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ORIGINAL ARTICLE

Antimicrobial chlorhexidine/silver sulfadiazine-coated central venous catheters versus those uncoated in patients undergoing allogeneic stem cell transplantation

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Abstract
Introduction Only a minimum is known about clinical effect of antimicrobial-coated central venous catheters (CVC) in stem cell transplantation settings, where CVC-related infections impose major threat to severely immunocompromised patients.
Materials and methods In this prospective, non-sponsored and nonrandomized study, there were 49 uncoated multilumen and non-tunneled CVCs and 58 antimicrobial chlorhexidine/silver sulfadiazine-coated CVCs inserted in allogeneic stem cell transplanted patients to facilitate treatment during conditioning and pre-engraftment phase (<30days after transplantation).
Results and discussion No significant differences were found between the two groups with respect to gender, age, intensity of pretransplant chemotherapy conditioning, duration of leucopenia, number of days with inserted CVC, number of CVC occlusive dressing changes performed per patient, and number of non-CVC-related infections. In the antimicrobial coated CVC group, there were observed less median days with fever [2 (0–18) vs. 4 (0–16), p = 0,17], fever incidence (67% vs. 77.5%, p = 0.28), and less days with fever per 1,000 catheter-days (108 vs. 147, p = 0.001), less patients with positive CVC blood cultures (36% vs. 45%, p = 0.05), repeatedly positive CVC blood cultures (8.6% vs. 26%, p = 0,018), less positive CVC blood cultures per 1,000 catheter-days (14 vs. 29, p = 0.005), and less positive CVC tip cultures (17.3% vs. 34.6%, p = 0.065) observed.
Conclusion Lower number of patients with fever, days with fever, and lower number of patients with positive and repeatedly positive CVC blood cultures indicates less intensive antibiotic and antipyretic treatment probably needed in neutropenic allo-transplanted patients with indwelling antimicrobial-coated CVCs. Real impact on antibiotic consumption should be verified in large randomized study.

Keywords Central venous catheter · Infection · Transplantation · Chlorhexidine

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Introduction

Central venous catheters (CVC) facilitate several weeks long and intensive care in patients with hematological malignancies, especially in allogeneic stem cell transplantation settings. Specialized nursing care is necessary because of the risk of various CVC-related complications and infections that are crucial problems in all transplanted and severely immunocompromised patients. After full intensity conditioning regimens, almost all transplanted patients develop severe neutropenia and neutropenic fever as an early clinical sign of an infection, with the main sources of infection including CVC, mouth flora, and gut flora [3, 11]. Febrile episodes in the early phase after allogeneic stem cell transplantation are in the vast majority of cases caused by

infections and fever occurrence in neutropenic transplanted patients should result in broad-spectrum antibacterial treatment as only a few noninfectious causes of fever occurs during the early post-transplantation period, such as blood transfusions, acute graft versus host disease or drug-related fever. The source of infection can only rarely be identified in neutropenic patients on clinical grounds or with the help of imaging techniques. In contrast to the microbiologically documented infections in patients before hematopoietic engraftment of only 5–10%, the focus of bacterial infection can be identified in more than 50% of patients after hematopoietic engraftment [3, 11, 14]. The incidence of CVC-related infections in hematological patients has been reported to range between 35% and 45% [1, 4, 5, 13] and positive blood cultures have been found in 36–52% [2, 7].

The effect of CVCs impregnated with antimicrobial agents, such as chlorhexidine and silver sulfadiazine, in the prevention of catheter-related bloodstream infections (CRBSI) has been studied in several trials that were performed on intensive care patients not suffering from chemotherapy-induced immunosuppression [9]. Some authors found coated CVCs to be efficacious and cost-effective [12]; on the other hand McConnell's review in 2003 [6] and some other recent studies [8, 10], failed to demonstrate any significant clinical benefit associated with the use of antimicrobial impregnated CVCs for the purpose of reducing CRBSI. More over, interpretations of results are also difficult because of differences in definitions of CRBSI, diverse types of catheters and methodology and rare use of clinically relevant end-points [6, 9].

