Original article

The effectiveness of chlorhexidine-silver sulfadiazine impregnated central venous catheters in patients receiving high-dose chemotherapy followed by peripheral stem cell transplantation

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Immuno-compromised patients are at high risk for all kind of infections. Unfortunately, they need central venous catheters (CVCs), which are associated with infectious complications. In this study we examined the effectiveness of chlorhexidine-silver sulfadiazine impregnated CVCs to prevent catheter-related infections in patients receiving high-dose chemotherapy followed by peripheral stem cell transplantation. This historical cohort study evaluated 139 patients of whom 70 patients were provided with non-impregnated CVCs and 69 patients with impregnated CVCs. Patients were treated for different diagnoses. The median number of days a CVC stayed *in situ* was 18 in the non-impregnated group and 16 in the impregnated group. The median duration of neutropenia of patients with non-impregnated CVCs was 9 days compared with 7 days of patients with impregnated CVCs. We found less catheter colonization (CC) in patients with chlorhexidine-silver sulfadiazine CVCs (RR 0.63, 95% CI 0.41–0.96; $P = 0.03$). Catheter-related blood stream infections (CR-BSI) were also diminished, but this result was not statistically significant (RR 0.15, 95% CI 0.02–1.15; $P = 0.06$). The reduction in CC and CR-BSI did not diminish the incidence of fever. We conclude that the use of chlorhexidine–silver sulfadiazine impregnated CVCs provide an important improvement in the attempt to reduce CC and CR-BSI.

Keywords: central venous catheter, infection, peripheral stem cell transplantation, neutropenia, catheter-related colonization.

INTRODUCTION

Central venous catheters (CVCs) allow measurement of haemodynamic parameters, delivery of medication and nutritional support that cannot be provided safely through peripheral venous catheters. Unfortunately, the use of these CVCs is associated with complications and substantial costs (Arnow *et al.* 1993; Pittet *et al.* 1994; Richards

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et al. 1999). Infectious complications are reported to occur in 5–26% of the patients (Raad *et al.* 1997; Merrer *et al.* 2001; Traore *et al.* 2005).

Several methods have been used to prevent catheter-related infections. Aseptic insertion techniques and proper catheter care have been proven to be effective (Maki *et al.* 1991; Raad *et al.* 1994; Mimoz *et al.* 1996; McGee & Gould 2003; Gnass *et al.* 2004). Recently, chlorhexidine-silver sulfadiazine impregnated CVCs have been introduced as a new development in reducing catheter-related infections. Indeed, several studies have shown a significant reduction in catheter colonization (CC) in critically ill patients (Bach *et al.* 1996; Ciresi *et al.* 1996; George *et al.* 1997; Maki *et al.* 1997; Heard *et al.* 1998; Collin 1999; Richards *et al.* 2003; Jaeger *et al.* 2005; Ostendorf *et al.* 2005), but only few studies have shown a significant reduction of catheter-related blood stream infections (CR-BSI, George *et al.* 1997; Maki *et al.* 1997; Jaeger *et al.* 2005). Unfortunately, the results of these studies may only be compared with restraint, due to different definitions, heterogeneous patient groups, various types of catheters and different prophylaxis regimens. However, a meta-analysis suggests a reduction of CR-BSI when using chlorhexidine-silver sulfadiazine impregnated CVCs (Veenstra *et al.* 1999).

Cancer patients treated with high-dose chemotherapy followed by peripheral stem cell transplantation (PSCT) all need CVCs to support this treatment. However, this immuno-compromised patient population is at high risk for all kind of infections due to the underlying disease as well as the neutropenia caused by the treatment. There is little evidence that chlorhexidine-silver sulfadiazine impregnated CVCs have protective properties in this specific patient population.

The objective of this study is to evaluate the effectiveness of chlorhexidine-silver sulfadiazine impregnated CVCs compared with non-impregnated CVCs in patients receiving high-dose chemotherapy followed by PSCT. The outcomes assessed are CC and CR-BSI confirmed by catheter culture.

PATIENTS AND METHODS

The medical and nursing records of all 143 patients, admitted to the Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital (NKI-AVL), who received high-dose chemotherapy followed by PSCT between 1 June 1999 and 1 February 2006, were reviewed retrospectively. Patients admitted to the hospital in the period before June 2003 received a non-impregnated CVC. Patients admitted to the hospital after June 2003 were provided with a chlorhexidine-silver sulfadiazine impregnated CVC.

Both impregnated and non-impregnated catheters were double lumen catheters (Arrow International Reading, Philadelphia, PA, USA).

