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The Role of Tissue Plasminogen Activator Use and Systemic Hypercoagulability in Central Line Associated Blood Stream Infections (CLABSIs)

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Introduction

Health-care-associated infections (HAI) represent 5% of all adverse events in hospitalized patients in the US(1). Approximately one-third of HAI related deaths are attributable to bloodstream infections (BSI), the majority of which are central line-associated bloodstream infections (CLABSIs)(2). CLABSIs result in increased mortality, morbidity, hospital length of stay and cost. Although there are approximately five million central venous catheters placed in the US each year, resulting in over 15 million catheter-days in ICUs alone, the rate of CLABSI has decreased over the past decade(1–3). Standardized practice “bundles,” focusing on sterile insertion and continued line maintenance to decrease infection by skin flora have been integral in this achievement(4). Further reduction will be aided by identification, and enhanced care, of patients with central venous catheters (CVCs) who are at higher risk for developing CLABSIs.

Infections typically occur through adherence and migration of skin-dwelling organisms along the catheter into the blood(5). This process is enhanced by fibrin deposition on the catheter and biofilm formation, which can confer resistance to host immunity and antibiotic therapy(2, 6). Several studies have demonstrated a relationship between line thrombus and CLABSI(7–11). Since several of the host determinants involved in the infection process are

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activated and deposited products of the coagulation system, it is possible that patients with hypercoagulable states may be more susceptible to developing CLABSIs(7, 10). This risk could be mediated by either in situ line thrombosis or as a result of systemic immune and vascular changes. Further in vivo and epidemiologic research is required to elucidate the clinical relevance of these findings.

This study aimed to establish whether in situ thrombosis results in increased risk of infection. Furthermore, we evaluated the role of a systemic primary or secondary hypercoagulable state in modulating this relationship. Lastly, the contribution of increased age and multiple comorbidities to the development of CLABSIs was examined.

Methods

Study Design

This study was a retrospective analysis that included ICU and non-ICU adult patients with PICCs hospitalized at Boston Medical Center (BMC) between January 1, 2008 and December 31, 2011. BMC is a 508-bed tertiary care center with approximately 29,000 total discharges per year. The study was approved by the BMC Institutional Review Board.

PICC line data for admitted patients were obtained from the hospital's PICC line nursing team. At BMC, it is nursing practice to flush PICCs with alteplase, the tissue plasminogen activator used at our institution, when sluggish or blocked flow occurs upon use of lumens. TPA administration was used as a surrogate for line thrombosis. TPA administration records were obtained from the BMC pharmacy department and were cross-referenced with a list of patients with PICCs. Patients were divided into those who did and did not receive TPA during the admission when a PICC was placed. The infection control department provided CLABSI data for the duration of the study period. A CLABSI was defined as a positive blood culture documented more than 24 hours after PICC placement or within 72 hours of line removal(12). The rates of CLABSIs were compared between the two study groups.

Discharge billing codes were used to identify patients with hypercoagulable conditions and comorbid conditions. The first 99 ICD codes entered into every patient's chart were surveyed for this report. Patients were then divided into those with primary or secondary hypercoagulable states. Primary hypercoagulability was defined as an inherited condition such as factor V Leiden mutation, or protein C or protein S deficiency. Secondary hypercoagulability was defined as an acquired condition such as pregnancy, malignancy, obesity, immobility, heparin induced thrombocytopenia, nephrotic syndrome, HIV, congestive heart failure, or having antiphospholipid antibodies. Prognostic comorbidity was calculated using the Charlson comorbidity index and diagnosis codes were obtained to calculate each patient's index. The Charlson index utilizes a weighted score of 17 comorbidities to help predict long term mortality(13). It has been shown to be a good measure of in hospital mortality(14). A high Charlson comorbidity index score was defined as any score of two or greater.

Patients

All adult and pediatric patients with documentation of PICC line placement were included in this study. Both ICU and non-ICU patients were included. Patients without valid medical record numbers or dates of PICC line insertion were excluded from the study. If patients had multiple PICC lines placed between January 1, 2008 and December 31, 2011, the earliest date of insertion for patients with more than one PICC line was used.

PICC lines

PICC lines at our institution are silastic BARD PowerPICC™. PICCs are inserted by a certified team of PICC nurses (floor and ICU nurses may access the line after it is placed) or under ultrasound guidance in the interventional radiology suite. Standard procedures to reduce CLABSI rates are used in both context, which involve skin hygiene with chlorhexidine and Biopatch and limiting blood draws. Lines are stabilized with Stat Lock and Tegaderm dressings and patency is maintained 20cc saline flushes; no filters, stopcocks, or ethanol locks are used. TPA is instilled, and the catheter is clamped using positive pressure. After a 2 hour dwell time, the catheter is unclamped and aspiration is attempted using a pull/ pause technique.

