Aus dem Institut für Medizinische Mikrobiologie, Immunologie und Hygiene

der Universität zu Köln

Direktor: Universitätsprofessor Dr. med. Martin Krönke

Efficacy of two antiseptic regimens on skin colonization of insertion sites for two different catheter types: a randomized, clinical trial

Inaugural-Dissertation zur Erlangung der Doktorwürde

der Medizinischen Fakultät

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vorgelegt von

Isabel Victoria Maximiliane Diener

aus Bergisch Gladbach

Promoviert am 20. Juli 2020

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Die dieser Arbeit zugrunde liegenden Daten wurden von mir selbst im Sankt Vinzenz-Hospital zu Köln unter der Anleitung von Herrn Prof. Dr. med. Jürgen Thomas Lutz erhoben.

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Glossary

BAC = Benzalkoniumchlorid

CDC = Centers for Disease Control

CFU = colony forming unit

CLABSI = central-line associated blood stream infection

CRBSI = catheter-related blood stream infection

DGAI = Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin e. V.

EC = Epidural Catheter

HAI = healthcare-associated infection

HA primary BSI = healthcare-associated primary bloodstream infection

KBE = kolonienbildende Einheit

KRINKO = Kommission für Krankenhaushygiene und Infektionsprävention

OCT = Octenidin-Hydrochlorid

PDK = Periduralkatheter

ZVK = zentraler Venenkatheter

Introduction

The insertion of any foreign material into central veins or epidural spaces poses a risk of contamination and subsequent infection. Patients requiring a central venous or epidural catheter for diagnostic and/or therapeutic reasons are often in an intensive care setting or require surgery (Frykholm et al., 2014, Bos et al., 2017).

Among the high prevalence of healthcare-associated infections (HAIs), healthcare-associated primary bloodstream infections (HA primary BSI) have the second-biggest impact on patients from the European Union, as Cassini et al. found in their 2016 point prevalence survey (Cassini et al., 2016).
One of the biggest risk factors in attaining a blood stream infection is the insertion of central venous catheters which are susceptible to colonization by micro-organisms. After Pronovost et al. strove to address this risk and consequently decrease those infections in an article published 2006 (Pronovost et al., 2006), many similar studies followed. One of the more recent of these studies is the National Patient Safety Imperative to eliminate central-line associated blood-stream infections (Berenholtz et al., 2014). As Leistner et al. showed for a German hospital setting, blood stream infection caused by central venous catheters also increases cost, as well as length of stay (Leistner et al., 2014).
The German Medical Association (Bundesärztekammer) published recommendations for the prevention of central venous catheter-related blood-stream infections in 2017 and endorses both chlorhexidine and octenidine dihydrochloride for skin disinfection (Arvand et al., 2017). The recommendations are downgraded in an Erratum published 2018 (KRINKO 2018), but are still best practice nationwide (the cateogries I to IV, created in the style of the US-American Centers for Disease Control (CDC), indicate the quality of a recommendation uttered by a health authority. The originally issued category IA was reduced to category IB for chlorhexidine and II for octenidine dihydrochloride).

Much less data exists for epidural catheter site infection. Steffen et al. observed a contamination rate of nearly 6% for spinal catheter tips in a retrospective study from 2003. Close to 90% of those contaminated tips were colonized with skin flora including *Staphylococcus epidermidis* and *Staphylococcus aureus* (Steffen et al., 2004).
Yuan et al. observed similar results in a 2008 prospective study (Yuan et al., 2008). Both studies show that skin flora bacterial migration along the catheter line is the most common route of epidural catheter colonization and therefore emphasizes that effective *residual* suppression of skin *re*-colonisation is a key element in the prevention of catheter-related infections.
The German Society of Anaesthesiology and Intensive Care Medicine (Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin, DGAI) lists the remanent agents chlorhexidine or octenidine for skin disinfection prior to regional anaesthesia procedures such as epidural catheter insertion in an S1 guideline. Both antiseptics are also recommended for disinfection during the change of dressings (Kerwat et al., 2015).

Proven association between skin colonization and catheter-related infections put effective disinfection of the catheter insertion site into focus (Ponnusamy et al., 2014).

However, a 2016 Cochrane Review questions the connection between skin disinfection and central venous catheter colonization and demands more randomized controlled studies for a valid correlation (Lai et al., 2016).

Alcoholic agents have been used for skin disinfection “from time immemorial”, with a first explicit declaration of its germicidal activity by the German obstetrician Reinicke dating back to 1894 (Harrington et al., 1903).

Innumerable additives have been combined with alcohol since then. In the United States, the agent most commonly added to alcohol is chlorhexidine (Sidhwa et al., 2015), whereas European countries tend to also favour the addition of octenidine dihydrochloride, benzalkonium chloride and povidone iodine (Danilevicius et al., 2015).

Octenidine hydrochloride destabilizes the plasma membrane of microorganisms and thereby provides a residual or remanent microbiocidal effect that exceeds other skin disinfectants’ efficacy, as in vivo studies and studies on reconstructed human tissue show (Muller et al., 2014, Koburger et al., 2010). The term “remanence” describes the persistent effect of additives to skin antiseptic agents once the alcoholic part evaporated. First studies suggested its increased efficacy already in 2005 (Tietz et al., 2005).

The following journal article describes a randomized trial conducted in Cologne, Germany in 2014, which compared alcoholic skin disinfection with octenidine dihydrochloride to benzalkonium chloride prior to insertion of central venous and epidural catheters with regard to skin recolonization within a 48 hour interval (Lutz et al., 2016). Adult patients who gave their informed consent in written form and were scheduled for elective surgery were randomly assigned into study and control groups and received the different skin disinfectants prior to catheter insertion. The Ethics Comission of the North-Rhine-Westphalian Medical Association approved of the study design in July 2014.

