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Major article

A comparative evaluation of antimicrobial coated versus nonantimicrobial coated peripherally inserted central catheters on associated outcomes: A randomized controlled trial

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Background: Central line–associated bloodstream infections (CLABSIs) are a common life-threatening risk factor associated with central venous catheters (CVCs). Research has demonstrated benefit in reducing CLABSIs when CVCs coated with antimicrobials are inserted. The impact of chlorhexidine (CHG)-impregnated versus non-CHG peripherally inserted central catheters (PICCs) on risk of CLABSI is unknown. Venous thromboembolism (VTE) is also a complication associated with CVCs. This study compares the impact of both PICC lines on these outcomes.

Methods: Patients in 3 high-risk units were randomly assigned to receive either a CHG-impregnated or non-CHG PICC line. Laboratory data were collected and reviewed daily on all study patients. The PICC dressing site was assessed daily. Medical record documentation was reviewed to determine presence of CLABSI or VTE.

Results: There were 167 patients who completed the study. Three patients developed CLABSI (2 in the CHG group, and 1 in the non-CHG group), and 3 patients developed VTE (2 in the non-CHG group, and 1 in the CHG group). No significant relationship was noted between the type of PICC line on development of a CLABSI ($P = .61$) or VTE ($P > .99$). A significant difference was noted in moderate bleeding ($P \leq .001$) requiring thrombogenic dressing in the patients who had the CHG PICC line.

Conclusions: No differences were noted in the development of CLABSI and VTE between the CHG and non-CHG groups.

Central venous catheters (CVCs) are important in the medical management of acutely ill patients. The most common and life-threatening complication of CVCs is the risk for a central line–associated bloodstream infection (CLABSI). CLABSIs are preventable, and when they occur during hospitalization, they are considered to be a hospital-acquired infection (HAI). Subsequently, they impact patient outcomes and reimbursement of hospitalization costs from the Centers for Medicare and Medicaid Services and private insurance companies. It is estimated in the United States that 1 of 20 hospitalized patients will develop an HAI.[1] CLABSIs are the third leading cause of HAIs, after catheter-associated urinary tract infections and surgical site infections.[2]

According to the Joint Commission in 2012, 3 million central lines are used each year.[3] It is estimated that 41,000 CLABSIs occur in U.S. hospitals each year, with approximately 18,000 occurring in the intensive care unit and 23,000 occurring in nonintensive care unit populations.[4] CLABSIs are costly and associated with poor patient outcomes, such as increased length of stay, hospital costs, and mortality.[5,6] It is estimated that CLABSIs cost the health care system approximately $16,550 per episode[7] and are associated with a mortality rate of 15%-25%.[8] Reducing CLABSIs is a priority for improving patient safety and reducing health care costs.

Peripherally inserted central catheters (PICCs) are CVCs inserted via ultrasonographic technique into the upper veins of the arm, with the

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tip advanced to the superior vena cava. PICC lines provide intravenous access for the administration of parenteral fluids, medications, blood products, and nutrition and provide venous access for phlebotomy. PICC lines are a commonly used CVC, especially for patients requiring longer-term intravenous access. As with all CVCs, CLABSI is a potential risk in patients with PICC lines. Risk factors for the development of CLABSI include the number of times the line is manipulated, location of insertion,[9] prolonged dwell time,[10,11] and development of thrombus.[12] Trauma and critical care patients and those admitted with immune suppression are at an increased risk for CLABSI.[13,14]

In addition to the risk of CLABSI associated with PICC lines, upper-extremity venous thromboembolism (VTE) is another potential complication.[15,16] One study found 5% of hospitalized patients develop a symptomatic upper-extremity VTE post–PICC line insertion.[17] VTEs related to PICC lines present a challenge in clinical practice because they may interrupt or delay the patient's medical treatment plan. Factors associated with the development of VTE include catheter size, vein selection,[15] and number of insertion attempts.[18] In addition, researchers acknowledge there may be a reciprocal relationship where infection promotes thrombus formation or the presence of thrombus may facilitate the development of an infection.[16,19] Increased morbidity, hospital costs, and length of stay have been associated with PICC-related CLABSI and VTE.[5,6]

One of the most important aspects in the prevention of CLABSIs is the care and maintenance of the line. Evidence-based bundles for insertion and maintenance care have been developed to prevent CLABSIs. These include insertion techniques such as maximum sterile barriers, site preparation and disinfection using chlorhexidine (CHG), sterile insertion procedures (mask, gown, and gloves) and avoidance of femoral site selection.[3] In addition to these interventions, the use of antimicrobial or antimicrobial-impregnated catheters has been recommended if there is no change in CLABSI rate after the implementation of evidence-based bundles.[14] Research has demonstrated significant benefit in reducing CLABSIs when antimicrobial (CHG–silver sulfadiazine) or antibiotic (minocycline/rifampin) CVCs are inserted. A meta-analysis of randomized controlled trials (RCTs) demonstrated antimicrobial-impregnated CVCs were associated with a decrease in bacterial colonization and CLABSI.[20] However, most of the studies included in the meta-analysis focused on CVCs located in the femoral, subclavian, and jugular veins. There is a paucity of research related to the impact of antimicrobial-impregnated PICC lines on the development of CLABSIs or VTE.