Only a minimum is known about clinical effect of antimicrobial-coated CVCs in hemato-oncological and stem cell transplanted patients, and available data can be considered as controversial. An initial exploratory study by Ellis et al. [4] did not recommend impregnated CVCs for prolonged use in severely immunocompromised patients. Ostendorf [9], however, found reduction in risk of catheter colonization, although the incidence of catheter-related bacteremia was similar to a control group.

The present study was launched to get new experience and to verify if using antimicrobial-coated CVCs really is of any benefit for patients undergoing allogeneic stem cell transplantation.

Patients and methods

Patients enrolled into this single-center, non-sponsored, nonrandomized and prospective study were adults indicated to have allogeneic stem cell transplantation. Their skin at the infraclavicular CVC insertion site had to be intact, and an informed consent is signed. Patients with damaged skin at baseline, allergic to acrylate or polyurethane, and patients with radiotherapy of the chest in a history were excluded.

Central venous catheter

Multi-lumen, polyurethane, radiopaque, non-tunneled, and antimicrobial-uncoated indwelling central venous catheters (Brown), were used in patients since September 2003 until May 2005. Multi-lumen, polyurethane, radiopaque, non-tunneled, and antimicrobial chlorhexidine/silver sulfadiazine-coated CVCs (ARROW-Howes) were used in patients since May 2005 until September 2007.

The CVCs were inserted percutaneously by local medical staff into the vena subclavia under strict aseptic precautions and using the Seldinger technique. Povidone-iodine was used for skin disinfection before CVC insertion. Transparent polyurethane semipermeable occlusive dressings were used to cover the infraclavicular site of CVC insertion. The occlusive dressings were changed at minimum once weekly interval or whenever indicated—i.e., in case of unstitched, loose, or soiled dressing, insertion-site inflammation, local skin damage, in-site bleeding or for other clinical relevant reason. Povidone-iodine was used for skin disinfection before any new occlusive dressing application. Protocolised care was performed daily by experienced nurses. CVCs were removed under aseptic conditions when no longer needed for patient treatment and care or in case of adverse events, such as CVC-related infections and thrombosis.

Microbiological methods

Blood cultures were obtained under strict aseptic precautions, from all of the CVC lumena or peripheral vein directly into original Bactec bottles (Becton Dickinson Europe) both with aerobic and anaerobic media. The samples were then cultivated in Bactec 9240 Becton Dickinson automat. In the case of microbial presence and related metabolic activity, the growing concentration of CO_2 within the sample lead to fluorescent activity that was monitored by a detector and evaluated. Any positive sample was then examined and identified by means of standard microbial procedures and commercially available media.

Monitoring and assessment

The monitoring started on the day of CVC insertion at the start of chemotherapy conditioning and continued until the CVC removal. The insertion site was assessed daily. The highest temperature for a day was recorded. Blood cultures for aerobic and anaerobic microbiological testing were taken from all of the CVC lumena and peripheral vein on first fever occurrence (38st.C or more) and/or whenever indicated by medical staff,

i.e., in case of recurrent fevers. Peripheral vein blood cultures were allowed to be dispensed in patients with insufficient peripheral veins. Each individual indication to CVC or peripheral vein blood culture examination was considered as one individual case, although several blood samples were taken at the moment from multi-lumen CVC, and any blood sample positivity made the case positive as a whole (i.e., in triple-lumen CVC there were six blood samples obtained, three of them into aerobic and three into anaerobic media, and they represented one individual CVC blood culture examination case, and even if one blood sample was positive, it would made the case positive as a whole). Skin swabs for microbiological testing were obtained from around CVC insertion site on any dressing change and before local disinfection. Patient data and characteristics were registered daily in standardized preprinted forms and medical and nursing records.