Research Question

In 2014, German physicians used several different alcoholic skin disinfectants for the preparation of catheter insertions under sterile conditions.

The study described in the following publication addressed the question which of two antiseptics had the better and more residual (or remanent) effect and hence offered more protection against catheter-related infections.

The surrogate parameter of skin re-colonization in a 48-hour interval was used in order to deduce a correlation between pathogens on skin surrounding the insertion site and catheter-related infection. Patients with similar characteristics received skin disinfection with two different alcohol-based antiseptics and their skin was examined for an increase in colony-forming units before, right after and 48 hours after the primary disinfection.

The hypothesis was that octenidine as an additive to alcoholic skin disinfectants has a longer lasting antimicribiological effect on catheter-surrounding skin than benzalkonium chloride.

Original Paper

Efficacy of two antiseptic regimens on skin colonization of insertion sites for two different catheter types: a randomized, clinical trial

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ORIGINAL PAPER

Efficacy of two antiseptic regimens on skin colonization of insertion sites for two different catheter types: a randomized, clinical trial

Juergen Thomas Lutz[1] · Isabel Victoria Diener[1] · Kerstin Freiberg[1] · Robert Zillmann[1] · Kija Shah-Hosseini[2] · Harald Seifert[3] · Bettina Berger-Schreck[4] · Hilmar Wisplinghoff[3,4]

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Abstract
Purpose Catheter-related bloodstream infections affect patients in surgical and intensive care settings worldwide, causing complications, aggravation of existing symptoms and increased length of stay. The trial aimed at comparing two registered skin antiseptics with respect to their residual and therefore infection-preventing effects.
Methods In a parallel, monocentric, prospective, triple-blind, randomized trial the difference in bacterial recolonization of catheter skin sites in central venous (CVC) and epidural catheters (EC) was investigated by comparing two alcoholic-based skin disinfectants. Patients receiving planned surgeries or intensive care were eligible for the trial. Those in the trial group received skin disinfection with the additive octenidine dihydrochloride (OCT) ($n = 51$), those in the control group were treated with benzalkonium chloride as additive (BAC) ($n = 59$) prior to catheter insertion. Randomization was carried out by assigning patients to groups week-wise. Endpoints of the investigation were skin colonization of the catheter site counted in colony forming units per swab at three time points: (1) prior to catheter insertion, on untreated skin; (2) directly after catheter insertion, prior to sterile coverage; (3) 48 h after catheter insertion. The hypothesis was tested by a Wilcoxon test with a two-sided alpha = 5 %.
Results From second to third swab, recolonization of the catheter-surrounding skin was significantly lower in the trial group for both sorts of catheters: delta 2–3 OCT group: 0.72 (95 % CI: 0.42; 1.02); delta 2–3 BAC group: 1.97 (95 % CI: 1.45; 2.50); $p < 0.001$. None of the patients enrolled developed a catheter-related blood stream infection (CRBSI) during follow-up.
Conclusions Previous studies have shown that skin colonization is strongly associated with the occurrence of CRBSI. This randomized controlled trial supports the observations made in previous trials that octenidine dihydrochloride in disinfectants is more effective than agents containing other additives with regard to skin recolonization surrounding CVC and EC insertion sites. Therefore, it is likely to also reduce the risk of CRBSI in these patient groups. The trial was approved by the North Rhine Medical Association in July 2014 (application-no.: 2014222).

Keywords Alcoholic disinfection · Catheter-related bloodstream infection · Octenidine dihydrochloride · Benzalkonium chloride · Central venous catheter · Epidural catheter · Bacterial recolonization

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Background

Central venous and epidural catheters are commonly needed in patients prior to surgery, a variety of invasive procedures or in an ICU setting [1, 2]. Many patients suffer

from CRBSI originating from poorly disinfected or re-contaminated insertion sites around the catheter [3].

The minimization of catheter-surrounding skin recolonization is an effective step to avoid these infections [4], which are associated with many consecutive risks and cause an increase in treatment costs and lengths of stay [5]. As the amount of skin colonization is directly associated with catheter colonization and therefore with CRBSI risk, it is essential to focus on continuous skin hygiene [6].

Alcohol shows a strong immediate antimicrobial activity, but has no relevant residual activity on skin. Alcohol additives like benzalkonium chloride (BAC), chlorhexidine (CHX) or octenidine dihydrochloride (OCT) exert a different amount of residual activity on skin once the alcohol's immediate effect has worn off [7]. OCT offers a broad and fast acting fungicidal, bactericidal and partly virucidal effect in a 0.1 % concentration [8].

Earlier trials have shown the residual activity of some of these disinfectants. Particularly, CHX as a strong residual agent shows clinical evidence to prevent catheter colonization and catheter-related blood stream infections (CRBSI) when using CHX/alcohol combinations prior to vascular catheter insertion and during catheter care [9].

Similar clinical investigations have proven a residual effect for octenidine dihydrochloride which leads to a decrease in skin recolonization after the alcohol has evaporated from the skin [10, 11].

The objective of this study was to compare an alcohol-based skin disinfectant containing OCT with regards to its residual effect to a reference alcohol-based skin disinfectant containing BAC.

Methods

Trial description

A randomized, prospective, controlled trial was conducted to compare the skin recolonization at central venous catheter (CVC) and epidural catheter (EC) insertion sites over 48 h in patients receiving a skin disinfection with either a BAC- or an OCT-containing alcohol-based disinfectant.