Patients were excluded from the study when (1) they were provided a Hickmann catheter or Port-a-Cath; (2) the CVC was not inserted in the NKI-AVL; (3) the CVC was *in situ* for less than 48 h; or (4) there were clinical signs of an infection at admission. In case more than one CVC was inserted during treatment only the first CVC was evaluated in this study.

Data collected from the medical and nursing records included basic demographic data, diagnosis, duration of neutropenia, number of days the CVC was *in situ*, duration of hospitalization and bacteriological data. We also collected signs and symptoms of infection, such as fever and mucositis, the length of the fever period and antibiotic treatment. Data collection started on the first day of admission and ended on the day of discharge, or during admission when the CVC was removed or death occurred.

Consecutive blood samples were used for blood cultures. Ten mL of blood, aseptically collected, was inoculated into Bactec vials, 5 mL for aerobic culture and 5 mL for anaerobic culture. All positive vials were gram-stained, sub-cultured; and isolates were identified by microscopic examination. Blood cultures were obtained routinely twice a week during chemotherapy and three times a week during the neutropenic period, also on days when the patient was a-febrile. When a patient got fever, at least one (extra) blood culture was collected from both the CVC and the bloodstream, before antibiotic treatment was started.

Catheter colonization was defined as the presence of an organism isolated from a blood culture drawn from the CVC and/or from the tip of the CVC after catheter removal.

Catheter-related blood stream infection was considered to be present when the same organism was found in a blood culture taken from the CVC or catheter tip as well as in a blood culture of the peripheral blood of a patient, with accompanying clinical symptoms and no other apparent source of infection. Clinical symptoms as temperature >38°C, fever chill and hypotension were recorded.

A trained professional reviewed the medical and nursing records. In case the files were unclear or in case of possible different interpretation an oncologist and a nurse practitioner were asked for clarification. Data were collected on a Case Record Form and entered into a database by means of blinded double data entry.

Categorical variables were analysed, using the chi-square test, for small numbers the Fisher's exact test was used. Numeric data were analysed, using the Student *t*-test or Mann–Whitney *U*-test when appropriate. Multivariate logistic regression was performed to adjust for potential confounders. Based on a two-tailed test procedure, $P < 0.05$ was considered significant. In addition, statistical analyses were expressed with their 95% confidence intervals. All analyses were carried out using SPSS/PC+ Statistics 12.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

From June 1999 until February 2006, 143 patients were treated with high-dose chemotherapy followed by PSCT of which 139 were included in this study. Four patients were excluded because the CVC was to be a Hickmann catheter ($n = 2$) or the CVC was removed within 48 h, because of thrombotic complications ($n = 2$). Most patients were diagnosed with mamma carcinoma (42%) or non-Hodgkin lymphoma (28%). All patients were pre-treated with chemotherapy, of which 50 (36%) in combination with radiotherapy (Table 1).

Non-impregnated CVCs were inserted in 70 patients and chlorhexidine-silver sulfadiazine impregnated CVCs in 69 patients. Catheters were inserted into the subclavian vein in 92% of the patients. Only when this was contra indicated, the jugular vein or femoral vein was used. To obtain optimal sterile barrier precautions, all CVCs were inserted in the operating room. Standard preventive antibiotic usage was similar in both groups. In all patients blood cultures were taken according to the standard procedures.

The median number of days a catheter stayed *in situ* was 17 (range 3–80). The number of days the non-impregnated CVCs and impregnated CVCs remained *in situ* was 18 (range 12–80) and 16 days (range 3–33) respectively.

All patients developed severe neutropenia following chemotherapy. Neutropenia was defined as granulocyte count $<0.5 \times 10^9$/L. For all 139 patients, the median duration of neutropenia was 7 days (range 4–27). The median neutropenic duration of patients with a non-impregnated CVC was 9 days (range 4–27) and of patients with an impregnated CVC 7 days (range 4–22). As recovery of bone marrow was a criterion for discharge, a difference between the two groups occurred in the median number of days patients being admitted to the hospital (20 days, range 8–35 vs. 17 days, range 8–34).

Adverse events during admission, e.g. temperature above 38°C and chills, were observed equally in both groups: 53 patients (76%) with a non-impregnated CVC vs. 49 patients (71%) with an impregnated CVC. No difference was seen in the length of the feverish period (median 3 days, range 1–14 vs. median 3 days, range 1–13), nor in the use of antibiotics outside the standard prevention regimen (80% in both groups) (Table 2).

We found CC in 34 patients with non-impregnated CVCs and in 21 patients with chlorhexidine-silver sulfadiazine CVCs. This reduction is statistically significant: RR 0.63, 95% CI 0.41–0.96; $P = 0.03$.