Definitions

- Insertion-site inflammation: local circular redness accompanied in larger reactions with swelling and pain on palpation in the area surrounding the point of percutaneous insertion.
- Insertion-site infection: CVC insertion-site inflammation with detected bacteria of fungi-positive skin swabs.
- Bacteraemia: isolation of a bacterial species in a blood culture (positive blood culture) obtained either form CVC or peripheral vein.
- Catheter-related bloodstream infection: no apparent source for bloodstream infection with the exception of the CVC and blood culture positive with the same microorganism obtained from CVC and peripheral vein.
- The minimal clinically significant difference: difference that clinicians and patients would care about.

Statistical methods

P values compared the presence and the absence of the characteristics, and *P* values < 0.05 were considered as indicating statistically significant differences. Statistical analyses were performed using Statistica software (GraphPad InStat, GraphPad Software) and individual tests used, such as

Table 1 Characteristics of patients

Variable	Uncoated CVC	Antimicrobial coated CVC	*p*=value	Test
Number of patients:	*n*=49	*N*=58	–	–
Diagnoses				
Acute myeloid leukemia	20	31		
Acute lymphoblastic leukemia	0	7		
Chronic lymphocytic leukemia	5	5		
Chronic myeloid leukemia	6	1		
Myelodysplastic syndrome	1	4		
Hodgkin lymphoma	0	3		
Multiple myeloma	8	1		
Non-Hodgkin lymphoma	7	3		
Severe aplastic anemia	1	3		
Myelofibrosis	1	0		
Age: median (range)	51 (21–67)	53 (20–68)	0.98	Mann–Whitney
Gender: male/female	28/21	33/25	1.0	Fisher's
Conditioning chemotherapy regimen:				
Myeloablative/reduced intensity	23/26	23/35	0.55	Fisher's
Myeloablative (%)	(47%)	(39,5%)		
Myeloablative:				
BU/CY2	8	13		
BU/CY2/ATG	15	10		
Reduced intensity				
Flu/Mel	21	28		
Flu/Cy	5	6		
Cy/ATG	0	1		
Duration of leucopenia:	9(0–40)	10(0–30)	0.72	Unpaired *t*-test
Leucocytes $<1.0\times10^9$/l, median days				
Patients—median days with inserted CVC:	29 (6–52) 1396	30,5 (7–77) 1800	0.28	Unpaired *t*-test
Total days with CVC:				
patients—median number of CVC dressing changes:	9 (2–23)	8 (2–24)	0.23	Unpaired t-test

Table 2 Fever occurrence

Variable	Uncoated CVC	Antimicrobial coated CVC	*p= value*	Test
Patients with fever:	38/49 (77,5%)	39/58 (67%)	0.28	Fisher's
Patients–median days with fever:	4 (0–16)	2 (0–18)	0.17	Mann–Whitney
Days with fever per 1,000 catheter days:	147	108	0.001	Chi-square

Fisher's exact test, Mann–Whitney test, unpaired *t* test, and Chi-square test are recorded in appropriate tables in the text.

Results

During the period since September 2003 until September 2007, 49 patients with uncoated CVCs and consecutively 58 patients with antimicrobial coated CVCs were enrolled in the study. Altogether, 107 patients were evaluated. Patient characteristics are shown in Table 1.

In the uncoated CVC group, there were triple-lumen CVCs in 90% and double-lumen in 10% of patients used. In the coated CVC group, all patients had triple-lumen catheter inserted. There were no statistically significant differences found between the uncoated and coated CVCs groups for median age [51 (21–67) vs. 53 (20–68), p = 0.98], gender (male to female ratio: 28 out of 21 vs. 33 out of 25, p = 1.0), intensity of the pretransplant chemotherapy conditioning regimen (myeloablative vs. reduced intensity conditioning: 23 out of 26 vs. 23 out of 35, p = 0.55), median number of days with leucopenia (leucocytes below 1.0×10^9/l: 9 (0–40) vs. 10 (0–30), p = 0.726), median number of days with inserted CVC per patient [29 (6–52) vs. 30.5 (7–77), p = 0.28], and median number of CVC occlusive dressing changes performed per a patient [9 (2–23) vs. 8 (2–24), p = 0.23]. No difference and only a minimum of clinically or microbiologically defined infections, other then CVC insertion site inflammation or infection and positive blood cultures, were found [5 out of 49 (10%) vs. 6 out of 58 (10%)]. In the uncoated CVC group, there were colitis, pneumonia, urosepsis, upper airway infection, and pneumonia observed. In the coated CVC group, *Aspergillus* lung infection, dental infection, colitis, and three cases of pneumonia were observed.