Setting and participants

From July to December 2014, 216 patients in an academic teaching hospital in Cologne, Germany, were enrolled in the trial. The majority of patients received a catheter prior to surgery, all others (<2 %) were patients in the Intensive Care Unit (ICU).

The Ethical Review Board of the North Rhine Medical Association approved the trial in July 2014 (application-no.: 2014222).

Adult patients likely to receive a CVC or EC or both according to pre-operative standards were asked for their informed consent. Pre-trial exclusion applied for minors, emergency patients and patients with nosocomial infections. Patients whose swabs could not be obtained according to protocol were excluded. This applied for catheters being removed during the follow-up period as well as for patients whose sterile dressing did not cover the insertion site sufficiently after 48 h. Applying house standards according to National Hospital Hygiene Standards [12], all catheter insertions were carried out by experienced anesthesiologists, following a strict protocol including the use of surgical masks and caps, sterile gowns, gloves and catheter kits. The sterile dressing was applied right after the insertion, using a transparent foil to facilitate inspection of the insertion site. According to the study protocol, nurses or doctors changed the sterile cover every 48 h after disinfecting the catheter and its surrounding skin with a propranolol spray and a sterile pad.

Randomization

The disinfection regimen was changed at weekly intervals, thereby randomly assigning patients to the trial or control group, respectively. The patients, the microbiological laboratory and the statistician were blinded to the assignment. The medical staff could not be blinded due to the colorant solely in the BAC agent and the use of transparent dressings.

After having given their informed consent, patients received skin disinfection with either one of the following commercially available and legally registered antiseptics:

Trial group

Propan-1-ol 30 % (w/w), propan-2-ol 45 % (w/w), octenidine dihydrochloride (OCT) 0.1 % (w/w) (octeniderm®, Schülke & Mayr, Norderstedt, Germany).

Control group

Propan-2-ol 63 % (w/w), benzalkoniumchloride (BAC) and coloring agents (Cutasept G®, Paul Hartmann AG, Heidenheim, Germany).

The dressing chosen for all patients was a sterile, transparent gauze designed for close skin site monitoring. The procedure for the control group was the established hospital standard, the trial group's only alteration being the use of an alternative disinfectant. The staff only changed their routine throughout this trial by taking swabs at the fixed time points.

Settings of the trial

All patients enrolled were treated and followed-up between July and December 2014 in the Department of Anaesthesiology at St. Vinzenz-Hospital, Cologne, Germany. Patients received catheters prior to surgery in the hospital's departments of abdominal, thoracic, gynecological and traumatological surgery or as part of the intensive care or pain treatment in the ICU or the department of pain therapy respectively. The environment for catheter insertions was either the operating theater or the ICU.

Patients who were scheduled for catheters repeatedly during the same or various hospitalizations were allowed to be enrolled twice (respectively, three times) if at least 4 weeks had passed since the previous catheterization.

All adult patients scheduled to receive a CVC or EC who gave their written consent were included.

To reduce the loss of patients due to protocol deviations, the fixation especially for CVC was improved by applying strain-relief to the connected lines. In addition, all sterile covers were additionally fixated with adhesive tape on the rim. For EC patients, the sterile dressings' size was increased and its rims supported by adhesive tape.

Microbiological methods

All swabs were obtained by trained members of the trial team under standardized conditions using a sterile drape with a circular hole with a 7 cm diameter. The thereby marked skin surrounding the catheter insertion site was swiped with a sterile flocked swab (eSwab Liquid Amies, Copan, Brescia, Italy) with a movement ten times vertically and ten times horizontally. The tip was then immersed in the swabs' prefilled 1.0 mL sterile 0.01 M phosphate buffered saline (PBS) for transport to the microbiological laboratory.

To determine the bacterial burden, samples were cultured quantitatively (native, 1:10 and 1:100 dilution) on trypticase-soy-agar plates with sheep-blood (bioMérieux, Nürtingen, Germany). After vortex mixture, cultures were incubated for 36–48 h at 35 ± 1 °C. All tests were run in duplicate. The plates were inspected by a technician and the supervising microbiologist at 18–24 and 36–48 h. Results were expressed as CFU per swab.

Outcomes and follow-up

Main outcome parameter was the difference in CFUs/swab (colony forming units per swab) of swab 3 (i.e. 48 h after insertion of CVC or EC) in comparison to swab 2 (i.e. immediately after disinfection and insertion). Secondary objective was the comparison of swab 3 and swab 1 (i.e. before disinfection and insertion). Patients were divided into cohorts primarily by skin disinfection regimen and secondly by type of catheter, so that four groups could be compared (CVC with OCT, CVC with BAC, EC with OCT, EC with BAC).

Patients' comorbidity factors such as smoking, diabetes and permanent corticoid therapy were monitored. None of the enrolled patients suffered from chronic skin conditions. The amount of white blood cells and C-reactive protein were also taken into account.

Side effects, such as skin irritation (burning, itching, swelling, redness) were also closely monitored.

Statistical analysis

Statistical analysis based on the CFUs counted by the laboratory personnel was statistically conducted by the University Hospital of Cologne's Institute for Medical Statistics, Informatics and Epidemiology (Institut für medizinsche Statistik, Informatik und Epidemiologie, IMSIE).

The hypothesis was that octenidine as an additive to alcoholic skin disinfectants has a longer lasting antimicribiological effect on catheter-surrounding skin than benzalkonium chloride.