A multivariate logistic regression was performed to estimate the odd ratio adjusted for baseline imbalances. The most important factors considered were duration of catheterization and duration of neutropenia. The impregnated CVC was still significantly associated with CC: adjusted OR 0.33, CI 0.15–0.73, $P = 0.006$.

Catheter-related blood stream infections were also diminished, from 7 in the non-impregnated CVCs to 1 in the chlorhexidine-silver sulfadiazine CVCs. However, this difference was not statistically significant: RR 0.15, 95% CI 0.02–1.15; $P = 0.06$.

Table 1. Patient characteristics

	Non-impregnated CVC	Impregnated CVC
Number of patients	70	69
Gender		
Male	35	24
Female	35	45
Mean age (±SD)	42 (±12.8)	42 (±11.5)
Diagnosis		
Breast cancer	23 (33%)	36 (52%)
Non-Hodgkin lymfoma	25 (36%)	14 (20%)
Testicular cancer*	10 (14%)	2 (3%)
Hodgkin's disease	7 (10%)	4 (6%)
Kahler's disease	0	6 (9%)
Ewing sarcoma	3 (4%)	6 (9%)
Other	2 (3%)	7 (10%)
Prior chemotherapy	70 (100%)	69 (100%)
Prior radiotherapy*	36 (51%)	14 (20%)
Median number of days in hospital (range)*	20 (8–35)	17 (8–34)

*Significant differences between the two groups, defined as $P < 0.05$.
CVC, central venous catheter.

Table 2. Adverse events during admission

	Non-impregnated CVC	Impregnated CVC
Median number of days neutropenia (range)*	9 (4–27)	7 (4–22)
Temperature of >38°C	53 (76%)	49 (71%)
Median number of days fever (range)	3 (1–14)	3 (1–13)

*Significant differences between the two groups, defined as $P < 0.05$.
CVC, central venous catheter.

Table 3. Characteristics of central venous catheters

	Non-impregnated CVC	Impregnated CVC	*P*
Median duration of catheterization (range)	18 (12–80)	16 (3–33)	0.001
Insertion site			
Vena subclavia	66 (94%)	62 (90%)	n.s.
Vena jugularis	3 (4%)	3 (4%)	n.s.
Vena femoralis	2 (2%)	4 (6%)	n.s.
CC	34	21	0.03
CR-BSI	7	1	0.06

CC, catheter colonization; CR-BSI, catheter-related bloodstream infection; CVC, central venous catheter.

Again a multivariate logistic regression was performed to adjust for the duration of catheterization and the duration of neutropenia. The impregnated CVC was still not significantly associated with CR-BSI: adjusted OR 0.11, CI 0.01–1.01, $P = 0.05$ (Table 3).

DISCUSSION

Vascular access by means of CVCs is often necessary in the treatment of cancer patients, especially when they become neutropenic and require blood products and multiple drugs. At the same time, CVCs are considered to be a significant source of infection. Especially immuno-compromised patients are at great risk to acquire a life-threatening sepsis. Chlorhexidine-silver sulfadiazine impregnated catheters were introduced, in addition to a variety of existing methods to reduce these CVC-related infections.

The objective of this study was to evaluate the effectiveness of chlorhexidine-silver sulfadiazine impregnated CVCs compared with non-impregnated CVCs in patients receiving high-dose chemotherapy followed by PSCT. The present findings show a statistically significant reduction in CC when using impregnated CVCs compared with non-impregnated CVCs. This result is of major clinical importance, because from the colonized CVCs organisms could diffuse into the bloodstream and hence cause systemic infections. Catheter-related blood stream infections were found less frequently in patients with chlorhexidine-silver sulfadiazine CVCs compared with patients with non-impregnated CVCs. Despite the fact this study showed pretested sufficient power, this result did not meet statistical significance.

Our findings are consistent with results from other studies performed with comparable patients. A study in haematological patients shows a significant reduction in CC from 33% in non-impregnated to 12% in impregnated CVCs. Although the number of CR-BSI in patients with impregnated CVCs was lower than in patients provided with non-impregnated CVCs (3 vs. 7), this difference was not statistically significant (Ostendorf *et al.* 2005). Furthermore, we found one single study demonstrating a significant reduction of CC as well as CR-BSI in neutropenic patients using impregnated CVCs (Jaeger *et al.* 2005).

The present findings suggest a significant reduction in CC using an impregnated CVC compared with a non-impregnated CVC, but some critical remarks must be taken in consideration. The two groups in this study were not fully comparable with respect to underlying conditions that might predispose catheter-related infection.

