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Combined skin disinfection with chlorhexidine/propanol and aqueous povidone-iodine reduces bacterial colonisation of central venous catheters

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Abstract *Objective:* Central venous catheter (CVC)-related infections may be caused by micro-organisms introduced from the skin surface into deeper tissue at the time of CVC insertion. The optimal disinfection regimen to avoid catheter-related infections has not yet been defined. This study compares three different approaches. *Design:* Prospective randomised trial. *Setting:* A tertiary care hospital. *Patients and participants:* One hundred nineteen patients scheduled electively to receive 140 CVCs. *Interventions:* Skin disinfection was performed with either povidone-iodine 10% (PVP-iodine), chlorhexidine 0.5%/propanol 70%, or chlorhexidine 0.5%/propanol 70% followed by PVP-iodine 10%. Prior to disinfection, a swab from the site of insertion was taken for culture. CVCs were removed if no longer needed or infection was suspected. All catheters were cultured quantitatively after removal. *Measurement and results:* Bacteria could be isolated from 20.7% of the catheter tips. Bacterial growth was found in 30.8% of the catheters placed after skin disinfection with povidone-iodine, in 24.4% after disinfection with propanol/chlorhexidine and in 4.7% after disinfection with propanol/chlorhexidine followed by povidone-iodine (p=0.006). In 15 cases, the same organism was isolated from the skin swab and the catheter tip. Ten of these paired isolates showed the same pattern in a pulsed-field gel electrophoresis analysis. *Conclusions:* Skin disinfection with propanol/chlorhexidine followed by PVP-iodine was superior in the prevention of microbial CVC colonisation compared to either of the regimens alone. These results support the concept that catheter infections can originate from bacterial translocation at the time of catheter insertion.

Keywords Skin disinfection · Chlorhexidine · Propanol · Povidone-iodine · Central venous catheter · Infection · Bacterial colonisation

Introduction

Central venous catheters (CVCs) are widely used in patients who need i.v. access for infusion therapy [1, 2]. Device-related infection is a common problem and contributes substantially to morbidity and mortality. CVC-related infections may be responsible for as much as 90% of nosocomial bloodstream infections. Infection rates of 3–20 per 1,000 CVC days have been reported [3, 4]. Case-fatality rates of up to 10–20% have been observed and, for those patients who survive an episode of CVC-related infection, hospital stay is extended by 6.5 days, causing substantial extra cost [5, 6, 7, 8, 9]. This has led to the definition of guidelines for the prevention of CVC-related infections by the US infection control practices advisory committee and national societies and agencies in many other countries [10, 11].

Bacterial colonisation of the CVC is a prerequisite for catheter-related infections. Over the past few years it has become evident that bacterial colonisation of the skin at the site of CVC insertion is strongly associated with subsequent infection [12]. Despite disinfection of the skin prior to catheter insertion, bacteria may be introduced from the skin surface into deeper tissue layers during this procedure and subsequently establish a local infection [13, 14]. Therefore, more rigorous skin disinfection might be one of the keys to preventing CVC-related infections.

Centre of Disease Control guidelines suggest the use of 10% povidone-iodine (PVP-iodine) or 70% ethanol or propanol for skin disinfection and a disinfection time of at least 1 min prior to the insertion of a CVC. Recent publications have shown that skin disinfection with chlorhexidine 0.5–2% in aqueous or alcoholic solution was superior to 10% PVP-iodine or 70% alcohol in the prevention of CVC colonisation and infection [15, 16]. However, the optimal skin disinfection regimen has not yet been defined.

In this study we investigated the impact of three skin disinfection regimens using PVP-iodine, propanol/chlorhexidine or a combination of the two on CVC colonisation with micro-organisms, with special attention to the possible relatedness of CVC isolates and isolates cultured from the skin prior to disinfection and insertion of the catheter.

