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Skin disinfection with octenidine dihydrochloride for central venous catheter site care: a double-blind, randomized, controlled trial

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Abstract

To compare the efficacy of two commercially available, alcohol-based antiseptic solutions for preparation and care of central venous catheter (CVC) insertion sites, with and without octenidine dihydrochloride, a double-blind, randomized, controlled trial was undertaken in the haematology units and in one surgical unit of two university hospitals. Adult patients with a non-tunnelled CVC were randomly assigned to two different skin disinfection regimens at the insertion site: 0.1% octenidine with 30% 1-propanol and 45% 2-propanol, and as control 74% ethanol with 10% 2-propanol. Endpoints were (i) skin colonization at the insertion site; (ii) positive culture from the catheter tip (≥I5 CFU); and (iii) occurrence of CVC-associated bloodstream infection (defined according to criteria set by the CDC). Four hundred patients with inserted CVC were enrolled from May 2002 through April 2005. Both groups were similar in respect of patient characteristics and co-morbidities. Skin colonization at the CVC insertion site during the first 10 days was significantly reduced by octenidine treatment (relative difference octenidine vs. control: 0.21; 95%CI: 0.11-0.39, p<0.0001). Positive culture of the catheter tip was significantly less frequent in the octenidine group (7.9%) than in the control group (17.8%): OR = 0.39 (95%CI: 0.20-0.80, p 0.009). Patients treated with octenidine had a non-significant reduction in catheter-associated bloodstream infections (4.1% vs. 8.3%; OR = 0.44; 95%CI: 0.18-1.08, p 0.081). Side effects were similar in both groups. This randomized controlled trial supports the results of two observational studies demonstrating octenidine in alcoholic solution to be a better option than alcohol alone for the prevention of CVC-associated infections.

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Introduction

The use of central venous catheters (CVCs) is associated with a high risk of infectious complications [1-3]. In the USA up to 80 000 episodes of nosocomial bloodstream infection associated with CVCs (CA-BSIs) in intensive-care units are reported each year [2,4]. The average rate of CA-BSIs in neutropenic patients in ICUs ranges from 2-10/1000 to 14/ I 1000 catheter days in neutropenic patients [5]. The mortality attributable to these infections may exceed 25%, and the associated increase in morbidity leads to a substantial rise in health care expenditures [6-1 1].

Suppression of cutaneous colonization is an important strategy for reducing CA-BSI; thus use of skin antiseptics such as chlorhexidine is a CDC category IA recommendation [12]. The bispyridinamine octenidine dihydrochloride (referred to as octenidine) is an antimicrobial effective against most Gram-positive and Gram-negative bacteria [13-15]. At low concentrations (0.1%), it shows excellent bactericidal and fungicidal, and moderate virucidal, activity [16-18]. It displays minimal absorption (skin, mucous membranes) and no systemic toxicity [19].

An aqueous solution containing octenidine and phenoxyethanol has been shown to be safe for skin disinfection in pre-term newborns [20]. Used for care of CVC insertion sites in patients undergoing bone marrow transplantation, this antiseptic decreased bacterial density at the insertion site over time [21]. In an earlier clinical trial a residual or remnant effect of octenidine combined with propanol in microbial skin decontamination over a 24 h period was shown [22]. The objective of this study was therefore to evaluate further the preventive impact and tolerability of octenidine for the preparation and care of CVC insertion sites.

Methods

Design overview

A double-blind, randomized, controlled trial was conducted to compare the efficacy of two alcohol-based skin disinfectants, one additionally containing the substance octenidine.

Setting and participants

The study was carried out from 2002 through 2005 in the haematology units of University Medical Center Freiburg (FR; Freiburg, Germany) and University Hospital Basel (BS; Basel, Switzerland) and in one surgical unit (BS). Both institutions are tertiary care facilities. The study was approved by both local ethics committees and entered into the clinical trials registry of the University Medical Center Freiburg (UKF000502, http://www.zks.uni-freiburg.de/uklreg/php/show_study.php?STUDIEN_ID=000502&kindOfSearch=frei=DE) [23]. Subsequently the trial was registered at ClinicalTrials.gov (Identifier: NCT00515151).