Fever

Not statistically, however clinically significant differences were observed between the uncoated vs. coated CVC group with respect to fever incidence (Table 2) in patients [38 out of 49 (77.5%) vs. 39 out of 58 (67%), p = 0.28] and median number of days with fever in patients [4 (0–16) vs. 2 (0–18), p = 0.17). There were statistically significantly less days with fever per 1,000 catheter days in the antimicrobial-coated CVC group (147 vs. 108, p = 0,001).

Insertion site inflammation and infection

No statistically significant difference was observed between the uncoated vs. coated CVC group regarding the CVC insertion site circular inflammation [34 out of 49 (69%) vs. 41 out of 58 (70%), p = 1.0] including even minor circular redness round the point of CVC penetration into skin (Table 3). No difference was observed for insertion site infection occurrence [15 out of 49 (30%) vs. 17 out of 58 (29%), p = 0.83]. The mostly isolated bacteria were Staphylococci coagulase-negative in 81% and 100% of the cases, respectively.

CVC blood cultures

No difference was found between the uncoated vs. coated CVC group for the number of patients indicated to (Table 4) CVC blood culture testing [39 out of 49 (79.5%) vs. 44 out of 58 (76%), p = 0.81]; however, in the antimicrobial-coated CVC group, there were significantly less patients with

Table 3 Insertion site inflammation and infection

Variable	Uncoated CVC	Antimicrobial coated CVC	*p= value*	*Test*
Insertion site inflammation:	34/49 (69%)	41/58 (70%)	1.0	Fisher's
Insertion site infection:	15/49 (30%)	17/58 (29%)	0.83	Fisher's
Number of microbial species detected:	16	18		
Coagulase-negative Staphylococci	13/16 (81%)	18/18 (100%)		
Staphylococcus aureus	1/16	0		
Corynebacter sp.	2/16	0		

Table 4 CVC blood cultures

Variable	Uncoated CVC	Antimicrobial coated CVC	*p= value*	*test*
Patients–CVC blood cultures obtained:	39/49 (79.5%)	44/58 (76%)	0,81	Fisher's
Patients with positive CVC blood cultures:	22/49 (45%)	21/58 (36%)	0.05	Fisher's
Patients with CVC blood cultures repeatedly, two or more times, positive:	13/49 (26%)	5/58 (8,6%)	0.018	Fisher's
CVC blood cultures positive cases per 1000 catheter-days:	29	14	0.005	Fisher's
Number of microbial species detected:	40	37		
Coagulase-negative Staphylococci	30/40 (75%)	27/37 (73%)		
Staphylococcus epidermidis	(24/30)	(14/27)		
Staphylococcus haemolyticus	(4/30)	(11/27)		
Staphylococcus capitis	(0/30)	(1/27)		
Staphylococcus hominis	(2/30)	(1/27)		
Staphylococcus aureus	1	0		
Streptococcus anginosus	0	1		
Streptococcus mitis	1	1		
Enterococcus faecalis	4	4		
Pseudomonas aeruginosa	0	3		
Propionibacterium acnes	1	1		
Corynebacterium striatum	1	0		
Bacteroides sp.	2	0		

positive CVC blood culture [22 out of 49 (45%) vs. 21 out of 58 (36%), $p = 0.05$], repeatedly positive CVC blood culture [13 out of 49 (26%) vs. 5 out of 58 (8.6%), $p = 0{,}018$], and positive CVC blood cultures per 1,000 catheter-days (29 vs. 14, $p = 0.005$). The mostly isolated bacteria in both groups were coagulase-negative Staphylococci in 75% and 73% of the cases, respectively.

