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ORIGINAL ARTICLE

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Reduction of catheter-related infections in neutropenic patients: a prospective controlled randomized trial using a chlorhexidine and silver sulfadiazine-impregnated central venous catheter

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Abstract Antiseptic coating of intravascular catheters may be an effective means of decreasing catheter-related colonization and subsequent infection. The purpose of this study was to assess the efficacy of chlorhexidine and silver sulfadiazine (CH-SS)-impregnated central venous catheters (CVCs) to prevent catheter-related colonization and infection in patients with hematological malignancies who were subjected to intensive chemotherapy and suffered from severe and sustained neutropenia. Proven CVC-related bloodstream infection (BSI) was defined as the isolation of the same species from peripheral blood culture and CVC tip (Maki technique). This randomized, prospective clinical trial was carried out in 106 patients and compared catheter-related colonization and BSI using a CH-SS-impregnated CVC (n=51) to a control arm using a standard uncoated triple-lumen CVC (n=55). Patients were treated for acute leukemia (n=89), non-Hodgkin's lymphoma (n=10), and multiple myeloma (n=7). Study groups were balanced regarding to age, sex, underlying diseases, insertion site, and duration of neutropenia. The CVCs were in situ a mean of 14.3±8.2 days (mean±SD) in the study group versus 16.6±9.7 days in the control arm. Catheter-related colonization was observed less frequently in the study group (five vs nine patients; p=0.035). CVC-related BSI were significantly less frequent in the study group (one vs eight patients; p=0.02). In summary, in patients with severe neutropenia, CH-SS-impregnated CVCs yield a significant antibacterial effect resulting in a significantly lower rate of catheter-related colonization as well as CVC-related BSI.

Keywords Central venous catheter · Neutropenia · Catheter-related colonization · Catheter-related bloodstream infection

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Introduction

Multiple-lumen central venous catheters (CVCs) are essential in the management of patients with acute leukemia and high-grade lymphoma treated with aggressive chemotherapy. CVCs are widely used for parenteral nutrition as well as drug administration and antimicrobial or antineoplastic therapy. Patients with severe and sustained neutropenia are at high risk for infectious complications. CVCs are a major source of infection in these patients. Catheter-associated bloodstream infections are one of the most frequent serious complications and a major source of septicemia in cancer patients. Pittet et al. [1] demonstrated that extra costs attributable to the infection averaged US$ 29,000 per patient and US$ 40,000$ per survivor, respectively.

Bacterial colonization of CVCs, often initiated from the medical staff or environment and from the skin insertion site, is assumed to be the precursor of catheter-related bloodstream infection (BSI). At present, exact data on the incidence of CVC-related infections in neutropenic patients are only available from a few publications. Recent studies reported that neutropenia is associated with a higher risk of developing catheter-related infections (up to 13.9%), while there were substantially lower CVC-related infectious complications in non-neutropenic patients (<3%) [2, 3].

There have been controversial discussions about the use of venous catheters which have been impregnated with antimicrobial agents. Biotechnological modification of CVCs with benzalkonium chloride bonding was devel-

oped to prevent the progression from skin colonization to bacteremia. A coating with silver chloride and benzalkonium chloride revealed a broad spectrum of activity against bacteria and *Candida albicans* and prolonged antimicrobial activity for extraction periods of up to 30 days [4]. In an open, comparative, controlled, and randomized study, bacterial adherence to benzalkonium chloride-impregnated catheters was significantly reduced on both the internal (p=0.029) and external (p=0.016) catheter surfaces compared with a polyurethane catheter containing no antiseptic agent [5]. Several studies showed that the coating of the external catheter surface with chlorhexidine and silver sulfadiazine is associated with lower rates of catheter colonization, but this method did not succeed in reducing the incidence of bacteremia in these trials [6–8].