The analysis was conducted using the Statistical Package for the Social Sciences, version 22 (SPSS, IBM, Armonk, NY, USA). CFUs counted were logarithmized due to their great span. The disinfection regimen was compared at two time points: immediately after catheter insertion (swab 2) and 48 h after catheter insertion (swab 3). Swab 1 prior to skin disinfection was conducted as a baseline, as patients with different backgrounds were expected to start off with extremely different CFU amounts on their untreated skin. The hypothesis was tested by a Wilcoxon test with a two-sided alpha = 5 %.

Results

216 patients were enrolled in the trial from July to December 2014. 106 patients had to be excluded from further analysis due to manipulation, partial or complete loss of the sterile dressing on the insertion site during the first 48 h. Other reasons for exclusion were disinfection within 48 h prior to first change of dressings or catheter-removal for therapeutic reasons, and the patient's death or transferal to another hospital.

After having entered the trial, patients had to be excluded due to prematurely removed or loosened sterile covers on the catheter site. In addition, patients whose catheters had been removed in the 48 h follow-up period were excluded.

Patients entering the trial without any skin colonization in the first swab were excluded, as their skin swab result

could not be considered a reliable marker. The last reason for exclusion was a decrease in skin colonization from swab 2 to swab 3.

The remaining 110 patients were divided into two main groups (trial, $n = 51$ and control, $n = 59$) and into four subgroups (trial CVC, $n = 25$; trial EC, $n = 26$; control CVC, $n = 29$; control EC, $n = 30$). A significant difference in delta swab 3 to swab 2 and in delta swab 3 to swab 1 was expected for both regimens.

Group characteristics

Patients in the trial and control group, even when being catheterized for different reasons, showed similar characteristics regarding comorbidity, sex, age and physical constitution.

41 patients received both a CVC and an EC in one session, eight entered the trial twice, and one patient was enrolled three times in total. At least four weeks had to elapse after first catheterization to re-enter again.

Skin colonization

110 patients qualified for skin colonization analysis. There was no difference in the immediate effect (i.e. representing swab 2) between the trial and control group. The difference in CFUs from swab 2 to swab 3 showed a significantly lower value of recolonization in the trial group. In the subgroups, additionally divided by type of catheter, the values for CVCs were generally higher than for ECs in swabs 2 and 3 respectively, the level of recolonization again being much lower in the patients treated with OCT. Figure 1 shows the logarithmized amount of CFUs in all three swabs. The direct comparison of trial and control group shows the highly significant difference in recolonization from swab 2 to swab 3, as could be expected. The difference of mean values in patients treated with BAC was 1.97 (95 % CI: 1.45; 2.50), whereas the trial group treated with OCT only showed a delta of 0.72 (95 % CI: 0.42; 1.02; $p = 0{:}0005$).

Side effects

Side effects such as redness, swelling or pathological serum parameters were mild, rare and occurred in all groups. Few patients in all groups developed slight redness ($n = 7$, trial: $n = 3$; control: $n = 4$) or swelling ($n = 3$; trial: $n = 2$; control: $n = 1$) around the catheter insertion site (see Fig. 2; Table 1).

Complications

None of the patients developed signs of CRBSI or any other systemic side effects, which was expected due to the short period of follow-up.

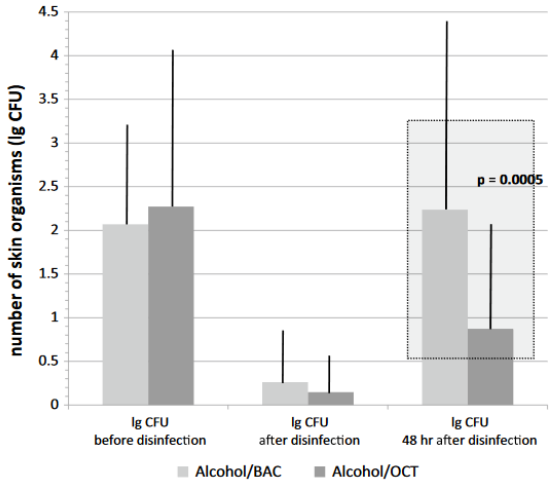

Fig. 1 Number of organisms (CFUs/swab) at the insertion sites of catheters. CFUs/swab are displayed before, immediately after disinfection and 48 h after disinfection with Alcohol/BAC or Alcohol/OCT. The difference in colony counts between Alcohol/BAC and Alcohol/OCT after 48 h was statistically highly significant ($p = 0.0005$)

Discussion

This randomized controlled trial is the first to compare the immediate and mid-term efficacy over a 48 h period of two alcohol-based skin antiseptics used for disinfection of catheter insertion sites. The trial setup demonstrates similarities in the immediate effect and differences in the residual effect of the two alcohol-based skin disinfectants. The third skin swab taken 48 h after catheter insertion revealed a highly significant inhibition of regrowth of the skin flora in the Alcohol/OCT group in comparison to the Alcohol/BAC group. This residual effect of the disinfectant in the trial group can most likely be attributed to octenidine dihydrochloride, confirming results of other clinical studies with this formulation.

Skin colonization is a very important risk and surrogate factor for CRBSI [2, 6]. Therefore, the results suggest that the use of octenidine-based disinfectants may decrease CRBSI risk in CVC and EC patients significantly [6, 13].

For reasons of quality assurance the swab collection was limited to a small trial team whose members underwent a specific training. All swabs were conducted in the same manner, e.g. even applying a constant pressure while swabbing.

Limitations to the trial are the monocentric setup and the relatively small number of patients included in the statistical analysis. Nevertheless, regarding antimicrobial effect the regimens applied were highly different and resulted in clearly significant differences between groups.

