE in our study. Our data suggest that the duration of PICC use is associated with the risk of developing a VTE event during hospital stay, yet without reaching statistical significance. In the absence of information regarding the underlying comorbidities and/or reasons for hospitalization, interpretation of PICC line duration remains elusive.

Anticoagulant Prophylaxis

Most of the subjects in our cohort did not receive VTE prophylaxis. The efficacy of anticoagulant prophylaxis for preventing catheter-associated VTE is controversial. In fact, current guidelines do not support VTE prophylaxis as a means to reduce rates of VTE associated with central venous catheters. Furthermore, recent controlled clinical trials of low-molecular weight heparins at standard prophylactic doses and low doses of warfarin for VTE prevention in patients with central venous catheters undergoing cancer chemotherapy have not demonstrated reductions in VTE rates.[20–22] In contrast, a recent meta-analysis suggests that anticoagulant prophylaxis is effective for preventing all catheter-associated DVT in patients with central venous catheters, but the effectiveness for preventing symptomatic VTE, including PE, remains uncertain.[23]

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Limitations

The small number of VTE and the lack of control for the underlying disease, concomitant therapy, and anticoagulant prophylaxis limited our ability to identify independent risk factors. Further studies are needed to confirm our finding that 1% of patients who receive a PICC will develop PE.

VTE were identified only when symptoms led to diagnostic testing, so our event rates likely underestimate the true rate of PICC-associated VTE. It is estimated that subclinical thromboses can be found in 30% to 60% of all central catheters.[10,24] The clinical significance of silent thromboses remains to be established.

Strengths

The Society of Interventional Radiology recommends uniform reporting requirements to assist in study design and outcomes reporting on central venous access devices.[25] We adhered to many of these guidelines which may facilitate comparison among studies from different institutions.

Our study is one of the largest studies to asses the rate of thrombosis among inpatients. We used broad eligibility criteria, included consecutive, unselected patients, in a large cohort of patients who were all hospitalized for acute medical illnesses. Furthermore, we used data collection that corroborated data across the entire range of hospital records, and as such we were able to determine accurately the incidence of thrombosis. UEDVT and PE were diagnosed objectively and, unlike previous studies, we also collected information on prophylaxis and treatment of VTE. To our knowledge, our study is the first to document an increased risk of symptomatic UEDVT and PE among acutely ill hospitalized patients who receive PICC.

Prior studies may be less applicable to PICC-associated VTE in hospitalized patients because the populations included a mix of inpatients and outpatients. Our results may be more applicable to hospitalized patients who receive a PICC because more severely ill patients who are hospitalized may be at higher risk of thrombosis than outpatients. Also, previous studies included some patients who received relatively small, 3-Fr to 4-Fr single-lumen PICCs, whereas the current practice is to insert larger, double-lumen, 5-Fr catheters. Today's PICCs may be more likely to result in vessel occlusion, venous stasis, and thrombosis.

In conclusion, we have shown that the incidence of VTE in our study population was 4.89% with a rate of 5.10 VTE/1,000 PICC-days. There were 27 patients who had a UEDVT over the 7444 PICC days yielding a rate of 365 UEVDVT/1000 PICC days. The most significant predictors of VTE were history of previous VTE and the location of the PICC tip at the time of insertion.

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