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E. W. Moretti
moret002@mc.duke.edu

C. Ofstead
Walden University

R. M. Kristy

H. P. Wetzler

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Impact of central venous catheter type and methods on catheter-related colonization and bacteraemia

E.W. Moretti^{a,*}, C.L. Ofstead^b, R.M. Kristy^c, H.P. Wetzler^d

^a*Department of Anesthesiology, Duke University Medical Center, P.O. Box 3094 DUMC, Erwin Road, Durham, NC 27710, USA*

^b*School of Health and Human Services, Walden University, St Paul, MN, USA*

^c*Research Data Operations, Fujisawa Healthcare, Inc., Deerfield, IL, USA*

^d*Branch Medical Clinic, Puget Sound Naval Shipyard, Bremerton, WA, USA*

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Summary A prospective, randomized, controlled, multi-centre clinical trial was performed to test the effectiveness of an antimicrobial central venous catheter (CVC) made of polyurethane integrated with silver, platinum and carbon black (Vantex®). Adults expected to require a CVC for more than 60 h were eligible, and were randomized to receive the test or control catheter. All CVCs were inserted with new venipunctures using full aseptic technique. Following catheter removal, the distal tip and an intracutaneous segment were removed and cultured using semiquantitative and quantitative methods. Peripheral blood samples were obtained and cultured to confirm cases of catheter-related bloodstream infection (CRBSI). Bacterial and fungal organisms were identified by standard microbiological methods. Catheter placement was performed primarily in the intensive care unit (50%) or operating theatre (42%). Complete data could be evaluated for 539 patients (77%). The mean duration of CVC placement was 149.3 h (six days). There were no significant differences in colonization or bacteraemia rates between the test and control catheters. The overall colonization rate was not particularly low (24.5%), and yet CVC-related bacteraemia occurred in only 1.4% of patients, and CRBSI occurred in only one patient from the control group (0.2%). Insertion site and dressing change frequency were significantly associated with the colonization rate. Although CVCs with antimicrobial features have been associated with a decrease in catheter-related colonization and bacteraemia, this study demonstrated that

* Corresponding author. Tel.: +1 919 668 3400; fax: +1 919 681 7893.

E-mail address: moret002@mc.duke.edu

infection rates may depend more on non-catheter-related factors, such as adherence to infection control standards, selection of insertion site, duration of CVC placement, and dressing change frequency. As microbial resistance increases, clinicians should make maximal use of these processes to reduce catheter-related infections.

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Introduction

Central venous catheters (CVCs) are essential for many critically ill patients, and the prevention of central line infections is vitally important. In the USA, approximately five million CVCs are inserted annually.¹ US Centers for Disease Control and Prevention (CDC) data have shown central-line-associated bloodstream infection rates of 5.3 per 1000 catheter-days.² There have been reports of catheter colonization rates greater than 50%,³ and catheter-related bloodstream infections (CRBSIs) occur with 3-8% of catheters.⁴ Given an estimated 15 million central-line-days annually in intensive care units, approximately 16 000 patients experience CRBSI each year.² Catheter-related infections increase patient morbidity, prolong hospitalization and raise mortality rates.⁵ These infections are also associated with higher costs (increases from \$6000 to over \$90 000 for those with CRBSI).^{4,6-9}

Risk factors for CRBSI include patient characteristics (e.g. age and immunity), technique-related variables, and features of devices.¹⁰ The CDC has recommended several techniques to reduce the risk of catheter-related infection. Foremost are meticulous aseptic procedures, including careful cleansing of the insertion site and the use of maximal barrier precautions.^{5,11} In recent years, there has been a concerted effort to apply antimicrobial technology to prevent infections, including the use of prophylactic antibiotics and catheters with special coatings and surface modifications.^{12,13} CVCs with chlorhexidine-silver sulphadiazine (CSS) or minocycline-rifampicin coatings have been associated with significant reductions in CRBSI.^{3,14} However, adverse reactions to chlorhexidine have been reported,^{10,15-17} and there are concerns related to potential antibiotic resistance with regard to rifampicin.^{14,16} These concerns and other technical issues may limit the widespread use of antibiotic-coated catheters.

The Vantex[®] CVC with Oligon[™] (Edwards Lifesciences, Irvine, CA, USA) is made of polyurethane integrated with silver, platinum and carbon black.

It was designed to reduce the risk of bacterial colonization on catheter surfaces. Oligon was reported to be effective against both Gram-positive and Gram-negative bacteria, including strains commonly associated with device-related infections in *in vitro* studies.^{12,13} The purpose of this study was to determine whether the Vantex CVC lowers the incidence of catheter colonization and CRBSI compared with a standard CVC (MultiMed[®]; Edwards Lifesciences), and to evaluate other factors that impact on CVC infection rates.