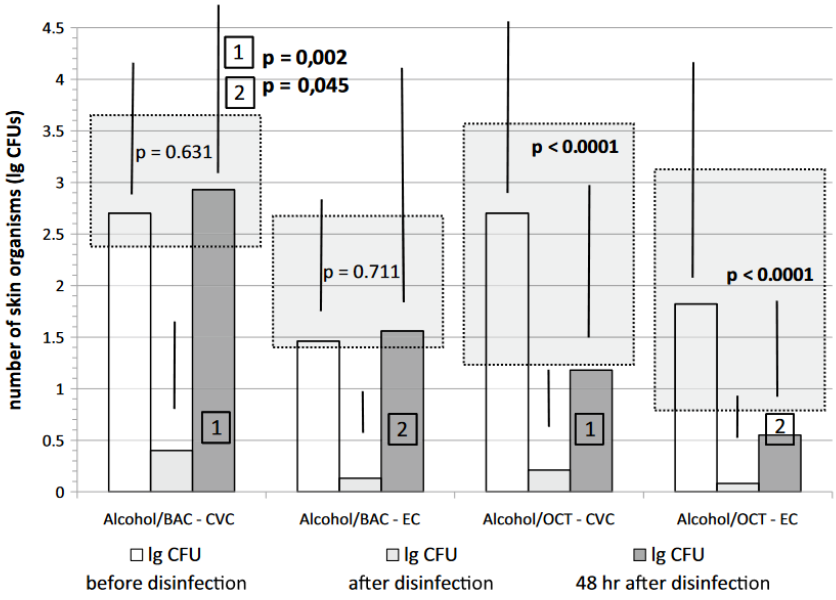

Fig. 2 Colony forming units at the insertion sites of catheters. CFUs/swab are displayed before, immediately after and 48 h after disinfection with Alcohol/BAC or Alcohol/OCT. Sites for CVC and EC are shown separately. Statistical analyses were carried out within and between groups (1 and 2)

Table 1 Patient characteristics

	Alcohol/BAC		Alcohol/OCT	
	CVC	EC	CVC	EC
Number of patients	29	30	25	26
Catheter insertion sites	26/0/3	16/10/4	23/1/1	10/14/2
(CVC: jugular vein/subclavian vein/no specification)				
(EC: thoracical/lumbal/no specification)				
Age (mean)	67.4	66.47	66.8	66,69
Sex (f/m)	12/17	14/16	15/10	11/15
BMI (mean)	25.2	26.15	27	27.7
Diabetes (y/n/not specified)	7/18/4	6/21/3	6/16/3	9/16/1
ASA-classification (I/II/III/IV/ not specified)	0/2/13/1/3	1/15/12/1/1	0/10/11/3/1	0/12/14/0/0
Allergy of any type (y/n/not specified)	4/21/4	6/23/1	6/18/1	7/19/0
Nicotine abuse (y/n/not specified)	9/16/4	12/17/1	5/18/2	3/21/2
Corticoid therapy (y/n/not specified)	3/22/4	0/30/0	3/22/0	1/24/1
Max. CRP (mean)	19	12.15	14.42	9.3
Max. white blood cells (mean)	10.6	12	13.01	9.35
Redness after treatment	2	2	2	1
Swelling after treatment	0	1	1	1

Furthermore, a long-term follow-up was not conducted, as the residual effect after initial disinfection was the focus of this study. Emergency patients, even though being at high risk for CRBSI [14], were excluded from the trial. For a long-term follow-up and thus a detection of potential differences in the incidence of CRBSIs, a much greater number of patients would have been needed to be examined, which was not possible in this monocentric setup. Furthermore, this study was not powered to answer this question.

The direct comparison of the current standard-antiseptic BAC and the octenidine-containing residual agent demonstrates the latter product's performance and its potential clinical advantage.

The patients' week-wise assignment to the groups prevented biases such as time of the day, temperatures in wards or physician in charge of catheter insertion. Generally, the patient population was homogenous as all of them

met criteria for elective surgery that required catheterization in advance.

The high number of exclusions is a major limitation resulting from three phenomena: especially in the beginning of the trial, many sterile covers on patients' insertion sites detached; the skin underneath could no longer be considered sterile. By standardizing the application of sterile dressings, the comparability of CFU results increased. Secondly, patients were excluded if they did not show any skin colonization in the first swab. Exclusion also resulted from a decrease in skin colonization from swab 2 to swab 3.

Furthermore, full barrier protection and close inspection for any early infection signs help to prevent CRBSI [5, 15, 16]. Regular training on hygiene measures and infection prevention also lowers the amount of CRBSI [17, 18].

Conclusions

This RCT showed highly significant differences in microbiological skin colonization around CVC and ED insertion sites and therefore superiority of an alcohol-based skin disinfectant containing OCT in comparison to one containing BAC. As other independent trials have shown, OCT is a well-tolerated, highly effective skin disinfectant that might change the approach in catheter hygiene for both CVC [10, 11, 19] and EC.

Compliance with ethical standards

Conflict of interest The study was financially supported by Schülke & Mayr GmbH. Travel expenses for J. T. Lutz and I. V. Diener were also covered by Schülke & Mayr GmbH for two conferences. Apart from this, all authors declare to have no conflict of interest.

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Discussion

The journal article “Efficacy of two antiseptic regimens on skin colonization of insertion sites for two different catheter types: a randomized, clinical trial” describes a comparison of four components: two skin disinfectants in two different procedures. Both are regularly administered, usually by anaesthesiologists, under elective and emergency conditions. Colony-forming units where measured by taking swabs of untreated skin, immediately after disinfection and 48 hours onwards when the first dressing was changed according to our protocol.