In 2011, a PICC line impregnated with CHG and with clearance as a device with a minimum 30 day antimicrobial and antithrombogenic protection was approved the U.S. Food and Drug Administration.[21] Although this device does not contain heparin, it has been shown to have antithrombogenic properties.[21] Two publications[22,23] noted decreases in CLABSI rates when the CHG-impregnated antimicrobial PICC lines were used, but they did not examine their impact on the development of VTE. One of the publications described the findings from a quasi-experimental study, whereas the other was a 2-year product evaluation.[22,23] To our knowledge, no RCTs have been conducted to examine the impact of CHG PICC lines. Therefore, the purpose of this study was to compare an antimicrobial PICC line impregnated with CHG with a non–CHG-impregnated PICC line on the development of CLABSI or VTE among high-risk hospitalized patients in the cardiovascular thoracic, medical intensive care (MICU), and oncology units.

METHODS

Study setting and design

This study was conducted over 18 months at a large, 800-bed tertiary community hospital in the Midwest. The study was approved by the hospital's institutional review board. To reduce the potential for bias, both the CHG and non-CHG PICC lines were purchased by the institution. Three units were chosen for study recruitment because of higher CLABSI rates than other units in the hospital. Patients were enrolled in the study if they met the following inclusion criteria: (1) PICC line insertion on the cardiovascular thoracic, cardiovascular thoracic, MICU, or oncology units; (2) inpatient ≥18 years of age; (3) no allergy to CHG; (4) insertion of a single- or double-lumen PICC line (the study PICC did not have a triple-lumen option); and (5) anticipated hospital length of stay >48 hours. Patients were excluded from the study for pregnancy and difficult PICC insertion requiring placement in vascular laboratory. Patients were notified on consent that if their hospital length of stay or duration of the PICC line was in <48 hours they would be excluded from the study.

Sample

Convenience sampling was used along with stratified sampling to ensure an equal number of participants came from each of the 3 designated study units. Target enrollment was set at 60 subjects (30 subjects in the control group, and 30 subjects in the standard of care group) from each of the 3 units for a total of 180 subjects. To reduce bias, randomization was conducted by a third party who randomly mixed and selected envelopes containing study assignment group for each unit. Sixty envelopes per unit were divided evenly (30 in each group) and randomly assigned to either group A (CHG PICC) or B (non-CHG). The randomized envelope(s) were selected and placed in the enrollment folder.

Procedures

After informed consent was obtained, patients were randomly assigned to receive either the CHG-impregnated antimicrobial PICC or the non-CHG PICC. The non-CHG PICC was the standard of care at the facility at the time of the study. Both PICC lines were power injectable.

The PICC lines were inserted by the hospital's specially trained PICC team. There are specific differences in the insertion technique between the 2 types of PICC lines. To ensure competency and consistency in placement, all PICC team members completed training on the insertion of the CHG-impregnated antimicrobial PICC prior to study initiation. Standard procedures were followed for insertion of both types of PICC lines. Postinsertion, the PICC team documented type of PICC placed (CHG or non-CHG), catheter size, number of lumens, insertion date, time, and initials of PICC team member responsible for insertion. The PICC team also documented postinsertion location, amount and extent of postinsertion bleeding, and if application of thrombogenic dressing or pressure dressing was required.

Data collection

Demographic information was collected at the time of enrollment and included sex, age, unit location, and duration of PICC line. The type of PICC line (CHG or non-CHG), insertion location, and number of catheter lumens were also collected. Daily inspection of the PICC dressing and site was conducted by a study investigator to assess for signs and symptoms of infection and VTE. The assessment for infection included daily observation and documentation of dressing integrity and appearance of insertion site for presence of redness, warmth, edema, purulent drainage, and bleeding. To control for variations in technique, patients in the study had PICC dressing changes completed by the PICC team nurses or study investigators. PICC team nurses and study investigators attended a

training review session with return demonstration to assure standard practice and competency in dressing change techniques prior to study initiation.