Schmitt et al. [9] revealed in an in vitro setting the reduction of catheter colonization in catheters impregnated with CH-SS compared to nonimpregnated catheters. Previous studies demonstrated the effectiveness of chlorhexidine and silver sulfadiazine (CH-SS)-impregnated CVCs in reducing the incidence of both catheter colonization and catheter-related bloodstream infection in critically ill patients [10–12]. Taken together, most recent trials confirmed a reduction of colonization, but advantages of coated catheters with regard to bacteremias are rarely reported, particularly in the neutropenic host. Neutropenic patients may benefit from coated CVCs, since they are at high risk for CVC-related infections.

Thus, in a prospective randomized clinical trial, we investigated the efficacy of CH-SS-impregnated CVCs in preventing catheter-related colonization and CVC-related BSI in immunocompromised leukemic patients following intensive antineoplastic chemotherapy.

Patients and methods

During a 7-month period (between March and October 2000) consecutive leukemic patients requiring CVCs for chemotherapy application were entered into the study. The study was approved by the Ethics Committee of Hannover Medical School (1316-bed university hospital). Informed consent was obtained from each patient on admittance to the Department of Hematology and Oncology (written for the insertion of a CVC and orally confirmed according to the type of catheter).

Patients were randomly allocated, either to a trial group (group I) with insertion of a CH-SS-impregnated CVC (ARROWg^{+}ard Blue, Arrow International, Inc., Reading, Pa., USA) or to a control group (group II) with insertion of a standard triple-lumen polyurethane CVC (Arrow-Howes, Arrow International, Inc., Reading, Pa., USA). The study was unblinded as the physician was only aware of the CVC type required after randomization. Microbiological analysis was performed by technicians and a laboratory physician who were unaware of the difference between the two CVCs.

Catheters were inserted into the jugular or subclavian vein using maximal sterile barrier precautions. Experienced physicians inserted the CVC with a full aseptic Seldinger technique, including use of a sterile gown, sterile gloves, sterile drapes, a mask, and a cap. To avoid the potential confounding effect of the controversial practice of catheter exchange over a guide wire, we studied only those catheters inserted through a new vein puncture. Central line positions were confirmed by electrocardiogram and chest radiographs. All patients received standard disinfecting agents (10% povidone iodine-based) for skin preparation before insertion of the CVC. The dressing of the insertion site was changed daily and the insertion site was inspected for signs of inflammation (erythema, swelling, tenderness) or infection (pus). The decision to remove the catheter was made solely by the patient's physician, who kept the catheter in place until it was no longer needed or until an adverse event, such as catheter-related colonization or CVC occlusion, necessitated its removal. The decision to remove the catheter was made independently of the research group.

Blood cultures were obtained from the catheter and at least one peripheral vein at the time of catheter removal and in the case of suspected catheter-related colonization or catheter-related bacteremia. For each catheter, two 5-cm catheter segments (tip and intracutaneous segment) were cultured semiquantitatively at the end of chemotherapy treatment [13]. Catheter-related colonization was defined as ≥15 colony-forming units of the catheter tip or intracutaneous segment. Catheter-related bacteremia was defined as growth of the same organism on the catheter and at least one peripheral blood culture. All CVCs were microbiologically evaluated (Maki technique).

Standardized data collection forms were completed for all patients. Data collected included demographic characteristics, underlying diseases, anatomical location of the CVC, and duration of catheterization. In addition, data were obtained on neutrophil counts, the presence of fever and infection during catheterization, reason for catheter removal, and results of microbial analysis.

Statistical analysis

We estimated the number of catheters required for an adequate assessment of the hypothesis that CH-SS-impregnated CVCs are significantly less likely to be colonized than uncoated catheters. It was determined that a sample size of 50 catheters in each of the two groups was required to detect with 80% power (β error=0.20) a significant difference in the rates of catheter-related colonization between the two types of CVCs at a significance level of p=0.05.