Adult inpatients scheduled to receive a non-tunnelled CVC for an expected period of 5 or more days were asked for their informed consent. Exclusion criteria were known sensitization to the proposed antiseptics, administration of antimicrobial drugs for therapy (not prophylaxis) < 1 week prior to catheterization, pre-existing BSI (i.e. fever and/or other signs of infection and positive blood culture), and existing burns. In addition, patients participating in a clinical trial of other antiseptics within a period of 4 weeks were excluded. Patients who received a new catheter after the follow-up period, i.e. at the earliest 30 days after removal of the first catheter, were permitted to enrol again.

Case report forms and corresponding patient files in 10% of all cases were checked by an independent monitor.

Randomization and interventions

The randomization code was produced by the independent Center for Clinical Studies (FR) using a computerized random-number generator. The study centre was used as a stratification factor and block randomization with randomly varying block length was performed. The randomization was realised using closed envelopes, ensuring that the sequence was concealed before patients entered the trial. The patients, the staff administering the interventions, the microbiology laboratory, and all the investigators assessing the outcomes were blinded to the assignment. Bottles containing the disinfectants were not distinguishable and were coded in random sequence. Both solutions were colourless with a predominantly alcoholic odour.

After obtaining their consent, patients were enrolled and randomly assigned to two different commercially available skin disinfection regimens: 0.1 % octenidine with 30% 1 -propanol and 45% 2-propanol (referred to as the octenidine group) and 74% ethanol with 10% 2-propanol (referred to as the control group). Before catheterization, the entry site was disinfected with the assigned solution over an area of >200 cm^2 for at least 1 min. After insertion, which was performed under sterile barrier precautions according to a standard protocol, the catheter was dressed with sterile gauze or a semi-permeable transparent dressing. During the change of dressings, the assigned solution was also used for care of the entry site following a standard protocol.

Outcomes and follow-up

The primary outcome variables, as per study protocol, were (i) skin colonization at the insertion site, (ii) positive culture from the catheter tip (≥I5 CFU), and (iii) occurrence of CVC-associated bloodstream infection (according to CDC definitions).

1 Quantitative skin cultures were obtained before insertion and at regular intervals (3 ± 1 days) during dressing change from a 6 X 4 cm area of skin around the catheter insertion site using a sterile template [24]. A sterile, moistened cotton applicator was swabbed around the insertion site and across the surrounding 24 cm^2 area. The applicator was placed in a tube containing 1.0 mL of 0.01 M phosphate-buffered saline and taken to the laboratory. After vortex mixing and diluting (1:10), aliquots of 0.1 mL of the suspension and of the dilution and 0.01 mL of the dilution only were plated onto blood agar plates. Colonies were counted after incubation at 35°C for 48 h and the mean value (CFU/24 cm^2) was calculated.

2 After removal, the CVC tip was cultured by the roll-plate technique. Colonization was defined as ≥I5CFU [25]. Results were standardized for a 5 cm segment of the catheter by dividing the CFU count by actual length of the CVC tip in cm and multiplying by five.

3 CVC-associated (primary), laboratory-confirmed bloodstream infection (CA-BSI) was defined according to CDC criteria [26] and observed up to 2 days after catheter removal or, in cases of transfer of the patient to another ward or hospital before catheter removal, up to 2 days after the end of treatment with the study medication (days at risk). Catheter-related (CR)-BSI was concluded if, in addition to the criteria for CA-BSI, the bacterial species isolated from blood and catheter tip cultures matched.

Additionally, as exploratory analyses, interactions between treatment and patients' diagnosis/centre were investigated with respect to the different endpoints.

Statistical analysis

Data were analysed according to a statistical analysis plan, which was pre-specified and signed before the code was broken, using STATISTICAL ANALYSIS SYSTEM version 8 (SAS, Cary, NC, USA).