Medical information on diagnosis, comorbidities, and laboratory and diagnostic tests results were collected on study subjects who developed a CLABSI or VTE, the outcomes of interest. When available, complete blood counts, specifically white blood cells, absolute neutrophil count, and platelets, were reviewed to assess immune status and risk for bleeding in subjects who developed CLABSI or VTE. Laboratory-confirmed CLABSIs not secondary to an infection at another body site were reviewed and verified by one certified infection prevention specialist based on the criteria established in the Centers for Disease Control and Prevention guidelines.[23] The laboratory-identified organism from the culture was also recorded. All of the patients were tracked for development of VTE in the upper extremity where the PICC line was placed. VTE was identified through clinical assessment of symptoms and diagnostic tests as ordered per standard practice for suspected occurrence. Postinsertion bleeding was defined as either moderate or severe dependent on the type of dressing required to control the bleeding. Moderate bleeding was defined as the need for application of a thrombogenic dressing. Severe bleeding was defined as bleeding that could not be controlled with the use of a thrombogenic dressing and required the application of a pressure dressing.

Statistical analysis

An a priori sample size calculation was conducted using the average CLABSI infection rate for the 3 selected units, a power of .80, and an α level of .05. Based on these numbers, a minimum sample size of 60 patients per unit (30 control and 30 experimental) was needed. Data were analyzed using IBM SPSS Statistics for Windows, Version 22.0 (IBM, Armonk, NY). All tests were 2-tailed, and an α level of <.05 was considered statistically significant. Descriptive statistics were used to describe the sample. Data were checked for normality using the Shapiro-Wilk test. The Mann Whitney *U* test was used to assess differences in patient age and duration of PICC lines. Fisher exact tests were used to assess for associations between the groups for the following outcomes: CLABSI, VTE, and severity of postinsertion bleeding. In addition, a Fisher exact test was used to determine if there was a significant difference in the postinsertion bleeding rate between the 3 hospital units.

RESULTS

Sample characteristics

One hundred eighty-nine subjects consented for participation, and 167 completed the study. Twenty-two patients were withdrawn from the study, most for not meeting the inclusion criteria of being hospitalized for at least 48 hours. Figure 1 shows the study flow diagram. Most study subjects were men. Most PICC lines placed in the study subjects were 5 French, double lumens and placed in the basilic vein. No statistically significant differences were noted in the demographic or participant characteristics between the 2 groups (Table 1). The study was discontinued after 18 months because of slow enrollment from the cardiovascular thoracic unit because of the frequent need for triple-lumen PICC placement, which at the time of the study was not available in CHG PICC product lines.

CLABSI

Results demonstrated no significant difference between the type of PICC line and the development of infection (Table 2). Three patients developed a CLABSI: two from the CHG group and 1 from the non-CHG group. The medical diagnoses of these subjects were

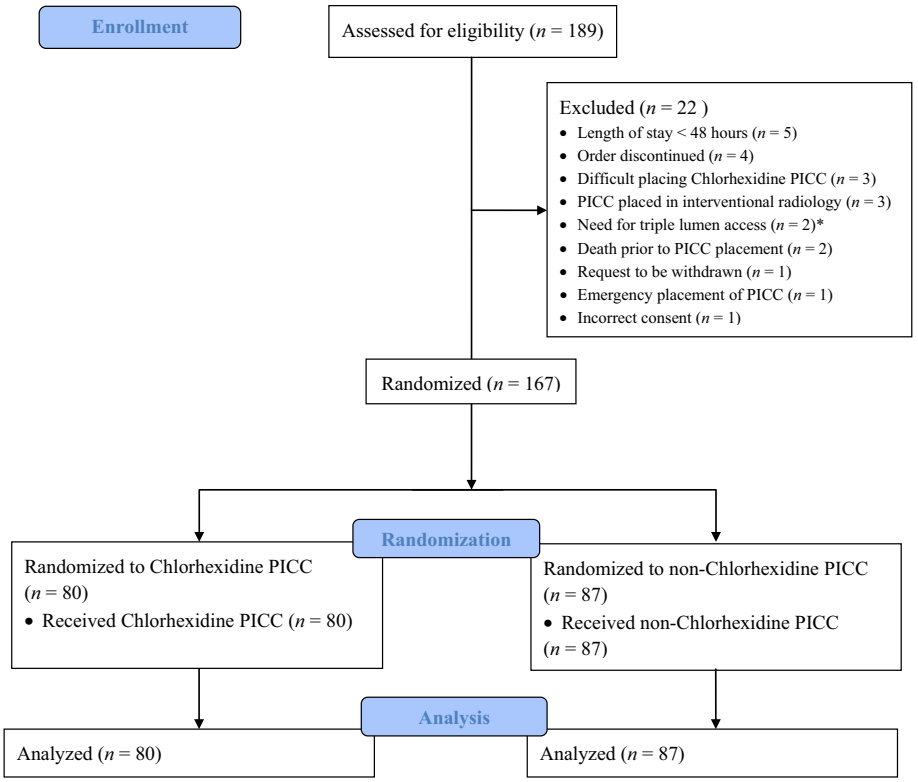

Fig 1. Study flow diagram. *PICC*, peripherally inserted central catheter. *At time of the study, the triple-lumen chlorhexidine PICC was not available.