Methods

Patient enrolment

This study was designed as a prospective, randomized, controlled, open-label, multi-centre clinical trial. Ten investigational sites obtained institutional review board approval and informed consent prior to patient enrolment. Adults expected to require a CVC for more than 60 h were eligible. There were no eligibility constraints related to diagnoses, hospital unit, or anticipated treatments or procedures. Patients were excluded if: they had a history of allergic reactions to silver, platinum or carbon black; were expected to live for seven days or less; had evidence of a burn or dermatitis at the catheter insertion site; were pregnant or lactating; or had a catheter placed in the same proposed site previously. A computer-generated randomization schedule was used to avoid potential bias in catheter selection. However, due to the difference in appearance of the CVCs, blinding could not be achieved. Determinations for inclusion were made at individual sites, and patients were enrolled from May 2000 until April 2001.

Catheter insertion and maintenance

The test and control catheters had similar designs (polyurethane 7-French, triple-lumen CVCs). All CVCs were inserted using full aseptic technique

(sterile gown, sterile gloves, masks and large sterile drapes), based on published guidelines by the CDC for insertion of CVCs.⁵ Patients received only one study catheter, and all CVCs were inserted through new venipunctures. Guidewire exchanges were not permitted. Patients were assessed daily for indications of infection, and dressing changes were performed according to local hospital policies. CVCs were removed when no longer required for patient care, when the patient experienced an adverse event, or when catheter exchange was necessary.

Definitions

The definitions of catheter colonization and CRBSI published by the CDC were used.⁵ Colonization was defined as the growth of 15 or more colony-forming units (CFUs) in cultures of catheter tips or segments prepared by the roll-plate method (semiquantitative) or more than 1000 CFUs by the sonication method (quantitative). CRBSI was defined as the isolation of the same organism (i.e. identical species) from the colonized catheter and peripheral blood in a patient with accompanying clinical signs and symptoms of bloodstream infection (BSI) and no other apparent source of BSI.⁵ Since a diagnosis of CRBSI relies on clinical judgment, we used bacteraemia as another category to document cases where the same organism was isolated from the catheter and peripheral blood cultures, regardless of documented signs and symptoms or other potential sources of infection. This definition for bacteraemia has recently been used by other investigators.^{1,18-20}

Cultures and antimicrobial susceptibility

Following catheter removal, the distal tip and a 3-mm intracutaneous segment were aseptically cut from the catheter and placed in individual containers for microbial evaluation. A core laboratory (Esoterix, Inc., San Antonio, TX, USA) was used to ensure consistency when performing and evaluating roll-plate, sonication and blood cultures. Both semiquantitative and quantitative methods were used for all samples, which adheres to the CRBSI diagnostic criteria recently used by other researchers.²¹ Aerobic and anaerobic blood cultures were performed. Gram stains were performed on blood cultures suspected of being positive and on all isolates from CVC cultures. Bacterial and fungal organisms recovered were identified by standard microbiological methods.

Statistical analysis

Sample size was determined based on the scientific literature and in vitro studies, which indicated that 2% of the test group and 7% of the control group were expected to experience CRBSI. In addition, it was anticipated that 15% of the patients would be non-evaluable. Therefore, to achieve 90% power with an alpha of 0.05 (i.e. for there to be a 90% chance of detecting a difference significant at the 5% level), 400 patients were required in each treatment group. Frequencies and percentages were calculated for categorical variables. Descriptive statistics were calculated for continuous variables. Comparisons of test and control groups were performed using the Wilcoxon rank-sum test for continuous variables and Fisher's exact test for ordinal variables. In addition, Chi-square analyses were performed to determine differences between patients with and without CFUs. Where appropriate, a Cochran-Armitage test was used to assess increasing or decreasing rates across categories. Multiple logistic regression was used to obtain estimates of the adjusted odds ratios for factors independently associated with colonization. Spearman rank correlation was used to calculate the correlation between colonization and bacteraemia. All statistical testing was two-sided and an alpha level of 0.05 was used to determine significance. Each analysis was reported separately, with no adjustment for multiple comparisons. All statistical analyses were performed in SAS (Version 8.0, SAS Institute, Cary, NC, USA).

Results

Patient demographics and characteristics

In total 699 patients were enrolled at 10 investigational sites before an interim analysis revealed that there were no differences in colonization or CRBSI rates between the test and control groups. At that time, it was determined that enrolment would have to be tripled to obtain a sufficient sample size, given the extremely low overall CRBSI rate. Therefore, enrolment in the trial was discontinued.

