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Major article

The role of tissue plasminogen activator use and systemic hypercoagulability in central line-associated bloodstream infections

Kinna Thakarar DO, MPH [a], Matthew Collins MD, PhD [b], Lana Kwong MPH [c], Carol Sulis MD [a], Cathy Korn RN, MPH [d], Nahid Bhadelia MD, MA [a,*]

[a] Section of Infectious Diseases, Boston Medical Center, Boston, MA
[b] Department of Medicine, Boston Medical Center, Boston, MA
[c] Department of Quality Improvement, Boston Medical Center, Boston, MA
[d] Department of Infection Control, Boston Medical Center, Boston, MA

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Background: Central line-associated bloodstream infections (CLABSIs) impact patient outcomes and increase cost of hospitalization. In situ thrombus is known to promote microbial adhesion and colonization and potentially lead to CLABSI. Clinical validation of this theory, adjusting for presence of systemic hypercoagulability, is needed.

Methods: This study is a retrospective review of all adult and pediatric patients with peripherally inserted central catheter placement over a 4-year period at our tertiary care center. Tissue plasminogen activator (TPA) use was utilized as indicator for line site thrombus. CLABSIs rates were compared in patients with or without TPA use, adjusting for the presence of hypercoagulable conditions, age, and severity of illness.

Results: A total of 3,723 patients with peripherally inserted central catheter lines was evaluated, 40% of whom received TPA. The adjusted odds of developing a CLABSI was 3.59 times greater in those patients who received TPA compared with those who did not (95% confidence interval [CI]: 1.86-6.94). Neither severity of illness (odds ratio [OR], 1.00; 95% CI: 0.51-1.96) nor primary (OR, 3.41; 95% CI: 0.43-26.7) or secondary hypercoagulability (OR, 0.91; 95% CI: 0.44-1.88) were statistically associated with a higher risk of infection.

Conclusion: The use of TPA, as a possible indicator in situ thrombus, was associated with a higher risk of developing CLABSI. Neither primary nor secondary hypercoagulability was correlated with risk of developing CLABSI.

Health care-associated infections (HAI) represent 5% of all adverse events in hospitalized patients in the United States.[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 5 million central venous catheters (CVCs) placed in the United States each year, resulting in over 15 million catheter-days in intensive care units (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 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] Because several of the host determinants involved in the infection process are 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

* Address correspondence to Nahid Bhadelia, MD, MA, Section of Infectious Diseases, Boston Medical Center, Director of Infection Control, National Emerging Infectious Diseases Laboratory, 850 Harrison Avenue, Dowling 3N Room 3104, Boston, MA 02118.
E-mail address: nbhadeli@bu.edu (N. Bhadelia).

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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 peripherally inserted central catheter (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 (TPA) 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 2 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 2 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 (Bard Access Systems, Inc, Salt Lake City, UT). 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 contexts, which involve skin hygiene with chlorhexidene and Biopatch dressing (Johnson & Johnson Wound Management, Ethicon, Inc, Somerville NJ), and limiting blood draws. Lines are stabilized with StatLock (Bard Medical Division, Covington, GA) and Tegaderm dressings (3M, St Paul, MN), and patency is maintained with 20-cc 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.

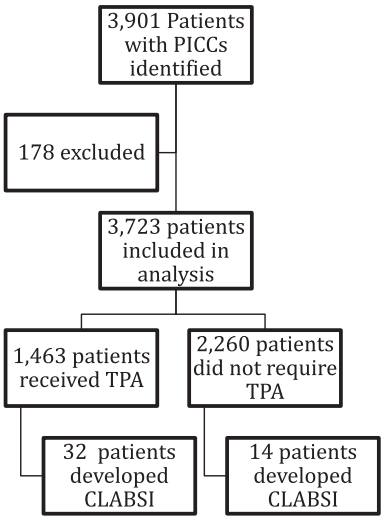

Fig 1. Study enrollment and outcomes.

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 2-sided α level of .05.

Univariate and multivariate analyses of CLABSI rates were performed using logistic regression. The χ^2 and Fisher exact statistical tests 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 2-sided; an α level of .05 was considered to indicate statistical significance. We used an α level of .1 for variable inclusion in multivariate models. STATA software, version 9.2 (STATA Corp, College Station, TX), 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 was identified. Because of invalid medical record numbers, date of insertion, or age of patients, 178 cases were excluded. Therefore, 3,723 patients were included in the overall analysis (Fig 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