Peripheral vein blood cultures

No statistically significant difference was found between the uncoated vs. coated CVC group with respect to the number of patients indicated for peripheral blood culture testing [22 out of 49 (45%) vs 19 out of 58 (33%), $p = 0.23$]; however, in the antimicrobial-coated CVC group, there were significantly less patients with positive peripheral blood culture [8 out of 49 (16%) vs. 1 out of 58 (1.7%), $p = 0.005$] and repeatedly positive CVC blood culture [13 out of 49 (26%) vs. 5 out of 58 (8.6%), $p = 0.018$] (Table 5). The mostly isolated bacteria in both groups were coagulase-negative Staphylococci in six out of seven (86%) and two out of two (100%) of the bacteria species, respectively.

Catheter removal and tip cultures

After CVC had been removed under aseptic conditions from a patient, the catheter tip was subjected to microbial testing. There were nearly statistically significantly more positive cultures detected in the uncoated CVC compared to those antimicrobial-coated [17 out of 49 (34,6%) vs. 8 out of 46 (17.3%), $p=0{,}065$].

The CVC was removed because of assumed or proved catheter-related infection in 18 out of 49 (36.7%) patients with the uncoated CVC and in 12 out of 58 (20%) patients with the antimicrobial-coated CVC, and the difference between the groups was almost statistically significant ($p=0.08$).

Table 5 Peripheral vein blood cultures

Variable	Uncoated CVC	Antimicrobial coated CVC	*p= value*	*Test*
Patients—lood cultures obtained:	22 out of 49 (45%)	19 out of 58 (33%)	0.23	Fisher's
Patients with positive blood cultures:	8/49 (16%)	1/58 (1.7%)	0.005	Fisher's
Number of microbial species detected:	7	2		
Coagulase-negative Staphylococci	6/7 (86%)	2/2 (100%)		
Staphylococcus epidermidis	(5/6)	(0)		
Staphylococcus hominis	(1/6)	(0)		
Enterococcus faecalis	1	0		

Discussion

The study was set up to help define the role, effect, and to verify if using antimicrobial chlorhexidine/silver sulfadiazine-coated non-tunneled multi-lumen CVCs really is of any benefit for hemato-oncological patients undergoing allogeneic stem cell transplantation, as only a minimum and controversial data are known about clinical effect of such CVCs in this setting of high-risk patients.

This prospective, non-sponsored, and nonrandomized study compared fever occurrence, CVC insertion site inflammation and infection, CVC and peripheral blood cultures and other infections in a group of patients with uncoated or antimicrobial-coated CVCs, respectively. Both groups of patients were well balanced, without any statistically significant differences, with respect to age, gender, pretransplant conditioning regimen, leucopenia duration, and number of days with inserted CVC per patient and incidence of other defined non-CVC-related infections.

A certain methodological limitation of this trial is represented by the fact that the experimental care is compared with historical controls, which may cause doubts about consistency of nursing and supportive care procedures. However, there has not been any change and difference between the study groups for procedures of nursing (with the only exception of CVC antimicrobial coat) and medical care, and the trial protocol was strictly kept the same during the period of the assessment.

Half of the observed parameters did not reach differences with statistical significance, probably because of relatively low number of patients in the study groups; however, even these results still posses certain clinical relevancy in some aspects concerning highly specific care and management in transplanted and neutropenic patients. Moreover, only limited literature data targeting this study issue and patients cohort are available.