Materials and methods

The prospective, randomised study was conducted from May, 1999, to August, 2002, at the Medical Centre of the University of Regensburg, Germany. Adult in-patients scheduled for elective CVC placement during normal working hours were eligible for participation in the study. Patients from normal wards as well as from the intensive care units were included. Patients known to be allergic to iodine or chlorhexidine were excluded as were all patients who needed a CVC placed under emergency conditions. No underlying disease was defined as an exclusion criteria. The study was approved by the ethics committee of the University of Regensburg Medical Centre. Written informed consent was obtained prior to a patient's inclusion in the study.

At the time of insertion, each catheter was randomised to one of three disinfection regimens:

1. povidone-iodine 10% aqueous solution (Betaisodona, Mundipharma, Limburg, Germany) for 1 min
2. propanol 70%/chlorhexidine 0.5% (Skinsept F, Henkel-Ecolab, Düsseldorf, Germany) for 1 min
3. propanol 70%/chlorhexidine 0.5% (Skinsept F) for 1 min followed by PVP-iodine 10% (Betaisodona) disinfection for 1 min.

Sealed and numbered envelopes contained the randomisation code together with the instructions for skin disinfection and forms for the documentation of the procedure.

There was a protocol amendment (Fig. 1): after 95 patients had been enrolled in the trial, the application times for both the PVP-iodine and the propanol/chlorhexidine disinfection regimens were extended to 2 min in order to make sure that the skin was exposed to the disinfectants in all patients for the same amount of time. There was no change in the double disinfection arm of the study, meaning that the single agents continued to be used for 1 min each in this regimen. The study was in abeyance for several months for organisational reasons before the protocol amendment became effective.

One hundred forty catheters had to be included to achieve a power of 80% at an estimated difference between groups of 30%. In addition to the 140 catheters evaluated, 60 more catheters had been included but had to be excluded from analysis: in 5 cases, patients had died with the catheter in place, in 38 cases microbiological analysis of the catheter tip had not been performed and 17 catheters were lost during follow-up (e.g. the patient was taken to a different clinic with the CVC in place). No records are available from CVCs which were placed by attending physicians without giving notice to the study team. All elective catheters of which the study team received notice were included primarily. Two or three lumen CVCs or three lumen dialysis polyurethane catheters were used in this study. All catheters were purchased from Arrow, Reading, PA, USA.

Patients requiring multiple CVC during their hospitalisation were eligible to enter the study repeatedly, provided that the catheter was not changed over a guidewire at the same anatomical site and the patient did not receive two catheters at the same time.

Insertion and care of the catheters

Before the application of the disinfectant and without any prior preparation of the skin, the intended site of catheter insertion was swabbed with a cotton tip applicator (Transwab, Mast Diagnostica, Reinfeld, Germany) pre-moistened with sterile 0.9% saline. Disinfection of the skin with propanol/chlorhexidine was done by spraying the solution on the skin followed by wiping the area with a sterile gauze pad. Application of the propanol/chlorhexidine solution was repeated at least twice for a total disinfection time of 1 min (2 min in the amended protocol). Disinfection with PVP-iodine was done by wiping the skin repeatedly for 1 min (2 min in the amended protocol) with sterile gauze pads soaked with the disinfectant.

After skin disinfection, the CVC was inserted according to Seldinger's technique using the materials provided in the catheter kit. Maximum aseptic precautions were applied as recommended by the CDC guidelines for the prevention of nosocomial intravascular device-related infections [10]. In brief, the physician inserting the catheter had to wear sterile gloves, sterile surgical coat, cap and face-mask, and a large sterile drape had to be used to cover the area around the catheter insertion site. After CVC placement, the entry site was covered with a sterile dressing (Cutiplast, Beiersdorf, Hamburg, Germany).

Catheter care included daily changes of the dressing and cleaning of the catheter entry site with a sterile gauze pad moistened with the chlorhexidine/propanol skin disinfection solution. No topical antimicrobial or antiseptic ointments were applied at the skin entry site in this study. CVCs were removed if no longer needed or if a patient developed signs of CVC infection such as local pain, erythema or pus at the insertion site, or systemic signs such as fever or leukocytosis in the absence of another obvious infectious focus, or other symptoms suggesting a catheter infection according to the judgement of the physician responsible for the individual patient. Catheters were removed in sterile technique, the distal 5 cm was cut off using sterile scissors, immediately placed in a sterile transport tube (Transwab, Mast Diagnostica, Reinfeld, Germany) and sent for culture to the microbiology laboratory.