The comparison between untreated (= first swab) and just disinfected skin (= second swab) in all four subgroups revealed similar results, showing that both agents have comparable *immediate* antiseptic effect. However, the 48-hour results differed significantly in the two study arms, showing a highly significant inhibition of regrowth of the skin flora in the alcohol/octenidine group in comparison to the alcohol/benzalkoniumchloride group. The instant antiseptic effect of the alcoholic component in both agents attributed for the second swab results, whereas the non-volatile additives octenidine and benzalkoniumchloride determined the difference in skin flora regrowth over time. The residual effect of the disinfectant in the trial group can most likely be attributed to octenidine dihydrochloride, confirming results of other clinical studies with this formulation (Koburger et al., 2010, Dettenkofer et al., 2010).

Catheter-related (blood stream) infections are directly linked to skin colonization (Ponnusamy et al., 2014), therefore the amount of re-colonization is a surrogate factor for subsequent infection (Raad II et al., 1994, Lee et al., 2019). Therefore, our study did not determine infection directly.

In order to assure standardized data sets, a small number of employees were specifically trained in sample collection and operated according to a strict protocol.. Patients and statisticians were blinded, a randomization was established by alternately using the disinfectants for one week each.

For ethical and practical reasons, the trial has several limitations. First, monocentric setting and small sample size, which was further decreased by many drop-outs due to breach of dressing, limits its applicability to bigger settings.

The authors of the study identified three major reasons for exclusion: first and most importantly, breach of dressing led to a high number of drop-outs, as the dressing detached from the skin and a sterile coverage of the catheter insertion site could not be guaranteed anymore. A standardized protocol for the (intra-procedural) application of the first dressing increased staff awareness, adherence to the study protocol and consequently patient safety. It was also implemented as the hospital’s standard operating procedure for central venous and epidural catheter dressings from then on.
Other reasons for exclusion were a first swab not showing any skin colonization and a decrease in skin (re-)colonization from second to third swab.

Due to the different colours of the agents compared, the medical staff could not be blinded (the product with benzalconium was coloured for better visibility of already disinfected skin area, the other containing octenidine was only available as a transparent solution).

In retrospect, the connection between skin colonization and catheter-related infections need to be further investigated, as Lai et al. propose in their 2016 Cochrane Review (Lai et al., 2016). However, the review only investigates complications deriving from central venous catheters, whereas the presented study produced data for both central venous and epidural catheters. The study did not investigate long-term effects of the two different regimens applied, as it focussed on the first disinfections' residual effects. Emergency patients could not be included for ethical reasons, which is an important limit with regard to their slightly higher susceptibility for catheter-related infections (LeMaster et al., 2010).

The data collected in this study, however, showed highly significant differences in recolonization of both types of catheter insertion sites.

By deliberately comparing the 2014 state-of-the-art standard skin disinfectant with benzalkonium-chloride to the octenidine-containing residual agent, the study was powered to outline the latter product's features and possible clinical advantages.

The weekly randomization into either the octenidine or the benzalkonium group for both types of catheter insertion procedures guaranteed data collecting independent of possible bias factors such as team members, time of the day, ward temperatures or patient features.

Because only adult patients scheduled for elective surgery who required a central venous and/or epidural catheterization were included in this trial, the cohort homogeneity is given in all four sub-groups. This is shown in more detail in the patient characteristics table:

	Alcohol/BAC		**Alcohol/OCT**	
	CVC	**EC**	**CVC**	**EC**
Number of patients	29	30	25	26
Catheter insertion sites (CVC: jugular vein/subclavian vein/no specification) (EC: thoracical/lumbal/no specification)	26/0/3	16/10/4	23/1/1	10/14/2
Age (mean)	67.4	66.47	66.8	66,69
Sex (f/m)	12/17	14/16	15/10	11/15
BMI (mean)	25.2	26.15	27	27.7
Diabetes (y/n/not specified)	7/18/4	6/21/3	6/16/3	9/16/1
ASA-classification (I/II/III/IV/ not specified)	0/2/13/1/3	1/15/12/1/1	0/10/11/3/1	0/12/14/0/0

	Alcohol/BAC		Alcohol/OCT	
	CVC	**EC**	**CVC**	**EC**
Allergy of any type (y/n/not specified)	4/21/4	6/23/1	6/18/1	7/19/0
Nicotine abuse (y/n/not specified)	9/16/4	12/17/1	5/18/2	3/21/2
Corticoid therapy (y/n/not specified)	3/22/4	0/30/0	3/22/0	1/24/1
Max. CRP (mean)	19	12.15	14.42	9.3
Max. white blood cells (mean)	10.6	12	13.01	9.35
Redness after treatment	2	2	2	1
Swelling after treatment	0	1	1	1

*
ASA = American Society of Anaesthesiologists
BAC = benzalkonium chloride
CRP = C-reactive protein
CVC = Central Venous Catheter
EC = Epidural Catheter
f = female
m = male
max. = maximum
n = no
OCT = octenidine dihydrochloride
y = yes

An effective skin disinfection regimen with residual antimicrobial effects is only one part of a multidimensional strategy for the prevention of catheter-related infection. Hospitals world-wide have implementted so-called “bundles” of peri-procedural, evidence-based interventions to ensure a minimum contamination of skin, inserted materials, fixation, and dressing (Lin et al., 2018). This involves hand hygiene, maximum barrier precautions, skin antisepsis and optimum selection and daily inspection of the insertion site (Furuya et al., 2016).

Summary

Skin disinfection prior to any catheter insertion is an integral procedure to prevent catheter-related infection. This applies both for central venous and epidural lines.

The presented 2014 study used swabs of untreated skin, disinfected skin and skin at the first change of dressing 48 hours after insertion to investigate possible differences in re-colonization of the skin at the catheter insertion site. The bacterial growth was measured in colony-forming units. The amount of re-colonization was statistically compared and showed a highly significant difference between the study and control group.