Statistical analysis

We estimated that a sample of 720 patients would provide 80% power to detect a 20% difference in CLABSI rates in patients who received TPA compared with those who did not receive TPA, assuming a CLABSI rate of 1.1% per year, at a two-sided alpha level of 0.05.

Univariate and multivariate analyses of CLABSI rates were performed using logistic regression. Chi-square and Fisher's exact statistics were utilized when appropriate. Based on clinical relevance of variables, the following potential confounders were used in the multivariate model where the binary outcome was presence or absence of CLABSI: TPA, patient age, any hypercoagulability, and Charlson index. All reported p-values were two-sided; an alpha level of 0.05 was considered to indicate statistical significance. We used an alpha level of 0.1 for variable inclusion in multivariate models. STATA software, version 9.2, was used for statistical analysis.

Results

After selecting the earliest date of insertion for all eligible patients, a total of 3,901 unique medical record numbers were identified. Due to invalid MRNs, date of insertion, or age of patients, 178 cases were excluded. Therefore, 3,723 patients were included in the overall analysis (Figure 1). Forty-six (1.2%) of these patients developed a CLABSI (Table 1). The age of patients ranged between less than 1 to 112 years old. The mean age of patients who developed a CLABSI was 47.0 years whereas the mean age of patients who did not develop a CLABSI was 57.1 years. TPA was administered to 39.3% (1463/3723) of patients. The CLABSI rate was significantly higher in those receiving TPA compared with those who did not (2.2% vs 0.62%, $p<0.001$, Table 2). The reciprocal was also true, in that a higher percentage of patients with CLABSI were given TPA (69.6% vs 38.9%, $p<0.001$, Table 1). The adjusted odds of developing a CLABSI was 3.59 times greater in those patients with

PICC lines who received TPA compared with those who did not receive TPA (95% CI [1.86, 6.94], $p < 0.001$, Table 3).

Twenty-six patients had a documented primary hypercoagulability, but only one developed a CLABSI (Table 1). Less than 1 % (10/1043) of those with secondary hypercoagulability developed CLABSIs. Neither primary nor secondary hypercoagulability was associated with increased TPA use. Patients who received TPA did tend to have more comorbidities (Table 2).

In the multivariate model, the Charlson comorbidity index and secondary hypercoagulability did not prove to be a statistically significant predictor of developing CLABSIs. Primary hypercoagulability was associated with increased odds of developing CLABSI (OR 3.41, 95% CI [0.43, 26.7], $p = 0.24$), but this result was not statistically significant. Increased age was associated with decreased odds of developing CLABSI (OR 0.59, 95% CI [0.96, 0.99], $p = 0.08$).

Discussion

This study demonstrated that the relative risk for CLABSIs in patients that receive TPA for PICC maintenance was over three times that of patients who did not require TPA. Furthermore, this association remained significant after adjustment for patient comorbidities. These results support the notion that clotting in and around a CVC facilitates adhesion, colonization, and infection by bacteria(2, 5, 6). Thrombus formation, signaled by need for TPA administration, may identify patients that would benefit from close surveillance for development of BSI. In a recent retrospective study of pediatric oncology patients with CVC, Rowan *et al* reported an OR of 2.87 for developing CLABSI when TPA was used(9). Interestingly, in 28% of cases, TPA was administered within five days preceding the positive blood culture, further suggesting that line thrombus can herald CLABSI.

Contrary to our expectations, a strong relationship of CLABSI with either primary or secondary hypercoagulable states was not found. In a prior study, a polymorphism in a platelet integrin was associated with increased incidence of CLABSI. However, known hypercoagulable states such as factor V Leiden did not confer an increased risk for CLABSI(15). There are multiple host, device, and bacterial factors that all converge in the etiology of CLABSI(5), and an altered hemostatic set point alone may not be sufficient to result in clinical relevant outcomes. Furthermore, the development of CLABSIs appears to depend more on local phenomena (such as endothelial disruption, dysfunction, or activation) rather than systemic ones. For example, in autopsy specimens from patients with CVCs, Raad *et al* identified thrombus only in catheterized veins and not untouched contralateral veins. Twenty percent of the patients with evidence of thrombosis had a history catheter related blood stream infection, whereas none of the patients without thrombus had developed a CLABSI(8).