Microbiological methods

The specimens from the skin were inoculated onto Columbia agar supplemented with 5% sheep blood. The catheter tips were cultured quantitatively on Columbia agar supplemented with 5% sheep

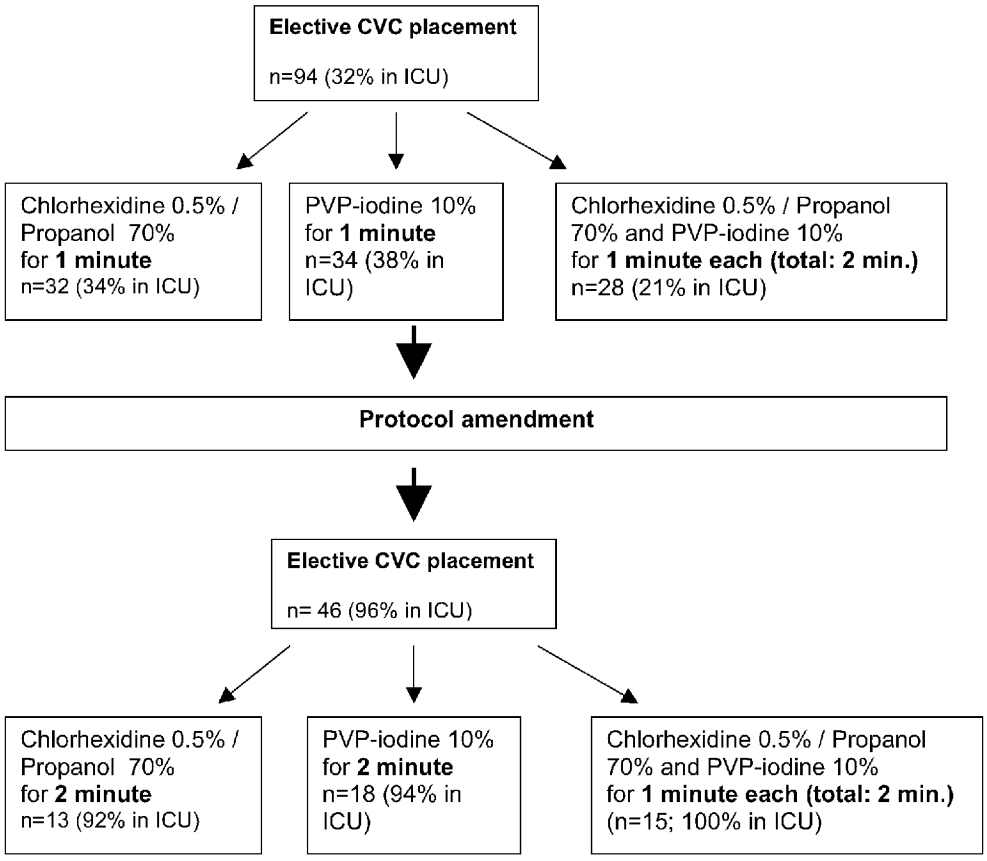

Fig. 1 Study protocol

blood using the plate-roll technique [17]. Incubation of agar plates and identification of micro-organisms were carried out according to standard methods. Catheter-tip colonisation was defined as more than 15 colonies/plate in the semiquantitative culture of the intravascular catheter segment [17].

If the same species grew from the skin swab and the catheter tip, these were compared and further analysed by pulsed-field gel electrophoresis (PFGE) [18] according to Gantom et al. for Gram-negative isolates [19], according to Morrison et al. and Turabelidze et al. for *Enterococci* [20, 21] and, with a modification of the technique by Sloos et al. [22], for coagulase-negative *Staphylococci*.