Treatments were compared with respect to three efficacy criteria: (i) skin colonization within the first 10 days after CVC insertion, (ii) positivity of the catheter tip, (iii) occurrence of CVC-associated BSI. A 10-day analysis was chosen because the main source of colonization in this time-frame is the skin, with extraluminal bacterial spread alongside the catheter. If there was no difference between treatment groups with respect to criterion (i), it was assumed that there was also no difference with respect to criteria (ii) and (iii). Therefore, statistical tests (two-sided alpha = 5%) for comparison of the treatment groups with respect to the three efficacy criteria were performed in the *a-priori* specified sequence. Thus, no alpha correction of the individual tests was necessary.

Sample size calculation was performed in order to show a relevant difference with respect to criterion (ii). The expected probability of a positive catheter tip was 20% in the control group and 10% in the octenidine group. To show this difference with a two-sided test (alpha = 5%) with a power of 80%, a sample size of 400 patients was calculated. With respect to criterion (i), a larger difference was expected.

The efficacy analyses were performed according to the intention-to-treat principle, including all randomized patients for whom the respective criteria were available. All patients who received the study drug at least once were included in the safety analysis. For the analysis of criterion (i), the mean of the logarithm of the CFU values measured within the first 10 days was calculated. The effect of treatment on this outcome was analysed with a linear regression model including centre and diagnosis as covariate for adjustment. The effect was tested with alpha = 5% using type III sum of squares. To quantify the effect, the relative difference between treatment groups was calculated as the difference of the adjusted means of the logarithm of the CFU values from this model, transformed with the exponential function, with 95% confidence interval (CI). For the analysis of criteria (ii) and (iii), logistic regression was used including treatment and centre as covariates. The effect was tested with alpha = 5% using the Wald test. To quantify the effect, the odds ratio (OR) was calculated with 95% CI.

An interim analysis was undertaken after the randomization of 258 patients in order to allow termination of the study if no difference in efficacy between treatment types would be expected. For this purpose, the conditional power for criterion (i) was calculated [27]. All the clinical investigators were fully blinded to the results of this analysis except the conclusion that the study would be continued. Since this analysis was not intended to conclude superiority of one of the treatment arms no alpha-adjustment in the final analysis was necessary.

Results

Four hundred patients were enrolled from May 2002 through April 2005 (Fig. S1). In 11 patients, none of the criteria (i)-(iii) could be analysed because no skin sample, catheter tip and information on BSI were available.

Comparison of groups

Patients were under surveillance for BSI until 2 days after catheter removal (octenidine group: 155; control group: 147), or until 2 days after study treatment was stopped before catheter removal (39 vs. 46). The total number of days at risk for BSI was 2760 in the octenidine group, and 2537 in the control group.

Both groups were similar regarding patient characteristics (Table 1). Patient diagnoses differed between centres since BS also randomized patients undergoing cardiothoracic surgery (181 of 246 patients), while all patients at FR were haemato-oncological patients. Twelve patients were randomized twice with at least a 30-day interval before re-randomization. A sensitivity analysis showed no relevant differences if the patient's second course was excluded from the dataset (Tables S4 and S5).

Skin colonization

Three hundred sixty five patients with at least one sample after catheter insertion could be included in the analysis

TABLE 1. Patient characteristics

	Octenidine group	Control group
Number of patients	201	199
Centre (FR/BS)[a]	77/124	77/122
Age (25% quantile/median/75% quantile)	47/59/68	48/59/70
Sex (female/male)	66/135	70/129
Haemato-oncological patients (FR/BS)//surgical patients (BS)[a]	77/33//91	77/32//90
Haematopoietic stem cell transplantation	69	68
Duration of hospitalization before catheterization (£1 day/2—4 days/>5 days)	146/32/23	138/43/18
Duration of catheterization (days) (25% quantile/median/75% quantile)	3/10/24 (3 missing)	3/8/21 (4 missing)
Number of swabs (25% quantile/median/ 75% quantile)	1/2/5	1/2/4
Catheter type (antimicrobially coated[b]/un coated)	153/48	154/43 (2 missing)
Catheter insertion site (V. jugularis/V. subclavia)	167/34	159/38 (2 missing)
Neutropenia (yes/no)	113/84 (4 missing)	112/78 (9 missing)
Total parenteral nutrition (yes/no)	59/135 (7 missing)	49/139 (1 1 missing)
Blood transfusion (yes/no)	153/41 (7 missing)	143/45 (1 1 missing)