The study showed that octenidine dihydrochloride applied as an additive to an alcoholic skin disinfectant significantly decreases the re-colonization of skin over a 48-hour period, which is the standard period between changes of sterile dressings for catheters.

As a reaction to these and other findings, the German Medical Association recommends the use of octenidine dihydrochloride and other additives with remanent or residual microbiocidal capacity for any skin-penetrating procedure. Octinidine dihydrochloride is increasingly used nation-wide in skin and hand disinfection products.

Zusammenfassung in Deutscher Sprache

Die Hautdesinfektion vor der Anlage eines Katheters ist eine integrale Maßnahme zur Prävention Katheter-assoziierter Infektionen. Dies gilt sowohl für zentrale Venenkatheter (ZVK), als auch für Periduralkatheter (PDK). Als Surrogat-Parameter dient hier und in vielen anderen Studien, die diesen Zusammenhang untersuchen, die Re-Kolonisation der Haut. Ein hoher Anstieg des Re-Kolonisationswertes wird mit einer wahrscheinlicheren Katheter-assoziierten Infektion assoziiert. Eine jüngere Meta-Analyse (Cochrane Systematic Review) kann diesen Zusammenhang für zentrale Venenkatheter jedoch nicht belegen.

Die hier präsentierte Studie von 2014 ging der Frage nach, ob sich zwei zu diesem Zeitpunkt handelsübliche Hautdesinfektiva auf Alkoholbasis in ihrer remanenten, also über einen längeren Zeitpunkt aktiven Wirkung auf die Haut, unterschieden. Der hierzu genutzte Parameter war ein Anstieg in kolonien-bildenden Einheiten (colony forming units, CFU) vom Ausgangszeitpunkt unmittelbar nach der Hautdesinfektion zur Vorbereitung der Katheteranlage bis zum Zeitpunkt des ersten Verbandwechsels 48 Stunden später.
Die Ethikkommission der Ärztekammer Nordrhein genehmigte das Studienprotokoll im Juni 2014.

216 volljährige Patientinnen und Patienten mit ähnlichem Morbiditätsprofil und Indikation für eine elektive Operation mit ZVK- und/oder PDK-Anlage wurden nach ihrer schriftlichen Zustimmung in das Studienkollektiv aufgenommen und randomisiert den vier verschiedenen Gruppen zugeordnet:
A: Zentraler Venenkatheter (CVC), mit Additiv Benzalkonium-Hydrochlorid (BAC) desinfiziert
B: ZVK, mit Octenidin-Dihydrochlorid (OCT) desinfiziert
C: Epiduralkatheter (EC), mit BAC desinfiziert
D: EC, mit OCT desinfiziert.

106 Patientinnen und Patienten mussten aus unterschiedlichen Gründen nachträglich ausgeschlossen werden. Hauptsächlich erfolgte die Exklusion, weil die sterilen Verbände sich vor Ablauf des Beobachtungsintervalls gelöst hatten und somit Ausgangs- und Folgewert nicht mehr verglichen werden konnten.

Die Anstiege der Rekolonisation wurden statistisch verglichen und ergaben hoch-signifikante Unterschiede zwischen Studien- und Kontrollgruppe. Der durchschnittliche CFU-Anstieg aller mit Benzalkonium-haltigem Desinfektivum behandelten Patientinnen und Patienten lag bei 1.97 (95 % CI: 1.45; 2.50), während er in den Gruppen der mit Octenidin-Dihydrochlorid-haltigem Antiseptikum Behandelten nur bei 0.72 (95 % CI: 0.42; 1.02; p = 0:0005) lag.

Die Studie zeigte somit, dass der Zusatz von Octenidin-Dihydrochlorid zu alkoholischen Haut-Antiseptika die Rekolonisation der Haut über 48 Stunden signifikant verringerte (dies stellt den Standard-Zeitraum zwischen zwei sterilem Verbandwechseln dar).

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Appendix

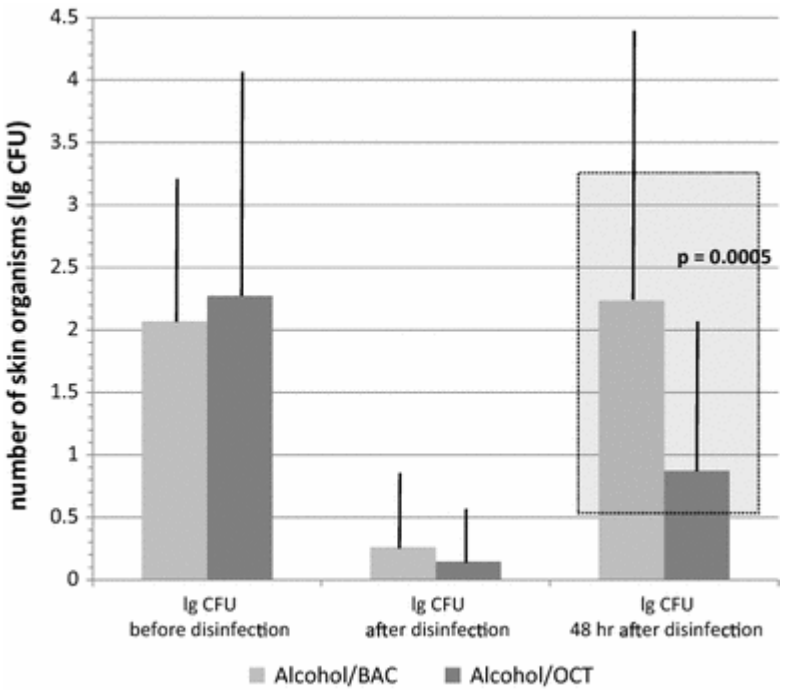

Figure 1: Number of organisms (CFUs/swab) at the insertion sites of catheters. CFUs/swab are displayed before, immediately after disinfection and 48 h after disinfection with alcohol/BAC or alcohol/OCT. The difference in colony counts between alcohol/BAC and alcohol/OCT after 48 h was statistically highly significant (p = 0.0005)