Data could be evaluated for 539 patients (77%). Patients were excluded from analysis when the CVC was inadvertently contaminated or discarded (64 catheters), or when samples were transported to the core laboratory more than 24 h after CVC removal. There were no significant differences in patient characteristics between the evaluable (266 control, 273 test) and non-evaluable (83 control,

77 test) groups. The mean duration of CVC placement was 149.3 h (6.2 days) for evaluable and 136.9 h (5.7 days) for non-evaluable patients.

For the evaluable patients, the test and control groups were similar in demographics and patient characteristics (Table I). Both groups had similar indications for CVC placement and removal. Catheter placement was performed primarily in the intensive care unit (50%) or operating theatre (42%); 8% were inserted in other units. More than 70% of catheters in both groups were removed because the CVC was no longer required. Approximately 15% of patients in both groups had clinical signs or symptoms of infection (e.g. oedema, erythema, skin irritation, tenderness, purulent drainage, increased white blood cell count, increased heart rate or fever) that led to the decision to remove the catheter. In most cases, cultures of the catheter and peripheral blood samples failed to confirm catheter-related bacteraemia or infection. In 16 cases (3%), the catheter was removed after the patient's death.

Catheter-related colonization and infection

Quantitative cultures were positive more frequently than semiquantitative cultures, and 24.5% of all samples were colonized according to at least one definition (Table II). Among colonized catheters, the most frequent genus isolated was *Staphylococcus* (isolated on >15% of the catheters in both groups). The most common species of *Staphylococcus* were *S. epidermidis* (11.6% control and 12.1% test) and *S. aureus* (2.6% control and 1.5% test). Other bacteria cultured were *Enterococcus*

faecalis, *Pseudomonas aeruginosa*, *S. capitis*, *S. haemolyticus* and *S. warneri* (1-2% of patients in each group). *Candida* was found in fewer than 1% of cases. There were no significant differences in colonization rates between test and control groups.

Initially, only patients with clinical signs or symptoms of infection had peripheral blood samples drawn. However, after 331 patients were enrolled, no CRBSI cases had been detected. Therefore, the protocol was revised to require peripheral blood samples to be drawn upon catheter removal, regardless of clinical signs and symptoms of infection. All 368 patients enrolled subsequently had blood cultures drawn within 4 h of catheter removal. Of the patients positive for colonization by any criterion, there were only four control patients (1.5%) and three test patients (1.2%) with a genus/species match between the catheter tips or segments and peripheral blood samples (i.e. bacteraemia cases). Only one patient (control group) with bacteraemia also showed clinical signs of infection. Thus, during the entire trial, CRBSI occurred in just 0.2% of patients. There were no cases of CVC-related sepsis.

Factors associated with colonization

The duration of CVC placement was greater than 60 h for most patients (92%). There was a linear relationship between duration of CVC placement and colonization rate (Figure 1). Although the confidence intervals (CIs) for each of the individual categories overlap, the trend was significant with increasing time ($P=0.021$).

Colonization rates differed significantly by insertion site (Figure 2). The colonization rates for the right internal jugular (31%) and both subclavian sites (left 15%; right 27%) were significantly below ($P<0.05$) that for the left internal jugular (53%). There were too few femoral cases to permit statistical comparisons. Approximately equal proportions of test and control catheters were used at each insertion site [e.g. right internal jugular vein (44.4% test; 46.9% control); right subclavian vein (18.4% test; 22.3% control)].

The mean time between dressing changes was two days for both groups (range 1-15 days). Patients receiving dressing changes more frequently than every six days had a colonization rate of approximately 25%. For patients with dressing change intervals of six days or more, the colonization rate increased to 35% ($P=0.0013$; odds ratio 1.84, 95% CI 1.27-2.68). There were no significant differences in colonization rates by sex or hospital unit (intensive care unit versus operating theatre). Colonization

Table I Patient characteristics

| | Control % N=266 | Test % N=273 |
|----------------------------------|--------------------|-----------------|
| Sex (male) | 63.5 | 56.8 |
| Age (years) | 55.2 | 55.4 |
| Antibiotic use within seven days | 73.9 | 79.0 |
| Trauma within 30 days | 29.7 | 28.2 |
| Surgery within 30 days | 43.6 | 40.3 |
| Urinary catheter | 89.1 | 90.5 |
| Other intravascular catheter | 80.8 | 79.1 |
| Mechanical ventilation | 77.1 | 78.4 |
| Immunosuppressive therapy | 7.1 | 5.9 |
| Corticosteroid use | 9.0 | 9.9 |
| Total parenteral nutrition | 10.1 | 8.4 |
| Diabetes | 21.4 | 19.4 |
| Cardiovascular disease | 62.0 | 62.6 |
| Pulmonary disease | 38.0 | 44.7 |
| Gastrointestinal disease | 44.0 | 46.2 |
| Neurological disorder | 28.6 | 30.0 |