Patients with non-impregnated CVCs were neutropenic during a longer period compared with patients with impregnated CVCs (9 days vs. 7 days). It is well known that neutrophil counts below 1000 per microliter causes a progressive increase in the susceptibility of the patient to infections and a progressive decrease in localizing signs and symptoms of inflammation. Neutropenia as a significant risk factor for the development of CVC-related sepsis is proven in several studies (Tacconelli *et al.* 1997; Nador *et al.* 2006). Unexpectedly, univariate analysis of our data does not identify duration of granulopenia as a significant risk factor for CC (OR 0.99, CI 0.91–1.08, $P = 0.86$) or catheter-related infection (OR 0.96, CI 0.84–1.10, $P = 0.55$). Furthermore, the difference in duration of granulopenia in our data set was caused by patients with lymphoma, who showed a median of 12 days granulopenia. Analyses of the data without the lymphoma group show less CC in patients with chlorhexidine-silver sulfadiazine CVCs (RR 0.55, 95% CI 0.32–0.95; $P = 0.03$), a result that does not differ from the result of the total group.

Another factual consideration concerns the duration of catheterization. Tacconelli identifies duration of catheterization as a significant risk factor for CR-BSI in a varied population (Tacconelli *et al.* 1997). Recently, the same result was presented for haematological patients (Nador *et al.* 2006).

In our study the median duration of catheterization is significantly longer in the non–impregnated group compared with the impregnated CVC group (18 days vs. 16 days, $P = 0.001$), but univariate analysis of the data does not support the conclusions of above-mentioned studies with respect to CR-BSI (OR 1.02, CI 0.92–1.12, $P = 0.76$).

Also, the multivariate logistic model adjusted for duration of catheterization and duration of neutropenia did not essentially alter our study results.

The reduction in CC and CR-BSI did not lead to a reduction in clinical symptoms; the number of patients who developed fever did not change. Frequently, the origin of fever was unknown and clinical symptoms implicating the CVC as the cause of infection were often absent, due to the lack of neutrophils in the population involved.

A limitation of this historical cohort study is its reliance on the review of patient records. The detailed chart review, although performed and discussed by experienced professionals, was somewhat subjective.

Being a historical cohort study and due to the lack of randomization, differences in clinical practices could introduce bias. Therefore we studied concomitant aspects like catheter lock technique, conditions during insertion, antibiotic regimes and the wound dressing protocol; we found no differences in the protocols during the timeframe of this study.

We conclude that the use of chlorhexidine-silver sulfadiazine impregnated CVCs provides an important improvement in the attempt to reduce CC and CR-BSI in patients receiving high-dose chemotherapy followed by PSCT. Future studies should concentrate on reduction of clinical important symptoms like fever.

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REFERENCES

Arnow P.M., Quimosing E.B. & Beach M. (1993) Consequences of intravascular catheter sepsis. *Clinical Infectious Diseases* **16**, 778–784.

Bach A., Schmidt H., Bottiger B., Schreiber B., Bohrer H., Motsch J., Martin E. & Sonntag H.G. (1996) Retention of antibacterial activity and bacterial colonization of anti-septic bonded central venous catheters. *Journal of Antimicrobial Chemotherapy* **37**, 315–322.

Ciresi D.L., Albrecht R.M., Volkers P.A. & Scholten D.J. (1996) Failure of anti-septic bonding to prevent central venous catheter-related infection and sepsis. *American Surgeon* **62**, 641–646.

Collin G.R. (1999) Decreasing catheter colonization through the use of an antiseptic-impregnated catheter: a continuous quality improvement project. *Chest* **115**, 1632–1640.

George S.J., Vuddamalay P. & Boscoe M.J. (1997) Antiseptic-impregnated central venous catheters reduce the incidence of bacterial colonization and associated infection in immunocompromised transplant patients. *European Journal of Anaesthesiology* **14**, 428–431.

Gnass S.A., Barboza L., Bilicich D., Angeloro P., Treiyer W., Grenovero S. & Basualdo J. (2004) Prevention of central venous catheter-related bloodstream infections using non-technologic strategies. *Infection Control and Hospital Epidemiology* **25**, 675–677.

Heard S.O., Wagle M., Vijayakumar E., McLean S., Brueggemann A., Napolitano L.M., Edwards L.P., O'Connell F.M., Puyana J.C. & Doern G.V. (1998) Influence of triple-lumen central venous catheters coated with clorhexidine and silver sulfadiazine on the incidence of catheter-related bacteremia. *Archives of Internal Medicine* **158**, 81–87.