Clinical data and statistical analysis

The following parameters were recorded for each catheter included:

1. results of microbiological cultures from the CVC-tip and the skin at the entry site,
2. patient's medical diagnosis,
3. any immuno-compromising condition
   Patients were considered immuno-compromised if they were neutropenic or were receiving chemotherapy or other immunosuppressive drugs including prednisone/prednisolone or equivalent at a dose more than 0.3 mg/kg body weight.
4. reason for CVC insertion,
5. anatomical CVC insertion site,
6. duration of the procedure,
7. a grading for the difficulty of the procedure estimated by the physician placing the catheter: easy - 1 or 2 prick attempts, difficult - several prick attempts, very difficult - several prick attempts including an unintended arterial puncture
8. number of days the catheter was in place,
9. any signs of infection at the time of catheter removal,
10. application of lipid infusions.
11. Additionally, the physician placing the catheter had to judge his own skill in inserting a CVC (Table 1).

The Chi-square test (in a 3×2 table for comparison of the different disinfection regimens) and the log rank test were used for the statistical analyses, where appropriate. A p value less than 0.05 was considered significant. If interim analysis and final analysis would have been regarded as two non-independent statistical procedures, a p value of less than 0.025 would have had to be considered significant (according to Bonferroni).

Results

One hundred forty central venous catheters were assessed in 119 patients, representing 1,910 catheter days. Of these catheters, 52.8% were placed in ICU patients. No significant differences were found between the patients assigned to the three regimens with respect to sex, age, catheter attributes, physician's experience in placing catheters, duration of the procedure, patient's immune status, duration of catheterisation or any other parameter presented in Table 1. Two-lumen CVCs were used in

Table 1 Patient characteristics, type of catheter and insertion site

	Chlorhexidine 0.5% /propanol 70%	Povidone-iodine 10%	Chlorhexidine 0.5%/propanol 70% and Povidone-iodine 10%
Catheters (*n*)	45	52	43
Sex (male/female)	28/17	35/17	22/21
Mean age, years (± SD)	56.6 (±14.8)	53.4 (±17.2)	50.5 (±17.2)
Central venous catheter use (%)			
(a) Nutrition	2.2	5.8	7.0
(b) Multiple infusion/ vasopressors	44.4	34.6	41.9
(c) Dialysis	6.7	1.9	2.3
(d) (a) and (b)	46.7	53.8	48.8
(e) (a), (b) and (c)	0	3.8	0
Catheter type (%)			
2 hub	6.7	3.8	0
3 hub	86.6	86.5	97.6
4 hub	0	3.8	0
Dialysis catheter	6.7	5.8	2.4
Anatomical location (%)			
Internal jugular vein	86.7	82.7	90.7
Femoral vein	11.8	17.3	9.3
Subclavian vein	0	0	0
Mean duration of procedure (min) (± SD)	20.2 (±9.9)	19.1(±11.4)	24.2 (±13.1)
Difficulty of insertion (%)			
Uncomplicated	73.3	65.4	67.4
Difficult	13.3	25.0	23.3
Very difficult	13.3	9.6	9.3
Multiple physicians involved	2.2	7.7	9.3
Self-evaluation of physician's experience (%)			
Little experience	26.7	32.7	34.9
Experienced	37.8	13.5	34.9
Very experienced	24.4	36.5	16.3
Expert	8.9	9.6	4.7
Mean duration of catheterisation, (days) (± SD)	13.3 (±10.0)	14.5 (±11.7)	13.3 (±7.2)
Patient's immune status (%)			
Immuno-compromised	42.2	29.4	51.2

3.6% of the cases, three-lumen CVCs in 90.7%, and three-lumen dialysis catheters in 5.0%. No coated or tunnelled catheters were used. Catheter tip cultures yielded more than 15 cfu/plate in 29 out of the 140 central venous catheters (20.7%). This indicates an average catheter colonisation rate of 15.0/1,000 catheter days. Nineteen out of 56 catheters (33.9%) removed for suspected catheter-related infection showed a positive culture in contrast to 8 out of 72 catheters (11.1%) without any clinical signs or laboratory findings indicating infection at the time of catheter removal (p=0.002). For 12 patients the reason for catheter removal was not recorded.