Table 1
Comparison of demographic and participant characteristics

Characteristic	Chlorhexidine PICC (n = 80)	Nonchlorhexidine PICC (n = 87)	*P* value
Sex	95 (57)	72 (43)	.76
Study unit			
Medical intensive care unit	28	31	.71
Cardiovascular thoracic unit	21	27	
Oncology unit	29	31	
PICC type			
5 French	74 (90.2)	77 (90.6)	1.0
Other	8 (9.8)	8 (9.4)	
PICC location			
Basilic vein	13 (15.9)	17 (20.0)	.55
Other	69 (84.1)	68 (80.0)	
No. of lumens			
Double	79	77	.20
Single	3	8	
Age, y, median (interquartile range)	62 (22)	64 (21)	.42
Duration of PICC line, d, median (interquartile range)	8 (8)	8 (8)	.86

NOTE. Values are n (%) or as otherwise indicated.
PICC, peripherally inserted central catheter.

Table 2
Comparison of outcomes by PICC group (N = 167)

Outcome	Chlorhexidine PICC (n = 80)	Nonchlorhexidine PICC (n = 87)	*P* value
Central line–associated bloodstream infection	2 (2.5)	1 (1.1)	.067
Venous thromboembolism	1 (1.3)	2 (2.2)	>.99
Moderate bleeding requiring use of thrombogenic dressing	26 (32.5	1 (1.1)	<.001
Severe bleeding requiring pressure dressing	5 (6.3)	1 (1.1)	.105

NOTE. Values are n (%) or as otherwise indicated.
PICC, peripherally inserted central catheter.

lymphoma (n = 1) and acute myeloid leukemia (n = 2). The median duration of the PICC lines prior to CLABSI in these 3 subjects was 18 days. The median number of days the 3 subjects were neutropenic, defined as an absolute neutrophil count <500 cells/mm^2, was 19. Organisms identified in these CLABSIs were *Klebsiella pneumoniae*, *Streptococcus viridans*, and *Kocuria* spp (gram plus cocci).

Venous thromboembolism

Results demonstrated no significant relationship between the type of PICC line and the development of VTE (Table 2). Three subjects developed VTE: 1 in the CHG group and 2 in the non-CHG group. All of the patients who developed VTE were in the MICU. The medical diagnoses for the 3 subjects were ischemic bowel disease, ovarian cancer, and hypotension. The median duration of the PICC lines prior to the development of VTE was 5 days. All of the study subjects had double-lumen, 5 French catheter size PICC lines inserted. Of the subjects that developed VTE, all had the PICC lines inserted in the basilic vein (2 in the right, and 1 in the left).

Postinsertion bleeding

Most (96%) who had postinsertion bleeding were in the CHG PICC group. Subjects with the CHG PICC line experienced moderate bleeding requiring application of a thrombogenic dressing more often than those with the non-CHG PICC line (Table 2). No difference in postinsertion bleeding was noted among the 3 units ($P = .97$).

Severe bleeding requiring the application of a pressure dressing occurred more often in subjects with the CHG PICC. Six of the subjects experienced severe postinsertion bleeding requiring application of a pressure dressing. Of those, 5 (83%) of the subjects had the CHG PICC line.

DISCUSSION

CLABSI

In this sample, no difference was noted in the development of CLABSI between the non-CHG and CHG PICC line study groups. Three patients from the oncology unit developed a CLABSI. Oncology patients present a unique challenge because they frequently experience immune suppression (neutropenia) as a result of treatment, leaving them vulnerable to infection.[13] Patients with hematologic cancers are susceptible to more days of neutropenia and subsequent infections.[24] Although this patient population has an increased risk of CLABSI, in this study other subjects with these hematologic diagnoses and similar characteristics were randomized to both types of PICC lines and did not develop CLABSI. Suggesting, as others have noted, that the care and maintenance of the PICC line may impact the development of CLABSI perhaps more than the type of PICC line used.[5]

Other studies have noted findings contrary to the findings of this study. In a quasi-experimental study of 260 patients receiving the CHG PICC (intervention) compared with 257 patients who received the non-CHG PICC (historical control), the authors noted those with the CHG PICC line had fewer CLABSIs than those with the non-CHG PICC line ($P = .013$).[22] These findings, however, need to be interpreted taking into consideration that this type of study design is less rigorous than an RCT and is more susceptible to bias. Additionally, the findings may have been influenced by

differences in the patient population or changes in management of patients between the 2 time periods.