This study has several limitations. Largely due to the retrospective nature of this work, it was not possible to extract complete clinical data from the electronic medical records, and we were unable to control for many potentially confounding variables. Data that may have

been informative (or would be useful to look at in a prospective study) include the following: The number and nature of substances infused into the PICC (medications, IV fluids, parenteral nutrition, etc), whether the line was used for blood draws, the number of times the PICC was accessed, and whether the patient was diagnosed with a localized infection in addition to their CLABSI. We did not have microbiology results for CLABSIs, and it would be interesting to include pathogen epidemiology as a component in subsequent studies. The timeline of PICC placement, TPA administration, and CLABSI diagnosis was not known and, therefore, a temporal causative association could not be confirmed. This information could be useful for several reasons. First, we could not adjust for the duration of time each PICC was in place. The time from line insertion to infection is associated with different modes of colonization. For example, the extension of skin flora into the insertion site predominates early and catheter hub contamination becomes more important by 30 days(11). However, no association was noted between catheter age and infection in one pediatric ICU study(9). The diagnoses for primary and secondary hypercoagulable states, as well as Charlson index, were determined by ICD-9 codes, and it is possible that cases of hypercoagulability or certain comorbidities were missed due to coding inaccuracy. Lastly, this study focused only on PICCs and these findings may not be generalizable to other types of catheter with varying lumen diameters and number.

These findings suggest that particular care should be taken in patients requiring PICC or other CVC to maintain device patency and that increased vigilance for infection should be practiced in those patients noted to have *in situ* thrombus. Animal models and prospective clinical trials have demonstrated lower CLABSI rates in lines treated with enoxaparin to reduce thrombus formation(16–18). Others have suggested that screening lines for thrombi in ICU patients may reduce infectious complications(19). However, the 2011 guidelines for preventing catheter-related infections recommend against anticoagulation for preventing catheter-related infections based on current evidence(3). Additional data may alter these recommendations. Prospective clinical trials are required to assess the conditions associated with CLABSIs and thrombotic complications, and the efficacy of risk reduction interventions. Further analysis would be needed to determine if practice alterations focused on thrombus identification are clinically beneficial and/or cost effective. Finally, these results supplement currently available epidemiological data on PICC complications that will guide clinical practice and policy as the use of PICCs continues to grow.

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Figure 1.
Study Enrollment and Outcomes

Table 1

Characteristics of Patients with CLABSI Compared to Those Without CLABSI, Univariate Analysis

	Patients with CLABSI N=46 n(%)	Patients without CLABSI N=3,677 n(%)	Unadjusted Odds Ratio OR (95% CI)	p value
Age over 65 ^a	20 (43.8)	2074 (56.5)	0.59 (0.33 – 1.07)	0.08
TPA	32 (69.6)	1,431 (38.9)	3.59 (1.91 – 6.75)	<0.001
Primary Hypercoagulability	1 (2.2)	25 (0.68)	3.25 (0.43 – 24.5)	0.25
Secondary Hypercoagulability	10 (21.7)	1,033 (28.1)	0.71 (0.35 – 1.44)	0.34
High Charlson Comorbidity Index ^b	13 (28.3)	1271 (34.6)	0.75 (0.39 – 1.42)	0.37

^a Age 65 used as reference group^b High Charlson Comorbidity index defined as Charlson Index score of 2

Table 2

Characteristics of Patients Who Received Alteplase Compared to Those Who Did Not Receive Tissue Plasminogen (TPA), Univariate Analysis

	Patients Who Received TPA N=1,463 n(%)	Patients Without TPA N=2,260 n (%)	Unadjusted Odds Ratio (95% CI)	p value
Age over 65 ^a	836 (57.1)	1,258(55.7)	1.06 (0.93–1.21)	0.37
CLABSI	32 (2.2)	14 (0.62)	3.60 (1.91–6.75)	<0.001
Primary Hypercoagulability	8 (0.55)	18 (0.80)	0.68 (0.30–1.58)	0.37
Secondary Hypercoagulability	266 (18.2)	777 (34.4)	0.42 (0.36–0.50)	<0.001
High Charlson Comorbidity Index ^b	304 (20.8)	980 (43.4)	0.34 (0.29–0.40)	<0.001

^a Age 65 used as reference group

^b High Charlson Comorbidity Index defined as Charlson Index score of 2

Table 3

Adjusted Odds Ratios for Risk Factors Associated With CLABSI

	Adjusted Odds Ratio OR (95% CI)	p value
Age over 65 ^a	0.59 (0.96 – 0.99)	0.08
TPA	3.59 (1.86 – 6.94)	<0.001
Primary hypercoagulability	3.41 (0.43 – 26.7)	0.24
Secondary hypercoagulability	0.91 (0.44 – 1.88)	0.81
High Charlson Comorbidity Index ^b	1.00 (0.51 – 1.96)	0.99

^a Age 65 used as reference group^b High Charlson Comorbidity Index defined as Charlson Index score of 2