The types and frequency of organisms recovered from the catheter tips and from the skin prior to catheter insertion are summarised in Table 2. Bacterial growth from the catheter tips differed significantly among the three disinfection regimens. Skin disinfection with PVP-iodine alone showed the highest colonisation rate (16/52, 30.8%; 21.0/1,000 CVC days; 95%CI: 18.7–45.1), followed by propanol/chlorhexidine disinfection (11/45, 24.4%; 18.4/1,000 CVC days; 95%CI: 12.8–39.5) and the lowest colonisation rates were found using propanol/chlorhexidine followed by PVP-iodine (2/43, 4.7%; 3.5/1,000 CVC days; 95% CI: 0.6–15.8); p=0.006. A Kaplan-Meier plot of the time to positive CVC-cultures in the first 28 days is depicted in Fig. 2 (log rank test; p=0.005). If all catheters were followed until removal beyond day 28, the differ-

Table 2 Spectrum of micro-organisms from skin and central venous catheter tips with more than 15 cfu/plate

	Isolates from skin (116 positive cultures)	Isolates from catheter tips (29 positive cultures)
Coagulase-negative *Staphylococci*	105	16
Staphylococcus aureus	2 (1 MRSA)	1 (MRSA)
Enterobacteriaceae	5	4
Enterococcus spp.	10	5
Candida spp.	8	1
Others	9	5