All numeric data showed a Gaussian distribution using the Kolmogorow–Smirnov test; because not all the data showed skewness $|\gamma|<0.4$ the nonparametric Mann–Whitney U test was used to compare intergroup data. Significance of differences between the two groups was determined using univariate analysis of variance (SPSS/

PC V 9.0 software package, SPSS, Munich, Germany). The incidence of catheter-related colonization and catheter-related bacteremia between the two groups was tested by χ^2 analysis. Results are expressed as mean±SD, and a $p<0.05$ was accepted as statistically significant.

Results

One hundred and six patients suffering from malignant hematological diseases and undergoing intensive chemotherapy were randomly and prospectively evaluated. Fifty-one CH-SS-impregnated CVCs and 55 nonimpregnated CVCs were inserted. Both groups of patients presented with similar baseline characteristics regarding age, sex, underlying diseases, anatomical site of insertion, and distribution of antibiotic agents used for treatment of febrile neutropenia. Neutropenia (<500 neutrophils per μl) occurred for a mean of 5.9±7.0 and. 7.8±8.6 days (mean ±SD) during catheterization, respectively (Table 1). Antibiotic usage was similar in both groups.

On average, the antiseptic-bonded and standard CVCs remained in situ for 14.3±8.2 days (mean±SD) and 16.6 ±9.7 days, respectively; the ranges were 2–52 days and 1–58 days. The duration of catheterization was lower in the study group; however, this did not reach statistical significance (Table 2). Comparable results were shown by both groups regarding reasons for catheter removal. There were no local or systemic detrimental reactions associated with the use of either CVC.

On removal, nine (16.4%) of the standard CVCs were colonized compared with five (9.8%) of the antiseptic-bonded type ($p=0.035$). This reduction in colonization with antiseptic-bonded CVCs was also seen in the catheters removed because of clinical evidence of CVC-related bacteremia (one vs eight patients; $p=0.02$). The patient who developed a catheter-related BSI in the study group was observed during neutropenia (neutrophil count 200 μl^{-1}). Six of eight patients with catheter-related BSI in the control arm had neutrophil counts less than 500 μl^{-1}, one additional patient had a neutrophil count <1000 μl^{-1}. The most common microorganism isolated from both the CH-SS-impregnated and the normal CVCs (17.4% and 52.2%, respectively) was *Staphylococcus epidermidis*, followed by *Staphylococcus haemolyticus*, *Staphylococcus aureus*, *Enterococcus faecalis*, and *Corynebacterium amycolatum*.

Table 1 Patient characteristics. No differences were seen between the two groups (defined as $p<0.05$). *AML* acute myelogenous leukemia, *ALL* acute lymphoblastic leukemia, *CLL* chronic lymphoblastic leukemia, *NHL* non-Hodgkin's lymphoma

Characteristics	Study	Control
No. of patients	51	55
Median age (years)	49	45
Underlying disease		
AML	34	39
ALL	7	5
CLL	2	2
NHL	4	6
Multiple myeloma	4	3
Duration of neutropenia (days)[a]	5.9±7.0	7.8±8.6
Insertion site		
Subclavian vein	5	7
Internal jugular vein	46	48

[a]Mean±SD

Discussion

Despite important advances in preventive measures, CVC-related infections are considered to be a significant source of bacteremia in cancer patients [14–16]. There has been an inconclusive discussion about the use of venous catheters which have been impregnated with antimicrobial agents. One of the approaches used to reduce CVC-associated infections is the use of catheters impregnated with antiseptic agents such as chlorhexidine and silver sulfadiazine, since bacterial colonization of CVCs is common. Incidence rates of catheter infections can only be compared with caution, owing to different definitions, heterogeneous patient groups (e.g., surgical patients, patients receiving bone marrow transplantation, or patients treated for acute leukemia), various types of catheters, and different methods of prophylaxis against infections [17–19].