A quality improvement project conducted over a 2-year period evaluated the CHG PICC line in 100 patients at a long-term acute care hospital. The authors reported no patients developed a CLABSI during the evaluation time period.[23] Quality improvement initiatives, although important, cannot be considered a robust research design, and the findings must be interpreted with caution.

VTE

The 3 subjects who developed PICC line–associated VTE were from the MICU and had 5 French PICC lines inserted in the basilic vein. In other studies, VTE has been shown to be associated with catheter size; specifically, researchers have shown the risk increases with catheter sizes ≥5 French. Patients with PICC catheter sizes 5 French and 6 French were found to have an earlier onset of VTE than patients with smaller size PICC lines.[12] Evans found a correlation between catheter size and incidence of VTE when progressing from smaller 4 French (0.6%) to 5 French (2.9%) to larger 6 French (8.8%) PICC lines.[7]

Location of vein chosen for PICC insertion has been shown as a contributing factor for VTE. Researchers noted PICC lines inserted into the basilic vein were associated with higher incidence (3.1%) of VTE than those inserted into the cephalic or brachial veins.[15] Location of the catheter insertion has been noted as a predisposing factor to the development of VTE. In a retrospective review of 400 cases, those with left-sided catheter insertion were noted to be more likely to develop a VTE.[6] The authors suggest the longer left innominate vein may be the reason for this finding.[6]

Mechanically ventilated patients have also been identified at higher risk for VTE because of decreased cardiac output, particularly in the presence of hypovolemia impaired cardiovascular reflexes or venous stasis.[25,26] Information on the subjects as it relates to the status of mechanical ventilator use was not collected or analyzed. Despite these risk factors, no statistically significant difference was noted in the development of VTE between the CHG or non-CHG PICC groups.

Postinsertion bleeding

The CHG PICC line has demonstrated antithrombogenic properties for up to 30 days in clinical testing, and postinsertion bleeding is a known potential side effect.[21] Thirty-three (20%) subjects experienced postinsertion bleeding. In this study, moderate bleeding requiring the application of a thrombogenic dressing occurred more often in subjects with the CHG PICC. The findings in this study are similar to another study where postinsertion bleeding occurred in 30% of patients.[23] For most patients the bleeding was resolved by the use of a thrombogenic dressing; however, in 6 (18%) instances severe bleeding occurred requiring the application of a pressure dressing.

Limitations

Limitations of this study include the small sample size and single institution location. The lack of statistical significance between groups for CLABSI and VTE could be because of insufficient power. Post hoc power analysis showed the study obtained a power of only 48.9% and that to have a study powered sufficiently to find a statistical difference with the infection rate found in the study would require a sample size of 348 (174 in each group).

Blinding of the study was not possible because the catheters differ in appearance and may have introduced bias into the study. It is possible that nurses (and patients) may have been more conscientious in the care and maintenance of the PICC lines because of their participation in the study. Another limitation of the study is that minimal demographic and patient characteristic information was collected on the participants. It is possible that there may be have been significant differences between the groups despite the use of randomized group assignment. Therefore, it is recommended that potential confounders, such as diagnosis, severity of illness, and comorbidities, be collected in future studies.

Strengths

These limitations notwithstanding, this study had important strengths, such as the study design. To our knowledge this is the first RCT examining the effect of CHG-impregnated antimicrobial PICC lines versus non-CHG PICC lines on the development of CLABSI or VTE. The inclusion of 3 high-risk units (cardiovascular thoracic, MICU, and oncology) with diverse patient populations is an additional strength of the study. Finally, the utilization of a dedicated team for insertion, daily assessment, and dressing changes of the PICC lines reduced the risk of variations in clinical practice techniques. The use of one infection prevention specialist for verification of CLABSIs reduced inter-rater reliability in this study.

CONCLUSIONS

In this study, no difference was noted in CLABSI or VTE between patients who received the CHG or non-CHG PICC line. More patients with the CHG PICC line had postinsertion bleeding requiring the application of a thrombogenic dressing and in some instances a pressure dressing. Additional RCTs with larger samples from multiple acute care hospitals are warranted to validate the findings of this study.

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