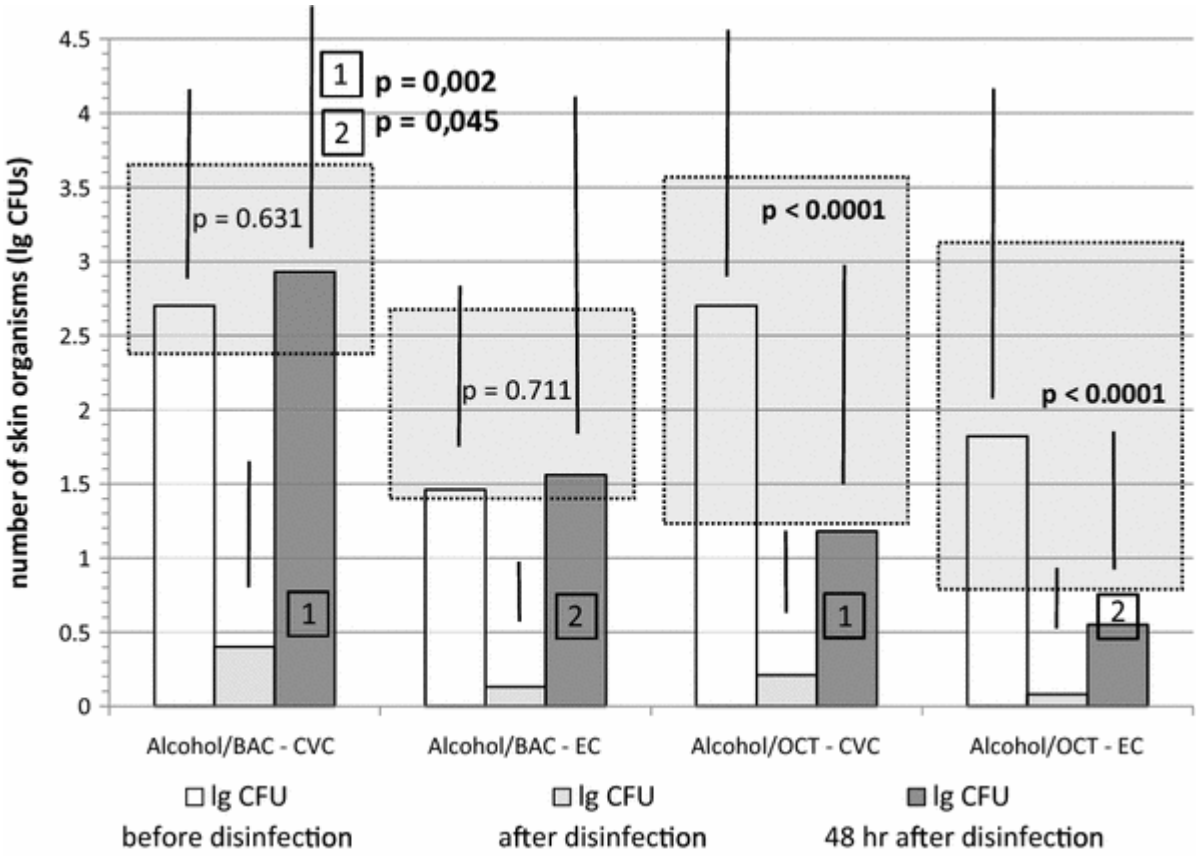

Figure 2: Colony forming units at the insertion sites of catheters. CFUs/swab are displayed before, immediately after and 48 h after disinfection with alcohol/BAC or alcohol/OCT. Sites for CVC and EC are shown separately. Statistical analyses were carried out within and between groups (1 and 2)

	Alcohol/BAC		Alcohol/OCT	
	CVC	**EC**	**CVC**	**EC**
Number of patients	29	30	25	26
Catheter insertion sites (CVC: jugular vein/subclavian vein/no specification) (EC: thoracical/lumbal/no specification)	26/0/3	16/10/4	23/1/1	10/14/2
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ASA-classification (I/II/III/IV/ not specified)	0/2/13/1/3	1/15/12/1/1	0/10/11/3/1	0/12/14/0/0
Allergy of any type (y/n/not specified)	4/21/4	6/23/1	6/18/1	7/19/0
Nicotine abuse (y/n/not specified)	9/16/4	12/17/1	5/18/2	3/21/2
Corticoid therapy (y/n/not specified)	3/22/4	0/30/0	3/22/0	1/24/1
Max. CRP (mean)	19	12.15	14.42	9.3
Max. white blood cells (mean)	10.6	12	13.01	9.35
Redness after treatment	2	2	2	1
Swelling after treatment	0	1	1	1

Table 1: Patient Charcteristics
*
ASA = American Society of Anaesthesiologists
BAC = benzalkonium chloride
CRP = C-reactive protein
CVC = Central Venous Catheter
EC = Epidural Catheter
f = female
m = male
max. = maximum
n = no
OCT = octenidine dihydrochloride
y = yes

Mein Lebenslauf wird aus Gründen des Datenschutzes in der elektronischen Fassung meiner Arbeit nicht veröffentlicht.