Table II Central venous catheter infection analysis by core laboratory

| | Control % N=262 | Test % N=252 | All patients % N=514 ^a |
|---|-----------------|---------------|-----------------------------------|
| Tip-roll plate ≥ 15 CFUs | 16.0 | 13.1 | 14.6 |
| Tip-sonication > 1000 CFUs | 5.0 | 5.6 | 5.3 |
| Segment-roll plate ≥ 15 CFUs | 18.7 | 15.1 | 16.9 |
| Segment-sonication > 1000 CFUs | 11.5 | 11.1 | 11.3 |
| Samples with any colonization (of tips or segments by roll plate or sonication) | 24.4 | 24.5 | 24.5 |
| Bacteraemia | 1.5 | 1.2 | 1.4 |
| Catheter-related bloodstream infection | 0.4 | 0.0 | 0.2 |
| Bacteraemia per 1000 catheter-days | 2.59 per 1000 | 1.79 per 1000 | 2.18 per 1000 |

CFU, colony-forming unit.

^a These data include only those patients for whom samples of both catheter tips and segments were submitted to the core laboratory.

rates ranged from 0% to 50% by investigational site, and the difference was not significant ($P=0.9$).

Multi-variate logistic regression analysis also confirmed that insertion site and dressing change frequency contributed independently to the risk of colonization. Specifically, the odds ratio for subclavian compared with internal jugular was 0.45 (95% CI 0.29-0.70). This indicated that the risk of CVC colonization with a subclavian insertion site was approximately one-half that where the internal jugular site had been used.

Discussion

CVC-related infections pose a substantial risk to patient health and constitute a large economic burden. This clinical trial was designed to test the effectiveness of a CVC made of polyurethane integrated with silver, platinum and carbon black, and to evaluate other factors that influence CVC infection rates. Unexpectedly, we found no significant differences in colonization or bacteraemia rates between the test and control catheters. The

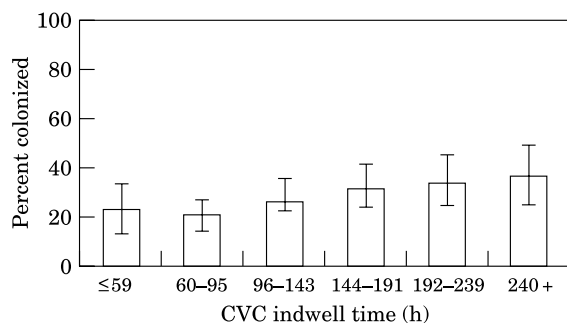


Figure 1 Percentage of central venous catheters (CVCs) colonized by duration of CVC placement. The error bars indicate 95% confidence intervals. The trend of increasing colonization with increasing duration of CVC placement is statistically significant ($P=0.021$).

overall colonization rate was 24.5%, yet CVC-related bacteraemia occurred in only 1.4% of patients, and CRBSI occurred in just one patient (0.2%).

Several factors may have contributed to the low rate of bacteraemia observed in our study. These include relatively short duration of CVC placement, more frequent use of subclavian or internal jugular insertion sites (rather than femoral), the high rate of antibiotic usage, and the prohibition of guidewire exchange. With regard to duration of CVC placement, 109 patients (20%) had CVCs for 60-95 h and 332 patients (62%) had CVCs for > 96 h, so there was ample time for colonization and CRBSI to develop in most patients. In the present study, insertion site was an independent predictor of colonization, and subclavian sites had less colonization than internal jugular or femoral sites. This is consistent with other recent reports.^{14,19,22,23} More important perhaps was strict adherence to infection control procedures by participating clinicians. A recent review concluded that these methods are essential when using intravascular catheters.¹⁰ The protocol used for the present study required that CVC insertion be performed in accordance with CDC guidelines for infection control (i.e. using strict

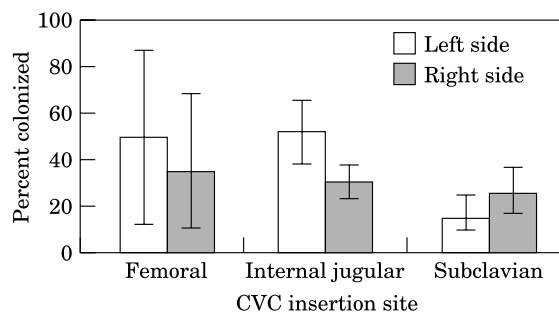


Figure 2 Percentage of central venous catheters (CVCs) colonized by insertion site. The error bars indicate 95% confidence intervals.

aseptic technique with maximal barrier precautions). In addition, all catheters were inserted through new venipunctures, and guidewire exchanges were not allowed.