[a]FR, study centre Freiburg; BS, study centre Basel.
[b]First generation chlorhexidine/silver sulfadiazine coated catheters were used in all surgical patients (181) and in 126 of 219 haemato-onco logic patients.

(Fig. S1). Skin colonization at the CVC insertion site during the first 10 days was significantly reduced by octenidine treatment (Table 2).

The size of the effect on skin colonization varied between patient groups (according to diagnosis and centre). However, this difference was not significant (Table S2).

Catheter tip colonization

Positivity of the catheter tip was significantly lower in the octenidine group (n= 13; 7.9%) vs. control (n = 28; 17.8%) (Table 2). With 5.1 positive catheter tips per 1000 catheter days the overall incidence in the octenidine group was noticeably lower than in the control group (11.3 positive catheter tips per 1000 catheter-days; log rank test, p 0.009). The reduction in the rate of positive catheter tips (octenidine vs. control) varied between haematological patients and surgical patients in FR (not significant, Table S2).

Catheter-associated bloodstream infections

There were fewer laboratory-confirmed CA-BSIs in the octenidine group (n = 8; 4.1%) than in the control group (n= 16; 8.3%) (Table 2).

With 2.9 CA-BSIs per 1000 days at risk, the overall incidence in the octenidine group was noticeably lower than that in the control group (6.3 CA-BSIs per 1000 days at risk; log rank test, p 0.051). The Kaplan-Meier estimates of BSI rates over time are displayed in Fig. S2.

All BSIs occurred in haemato-oncological patients, resulting in incidence densities in this population of 3.6 BSIs per 1000 days at risk in the octenidine group (n = 106), and 7.9

TABLE 2. Quantitative skin cultures during the first 10 days after catheter insertion, positive catheter tip culturesa and CA-BSI[b]; comparison between octenidine group and control group[c]

					Treatment comparison (Octenidine vs. Control)		
		Number of patients	Adjusted mean of CFU	95%%-CI	Relative difference of CFU	95%%-CI	p-value
Quantitative skin cultures	Control	178	100.0	[64.5155.1]	**0.21**	**[0.11,0.39]**	**<0.0001**
	Octenidine	187	21.0	[13.7,32.2]			
					Treatment comparison (Octenidine vs. Control)		
		Number of patients	Patients with positive catheter tip No. (%%)		Odds Ratio	95%%-CI	p-value
Pos. catheter tip culture[a]	Control	157	28(17.8)		0.39	[0.20,0.80]	**0.009**
	Octenidine	165	13 (7.9)				
					Treatment comparison (Octenidine vs. Control)		
		Number of patients	Patients with CA-BSI[b] No. (%%)		Odds Ratio	95%%-CI	p-value
CA-BSI[b],[d]	Control	193	16(8.3)		**0.44**	**[0.18,1.08]**	0.081
	Octenidine	194	8(4.1)				

*(≥l5CFU/5 cm).
[b]Catheter-associated bloodstream infections.
[c]Adjusted for centre and diagnosis (haem/onc Freiburg, haem/onc Basel, surgical Basel).
[d]Due to the small number of events exact logistic regression analysis was used.

TABLE 3. Side effects; comparison between octenidine group and control group[a]

	Octenidine (%) n =201	Control (%) n = 197[b]
Skin irritation	54 (26.9)	45 (22.8)
Burning	35 (17.4)	35 (17.8)
Skin irritation and burning	19 (9.5)	1 1 (5.6)
Itching	1 (0.5)	3 (1.5)
Skin lesions	0	2(1.0)
Burning and skin lesions	1 (0.5)	0
Itching and skin irritation	0	1 (0.5)

[a]Side effects in patients who received study medication at least once.
[b]Two patients did not receive the allocated study medication.