As fever in pre-engraftment phase is generally considered an early clinical sign of infection in stem cell transplantation setting, we monitored this phenomenon very closely in our study. During the hematopoietic pre-engraftment phase, only 5–10% infections are usually microbiologically documented [3, 11, 14], and fever on its own at that period of time leads to the start of intensive wide-broad antibiotic treatment to prevent fast developing and life-threatening infections. Though there were no statistically significant differences between the uncoated and antimicrobial-coated CVC group for fever incidence in patients (77.5% vs. 67%, p=0,28), tendency to better and, in our opinion, clinically significant results were observed. Moreover, there were also statistically significantly less days with fever per 1,000 catheter days (147 vs. 108, p= 0,001) in the antimicrobial-coated group.

In both of the study groups, we did not observe statistically and clinically significant differences regarding CVC insertion site inflammation occurrence and the insertion site infections with Staphylococci coagulase-negative being the most often isolated bacteria. Serious reactions with inflammation diameter of ≥20 mm appeared only in 6 out of 49 (12%) patients with uncoated CVC and in 2 out of 58 (3,5%) of those with antimicrobial-coated CVC. No fungal infection was detected at all. To be fair in considering these results, it is important to stress, that these variables included cases with only minor circular redness surrounding the point of CVC penetrating into the skin and that we observed also spontaneous resolution of such minor inflammation reactions in several patients. Based on these observations, it is very likely that minor local inflammatory reactions in the CVC insertion site area could otherwise be overlooked or missed if evaluated only at the time of CVC removal or on non-daily-basis observational trials. In addition to it, some cutaneous reactions at the insertion site need not necessarily always be considered infectious and may comprise local toxic or hypersensitivity reactions. Thus, we consider more appropriate to call them generally as “insertion-site inflammations”, rather then infections. All that can perhaps explain the relatively higher incidence of such inflammatory reactions in our patients, when compared to the incidence of 41.4% and 37.7% of “insertion-site infections” in hemato-oncological patients reported in the Ostendorf’s study [9].

The incidence of positive blood cultures observed in this study corresponds with previously reported incidence of CVC-related infections and positive blood cultures in hematological patients ranging between 35% and 52% [1, 2, 4, 5, 7, 13]. A lower number of patients with positive CVC blood cultures in the coated CVC group (45% vs. 36%, p=0.05), more repeatedly positive CVC blood cultures observed in the uncoated CVC group (26% vs. 8,6%, p=0.018), and highly significant difference in positive CVC blood cultures per 1,000 catheter-days (29 vs. 14, p=0.005) showed rather positive effect of the chlorhexidine/silver sulfadiazine-coated CVCs. Most of the isolated germs ever were coagulase negative staphylococci (75%); however, as two consecutive positive blood cultures of this species are needed, at least one from peripheral blood, for documentation of true bacteremia [15], there could also probably be some cases of only bacterial contamination of samples. Repeated and probably real positivity of the coagulase-negative staphylococci in blood cultures was 36% in the antimicrobial-coated CVC group and 55% in the uncoated one.

Obtaining peripheral vein blood cultures was a real problem in our patients, as a number of them suffered from insufficient and damaged peripheral veins from previous repeated courses of chemotherapies. This fact limited and

avoided any fair conclusions concerning the catheter-related bloodstream infection (CRBSI) occurrence, as both CVC and peripheral vein blood cultures would be needed and compared to fulfill the CRBI definition criteria. Only in approximately half of the patients in each of the study group was possible to keep the study protocol and to take CVC blood cultures together with peripheral vein samples.

Conclusion

From the clinical point of view, with respect to intensive antimicrobial treatment policy applied in the case of fever occurrence and persistence of it in severely immunocompromised neutropenic patients during the pre-engraftment phase after allogeneic stem cell transplantation, results of this study, where two well-balanced cohorts of patients were evaluated, poses highly clinical and in some characteristics also statistical significancy. Lower number of patients with fever, days with fever, and lower number of patients with positive and repeatedly positive CVC blood cultures indicates at least clinically significant positive effect of chlorhexidine/silver sulfadiazine-coated CVCs in these patients, with probably less intensive antibiotic and antipyretic treatment needed. Such a clinical benefit, however, should be further assessed in larger and randomized study to bring more objective results and data, as this study has some methodological limitations mentioned above.

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