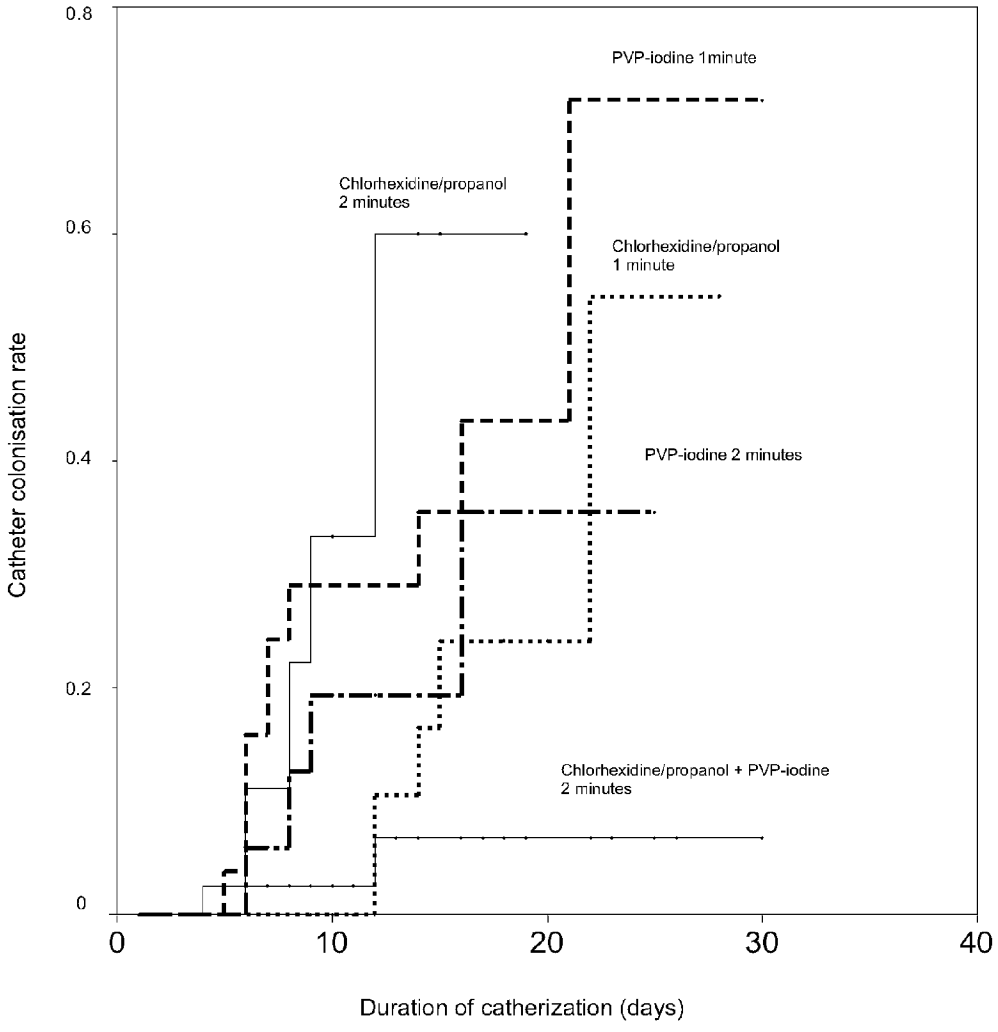

Fig. 2 Central venous catheter tip colonisation rates among the three disinfection regimens. Results of 1- and 2-min exposure times of the single disinfectant groups are given separately. (Kaplan-Meier plots for the comparison of the three disinfection regimens; p=0.024, log rank test)

Table 3 Colonisation rate and colonisation episodes per catheter days in terms of the disinfectant regimen

Disinfection regimen	Colonisation rate	Episodes/1000 catheter days
Chlorhexidine/propanol 1 min	18.8% (6/32)	12.6
Chlorhexidine/propanol 2 min	38.5% (5/13)	41
PVP-iodine 1 min	35.3% (12/34)	23.9
PVP-iodine 2 min	22.2% (4/18)	15.5
Chlorhexidine/propanol and PVP-iodine	4.7% (2/43)	3.5
Overall	20.7% (29/140)	15.0

PVP povidone

ence was still significant (log rank test; p=0.024). A subgroup analysis of the two antiseptic regimens using a single disinfectant did not detect significant differences (p=0.321). Significantly lower colonisation rates were observed by using the double disinfectant regimen as compared to PVP-iodine (p=0.001) or chlorhexidine/70% propanol (p=0.009).

The proportion of patients receiving lipid infusions was similar in all three groups (p=0.973). All disinfection regimens were well tolerated: no skin irritations and no allergic reactions were seen with any of the disinfection regimens.

Analysis of the subgroup of 46 catheters enrolled in the study under the amended protocol revealed colonisation rates of 5/13 (38.5%), 4/18 (22.2%) and 0/15 (0%) for disinfection with propanol/chlorhexidine, PVP-iodine and the combined regimen, respectively (p=0.0035). Colonisation rates and episodes per catheter days depending on the type of disinfectant and exposure time are given in Table 3.

Coagulase-negative *Staphylococci* were cultured most frequently both from the skin and from the catheter tips (Table 2). In 15 cases (51.7% of all positive catheter tip cultures), the same species of organisms were recovered from the skin prior to catheter insertion and subsequently from the catheter tip. Thirteen of these pairs were available for PFGE typing. One pair of coagulase-negative

Staphylococci and one pair of *E. faecium* could not be typed. However, the PFGE patterns of 10 out of the remaining 13 pairs (33.3% of all positive catheter tips) were identical, indicating that the isolates recovered from different sites at different time points represented the same organisms.

Discussion

There is now increasing evidence that a higher proportion of catheter-related infections may be caused by bacteria introduced into deeper skin structures during catheter insertion [10, 11]. Proper skin disinfection might, therefore, be one of the keys to reducing catheter colonisation at the time of catheter placement and, thus, preventing the development of subsequent infection. Previous reports have demonstrated differences in efficacy between the most commonly used skin disinfectants alcohol, chlorhexidine in alcoholic solution or PVP-iodine. Several randomised, controlled trials investigating different regimens for skin disinfection prior to catheter placement found chlorhexidine in aqueous or alcoholic solution to be more effective in reducing catheter colonisation and catheter-related infection when compared to PVP-iodine or 70% alcohol [15, 16, 23]. Others, however, did not show significant differences [24]. Skin preparation with chlorhexidine was also associated with a significantly decreased contamination rate of blood cultures with skin flora when compared to the use of PVP-iodine [25, 26]. This may be explained in part by the greater effect of chlorhexidine on Gram-positive bacteria, especially on coagulase-negative *Staphylococci*, when compared to other disinfectants [27, 28].