CA-BSIs per 1000 days at risk in the control group (n= 104). Of the 24 BSIs 22 occurred in the haemato-oncology unit in FR (Table S2).

CR-BSIs occurred in four cases (all in the control group: three caused by coagulase- negative staphylococci and one by *Staphylococcus aureus;* Fisher's exact test, p 0.12). In one patient with BSI caused by a coagulase-negative staphylococcus no catheter tip was available for analysis (octenidine group).

Microbiological results

For isolated microorganisms see Table S1. A detailed illustration of microorganisms involved in CVC tip colonization and BSI is given in Table S3.

Side effects

No systemic side effects were observed in either group. Local effects (mainly skin irritation/burning) in patients who received the study medication at least once showed no significant differences between the two groups (Table 3).

Five patients died, either while receiving the intervention under study or during follow-up (octenidine: four; control: one). However, these deaths originated from the underlying diseases and were not related to the antiseptics used.

Discussion

This is the first RCT evaluating the efficacy of octenidine in preventing catheter colonizations and CA-BSIs. Octenidine/propanol significantly reduced bacterial density at the catheter insertion site and colonization of the catheter tip and lowered the incidence of CA-BSI in comparison with alcohol (ethanol/propanol) alone. The residual effect of octenidine - similar to that of chlorhexidine - seems to be the most likely explanation of the main effect [19]. Octenidine has very little cytotoxic effect *in vitro* and is registered even for newborns, in contrast to chlorhexidine. Skin irritation and burning were commonly seen in this study. However, the equal occurrence of side-effects with and without octenidine provides evidence that the alcohol rather than octenidine was responsible for the phenomena.

Limitations should be mentioned. ICU patients were not included in the study despite having a high risk for CA-BSIs. However, haematology patients are similarly at high risk, and the average at period of catheterization is longer than in ICU patients. About 20% of the catheters were not cultured, which may have biased the results, but the non-cultured CVC tips were equally distributed within the treatment groups and the laboratory was blinded to catheter allocation.

The frequency of CA-BSIs among the patients of this trial is in accordance with data from systematic surveillance studies [5]. Of all CA-BSIs four cases were classified as CR-BSIs (microorganisms on catheter tip matching those in blood culture). Three out of four microorganisms were coagulase-negative staphylococci. As molecular analyses were not applied, some CR-BSIs may have been incorrectly classified.

General strategies to prevent CA-BSIs include the use of full barrier precautions during insertion [28], prospective surveillance and multifaceted prevention activities including the use of chlorhexidine/alcohol [29,30], the currently recommended first-line antiseptic for catheter care in the USA and UK [31,32].

In conclusion, this RCT demonstrated superior activity of octenidine/propanol compared to alcohol alone, supporting the results of independent observational investigations [21,22]. The similar *in vitro* activities of octenidine and chlorhexidine suggest that octenidine might be as effective as chlorhexidine in practice. However, only a comparative trial can answer the question whether octenidine would be at least as effective for preventing catheter colonization and CA-BSIs.

Author contributions

M. Dettenkofer, A. F. Widmer, C. Wilson and C. Schmoor contributed to the conception and design of the study. All authors participated in the study implementation and have seen and approved the final version of the manuscript.

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Transparency Declaration

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1. Flow diagram of the trial.

Fig. S2. Cumulative incidences for CA-BSI*; comparison between octenidine group and control group.

Table S1. Isolated microorganisms*.

Table S2. Summary of outcomes in different patient groups and interactions between treatment (octenidine vs. control) and patient diagnosis/centre.

Table S3. Catheter-tip colonisation, Bloodstream infection and associated pathogens.

Table S4. Patient characteristics, considering only first randomisation.

Table S5. Quantitative skin cultures during the first 10 days after catheter insertion, positive catheter tip cultures* and CA-BSI^; comparison between octenidine group and control group‡, considering only first randomisation.

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