Jaeger K., Zenz S., Juttner B., Ruschulte H., Kuse E., Heine J., Piepenbrock S., Ganser A. & Karthaus M. (2005) Reduction of catheter-related infections in neutropenic patients: a prospective controlled randomized trial using a chlorhexidine and silver sulfadiazine-impregnated central venous catheter. *Annals of Hematology* **84**, 258–262.

McGee D.C. & Gould M.K. (2003) Preventing complications of central venous catheterization. *The New England Journal of Medicine* **348**, 1123–1133.

Maki D.G., Ringer M. & Alvarado C.J. (1991) Prospective randomised trial of povidon-iodine, alcohol and chlorhexidine for prevention of infection associated with central venous and arterial catheters. *Lancet* **328**, 329–343.

Maki D.G., Stolz S.M., Wheeler S. & Mermel L.A. (1997) Prevention of central venous catheter-related bloodstream infection by use of an antiseptic-impregnated catheter: a randomized, controlled trial. *Annals of Internal Medicine* **127**, 257–266.

Merrer J., De Jonghe B., Golliot F., Lefrant J-Y., Raffy B., Barre E., Rigaud J-P., Casciani D., Misset B., Bosquet C., Outin H., Brun-Buisson C. & Nitenberg G. (2001) Complications of femoral and subclavian venous catheterization in critically ill patients: a randomized controlled trial. *Journal of the American Medical Association* **286**, 700–707.

Mimoz O., Pieroni L., Lawrence C., Edouard A., Costa Y., Samii K. & Brun-Buisson C. (1996) Prospective, randomized trial of two antiseptic solutions for prevention of central venous or arterial catheter colonization and infection in intensive care unit patients. *Critical Care Medicine* **24**, 1818–1823.

Nador G., Nosari A., De Gasperi A., Marbello L., Nichelatti M., Corti A., Mancini V., Molteni A., Barate C., Ricci F., Ciapanna D., Garrone F., Ravelli E., Greco A., Turrini M. & Morra E. (2006) Infectious complications in haematological patients with central venous catheters: a prospective analysis of risk factors and etiological agents. *Haematologica* **91** (Suppl. 1).

Ostendorf T., Meinhold A., Harter C., Salwender H., Egerer G., Geiss H.K., Antony D.Ho. & Goldschmidt H. (2005) Chlorhexidine and silver-sulfadiazine coated central venous catheters in haematological patients – a double-blind, randomised, prospective, controlled trial. *Supportive Care in Cancer* **13**, 993–1000.

Pittet D., Tarara D. & Wenzel R.P. (1994) Nosocomial bloodstream infection in critically ill patients: excess length of stay, extra costs and attributable mortality. *Journal of the American Medical Association* **271**, 1598–1601.

Raad I., Darouiche R., Dupuis J., Abi-Said D., Gabrielli A., Hachem R., Wall M., Harris R., Jones J., Buzaid A., Robertson C., Shenaq S., Curling P., Burke T., Ericsson C. & Study G. (1997) Central venous catheters coated with minocycline and rifampicin for the prevention of catheter-related colonization and bloodstream infections: a randomized, double-blind trial. *Annals of Internal Medicine* **127**, 267–274.

Raad I.I., Hohn D.C., Gilbreath B.J., Suleiman N., Hill L.A., Bruso P.A., Marts K., Mansfield P.F. & Bodey G.P. (1994) Prevention of central-venous catheter-related infections by using maximal

sterile barrier precautions during insertion. *Infection Control and Hospital Epidemiology* **15**, 231–238.
Richards B., Chaboyer W., Bladen T. & Schluter P.J. (2003) Effect of central venous catheter type on infections: a prospective clinical trial. *Journal of Hospital Infection* **54**, 10–17.
Richards M.J., Edwards J.R., Culver D.H. & Gaynes R.P. (1999) Nosocomial infections in medical intensive care units in the United States. *Critical Care Medicine* **27**, 887–892.
Tacconelli E., Tumbarello M., Pittiruti M., Leone F., Lucia M.B., Cauda R. & Ortona L. (1997) Central venous catheter-related sepsis in a cohort of 366 hospitalised patients. *European Journal of Clinical Microbiology and Infectious Diseases* **16**, 203–209.
Traore O., Liotier J. & Souweine B. (2005) Prospective study of arterial and central venous catheter colonization and of arterial- and central venous catheter-related bacteremia in intensive care units. *Critical Care Medicine* **33**, 1276–1280.
Veenstra D.L., Saint S., Saha S., Lumley T. & Sullivan S.D. (1999) Efficacy of antiseptic-impregnated central venous catheters in preventing catheter-related bloodstream infection: a meta-analysis. *Journal of the American Medical Association* **281**, 261–267.