In this study, we saw a non-significant trend towards lower catheter colonisation rates in the propanol/chlorhexidine skin disinfection regimen compared to disinfection with PVP-iodine, in accordance with previous findings of other investigators [23]. However, skin disinfection with propanol/chlorhexidine followed by PVP-iodine was associated with the lowest rate of microbial catheter colonisation. When evaluating the apparent differences between the three different disinfection regimens, it has to be kept in mind that, in this study, both propanol/chlorhexidine and PVP-iodine were used in the approved concentrations and recommended application-times (>1 min) for their use as skin disinfectants.

Analysis of the subgroup of catheters after the protocol amendment with an application time of 2 min in all disinfection regimens did not indicate that the higher colonisation rates in the propanol/chlorhexidine and PVP-iodine regimens were due to differences in the time period the skin was exposed to the disinfecting agents. Our study suggests that differences in colonisation rates between antiseptic regimens are observable at least as long as 30 days after insertion.

From these data we conclude that the combination of propanol/chlorhexidine followed by PVP-iodine performs better than either of the regimens alone in preventing the bacterial colonisation of CVCs, and that these agents may have a synergistic disinfection activity.

For this study, we defined catheter tip colonisation as the detection of more than 15 colony-forming units using the roll-plate technique, as has been done similarly in previous publications on catheter infection [16, 29, 30]. This cut-off has been debated recently. More than 15 colony forming units as a primary end point is just a surrogate and may not have direct clinical implications. Nevertheless, the differences between disinfectant groups are intriguing. Using a cut-off of more than 100 cfu might have yielded a better specificity, and bacteraemia as an end point would have been more indicative for catheter-related infection. However, the number of patients to be included in a study using these end points would have to be much higher.

As blood cultures were not performed routinely, our study can not answer the question of how many procedures using a special disinfection regimen are required to avoid an episode of bloodstream infection. Furthermore, in this study only electively planned CVCs were included. It is not clear whether the results can be extrapolated to other catheters such as PAC or other situations such as emergencies. The longest procedure times were found in the double disinfection groups. The duration was approximately 4 min. We can not exclude the possibility that the difference in colonisation rates between regimens was due to more time spent by care-workers in the double disinfection arm, but we doubt that this is clinically relevant. Furthermore, the differences were not statistically significant and procedure time is certainly influenced by many more factors than the disinfection regimen alone.

From the chemical characteristics of chlorhexidine and PVP-iodine, a loss of disinfecting activity can be expected if both agents are *mixed* together [31]. Our results, however, do not suggest that such an effect is operative if these two agents are applied to the skin *sequentially*. Furthermore, no adverse events were observed with the use of the skin disinfectants in any of the regimens.

In 51.7% (n=15) of all positive catheter tip cultures, the same species were isolated from the skin at the site of catheter insertion prior to disinfection. In 13 cases PFGE-typing was available. In 10 out of these 13 cases, the isolate from the skin showed the same PFGE pattern as the isolate from the catheter tip. Our findings suggest that a proportion of CVC colonisation may occur as early as at the time of catheter placement.

In summary, our results underline the importance of aggressive skin disinfection to minimise microbial colonisation and possibly subsequent clinical infection of CVCs. Moreover, the findings support the view that a significant proportion of catheter colonisation may emerge from micro-organisms introduced from the skin into deeper

tissues at the time of CVC insertion. There are also other routes by which a CVC can become colonised and subsequently give rise to infection, e.g. by contamination of the hub.

Skin disinfection with sequential application of propanol/chlorhexidine and PVP-iodine was shown to be safe and to be more effective than either of the disinfectants alone in reducing the colonisation rates of CVCs. Colonisation of catheters is a prerequisite of catheter-born bloodstream infections. A confirmatory study using the same disinfection regimens to investigate the influence of the different regimens on bloodstream infections is warranted in order to establish CVC insertion guidelines with an optimal skin disinfection protocol.

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