Two other trials have studied the Vantex catheter. Ranucci *et al.* reported the results of a similar multi-centre trial comparing the Vantex catheter with control CVCs coated with benzalkonium chloride (evaluable $N=545$). The overall colonization rate (24%) was nearly identical to our findings, but the overall CRBSI rate was much higher than found in our study (3.8% vs 0.2%).²⁴ A recent randomized trial by Corral *et al.*²⁵ evaluated the Vantex CVC compared with a standard polyurethane CVC. These investigators reported a statistically significant difference in CRBSI and colonization rates between test and control catheters (CRBSI: 1% test, 4% control; tip colonization: 15% test, 28% control). The higher CRBSI rates reported by Corral *et al.* may be due in part to the longer duration of CVC placement in that study (mean duration of CVC placement was 13 days) compared with others (e.g. nine days for Ranucci *et al.* and six days in our study). Another factor that may have contributed to the difference is that Corral *et al.*'s study was confined to a higher risk population (intensive care unit patients only). It is possible that a device made from a novel antimicrobial material would reveal its greatest benefit in higher risk populations with a longer duration of CVC placement.

The link between colonization and bacteraemia may be weaker than previously thought. Polderman and Girbes suggested that approximately 20% of colonized catheters proceed to catheter-related bacteraemia.⁸ Although this seems true overall, there is wide interstudy variability. Veenstra *et al.* performed a meta-analysis involving 13 studies comparing colonization and bacteraemia rates in CVCs coated with CSS with uncoated CVCs.³ Veenstra *et al.* found the overall bacteraemia-colonization ratio was 25%, but the range was 0–86%. The correlations between colonization and bacteraemia in these studies were only 0.25 and 0.22 for CSS-coated and uncoated catheters, respectively. However, the correlation between bacteraemia rates for the two types of catheters was 0.86. These correlations imply that the association between colonization and bacteraemia is much weaker than that of the intrastudy bacteraemia rates. Thus, factors inherent to the study appear to exert more influence on bacteraemia rates than the observed rate of colonization. These findings are based on a small number of studies, but they suggest that the causal linkage between colonization and bacteraemia may need

re-examination. Indeed, Maki *et al.* stated that CRBSI rates, rather than colonization rates, are the preferred measure when comparing CVCs.⁴

These results should be interpreted considering the limitations of this study. Patient populations were heterogeneous and not limited to patients prone to a high risk of infection. Most patients with bacteraemia were identified after the protocol change requiring peripheral blood cultures to be performed on every patient. It should be noted that many of the analyses performed for this study were ad hoc, and should therefore be considered exploratory and serve to generate hypotheses. Additional studies are needed to understand the relative contributions of various factors, perhaps including variables such as the site of insertion.

This trial evaluated the antimicrobial effectiveness of a CVC that integrates silver, platinum and carbon black, as well as other factors that influence colonization and CRBSI. Despite colonization rates that were not particularly low in either the test or control groups, both groups had low rates of catheter-related bacteraemia. The causal relationship between colonization and bacteraemia may be weaker than reported previously. Although other CVCs with antimicrobial features have been associated with a decrease in catheter-related colonization and bacteraemia, this study demonstrated that infection rates may depend more on non-catheter-related factors, such as insertion site, duration of CVC placement, dressing change frequency and guidewire exchange. Antimicrobial catheters may have a place in critical care, particularly in cases where the CVC is anticipated to be left in place for more than six days. In an era of increasing microbial resistance, it is even more important to identify and use non-pharmacological methods to reduce infection. Whenever possible, clinicians should consider using aseptic technique with maximal barrier precautions, subclavian insertion sites, and reduced duration of CVC placement with more frequent dressing changes to reduce the risk of CRBSI.

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Center (Tucson, AZ); University of Colorado (Denver, CO); University of Kentucky (Lexington, KY); University of Maryland Medical System (Baltimore, MD); and Wake Forest University School of Medicine (Winston-Salem, NC).

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