The presented prospective randomized clinical trial evaluated the antimicrobial properties of CH-SS-impregnated CVCs in a patient population at a very high risk of infection. All trial patients developed a severe (<500 neutrophils/μl) and sustained neutropenia following cytostatic chemotherapy. In our trial, nine (16.4%) of the standard CVCs were colonized compared with five (9.8%) of the antiseptic-bonded type ($p=0.035$). This significant reduction in colonization with the antiseptic-bonded CVCs studied corresponded with a reduction of CVC-related bacteremia (one vs eight patients; $p=0.02$). It remains a point of discussion whether microorganisms colonizing CVCs were identical with these bacteria causing bloodstream infections, since genotypic identification was not done.

Our findings demonstrate that the use of CH-SS-impregnated CVCs was associated with a significantly lower rate of catheter-related colonization and CVC-related BSI in immunocompromised leukemic patients following intensive antineoplastic chemotherapy. Most of the isolated microorganisms were identified as *Staphylococcus epidermidis*, which generally corresponds with the literature. No significant differences in the spectrum of colonizing bacteria were found between the two patient groups.

A range of substances have been investigated in vitro and clinically regarding their antimicrobial effects as catheter impregnation materials. Rifampin, minocycline, chlorhexidine silver sulfadiazine, and benzalkonium chloride are the materials best studied to date.

Table 2 Characteristics of central venous catheters

Characteristics	Study	Control	Mann-Whitney U test p
Duration of catheterization (days)[a]	14.3±8.2	16.6±9.7	n.s.
Reason for removal			χ^2 test p
End of treatment	21	22	n.s.
Suspicion of infection	28	33	n.s.
Microbiological analysis			
Colonization of the CVC	5	9	0.035
CVC-related bacteremia	1	8	0.02

[a]Mean±SD

In a meta-analysis of 11 studies, Veenstra et al. [20] demonstrated that the use of CVCs impregnated with chlorhexidine and silver sulfadiazine was associated with a lower rate (55%) of catheter-related colonization and, likewise, a lower rate (40%) of catheter-related bacteremia than the use of nonimpregnated catheters.

In a prospective, randomized clinical trial in 12 university-affiliated hospitals, Darouiche et al. [21] compared two different antimicrobial-impregnated CVCs coated with either chlorhexidine or silver sulfadiazine or with minocycline and rifampin. The antimicrobial efficacy of catheters impregnated with minocycline and rifampin was superior to that of catheters impregnated with chlorhexidine and silver sulfadiazine. Catheter-related colonization was found in 7.9% of antibiotic-coated catheters and in 22.8% of chlorhexidine and silver sulfadiazine-coated catheters ($p<0.001$). Catheter-related bacteremia occurred in 3.4% among the catheters impregnated with chlorhexidine and silver sulfadiazine compared with 0.3% among the catheters impregnated with minocycline and rifampin ($p<0.002$). In contrast to our approach, patients who were admitted to intensive care units owing to various diseases were also included in the study but only a small number of those patients suffered from neutropenia (4%).

George et al. [10] demonstrated that the incidence of bacterial colonization of CVCs could be reduced using a CH-SS-impregnated catheter compared to using a standard polyurethane catheter in immunocompromised transplant patients. Colonization was reduced from 25 of 35 standard catheters to 10 of 44 study catheters ($p<0.002$), a 68% reduction. Similarly, the incidence of concomitant infections by the same organism at another site was reduced from 10 of 35 standard catheters to 4 of 44 study catheters ($p< 0.03$), a 63% reduction.

We used a maximal sterile environment for inserting CVCs. Thus, further concomitant aspects that have been investigated and reviewed [22], such as training and strictly sterile conditions during catheter placement [23, 24], are not discussed, neither are the antibiotic-lock technique [25–27] or impregnated wound dressings to suppress cutaneous colonization [28, 29].

We conclude that CH-SS antiseptic-bonded catheters provide an important improvement in the attempt to reduce catheter-related colonization and CVC-related BSI in patients undergoing intensive cytotoxic chemotherapy which is followed by sustained and severe neutropenia. Apart from the use of CH-SS-bonded CVCs, however, meticulous attention to sterile technique during catheter insertion and routine maintenance still remain essential factors in the prevention of catheter-associated infection.

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