Chlorhexidine plus alcohol versus povidone iodine plus alcohol, combined or not with innovative devices, for prevention of short-term peripheral venous catheter infection and failure (CLEAN 3 study): an investigator-initiated, open-label, single centre, randomised-controlled, two-by-two factorial trial

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Summary

Background Two billion peripheral venous catheters are sold globally each year, but the optimal skin disinfection and types of devices are not well established. We aimed to show the superiority of disinfection with 2% chlorhexidine plus alcohol over 5% povidone iodine plus alcohol in preventing infectious complications, and of closed integrated catheters, positive displacement needleless-connectors, disinfecting caps, and single-use prefilled flush syringes used in combination (innovation group) over open catheters and three-way stopcocks for treatment administration (standard group) in preventing catheter failure.

Methods We did an open-label, randomised-controlled trial with a two-by-two factorial design, for which we enrolled adults (age ≥18 years) visiting the emergency department at the Poitiers University Hospital, France, and requiring one peripheral venous catheter before admission to the medical wards. Before catheter insertion, patients were randomly assigned (1:1:1:1) using a secure web-based random-number generator to one of four treatment groups based on skin preparation and type of devices (innovative devices or standard devices; 2% chlorhexidine plus alcohol or 5% povidone iodine plus alcohol). Primary outcomes were the incidence of infectious complications (local infection, catheter colonisation, or bloodstream infections) and time between catheter insertion and catheter failure (occlusion, dislodgment, infiltration, phlebitis, or infection). This study is registered with ClinicalTrials.gov, NCT03757143.

Findings 1000 patients were recruited between Jan 7, and Sept 6, 2019, of whom 500 were assigned to the chlorhexidine plus alcohol group and 500 to the povidone iodine plus alcohol group (250 with innovative solutions and 250 with standard devices in each antiseptic group). No significant interaction was found between the two study interventions. Local infections occurred less frequently with chlorhexidine plus alcohol than with povidone iodine plus alcohol (0 [0%] of 496 patients *vs* six [1%] of 493 patients) and the same was observed for catheter colonisation (4/431 [1%] *vs* 70/415 [17%] catheters among the catheters cultured; adjusted subdistribution hazard ratio 0·08 [95% CI 0·02–0·18]). Median time between catheter insertion and catheter failure was longer in the innovation group compared with the standard group (50·4 [IQR 29·6–69·4] h *vs* 30·0 [16·6–52·6] h; p=0·0017). Minor skin reactions occurred in nine (2%) patients in the chlorhexidine plus alcohol group and seven (1%) patients in the povidone iodine plus alcohol group.

Interpretation For skin antisepsis, chlorhexidine plus alcohol provides greater protection of peripheral venous catheter-related infectious complications than does povidone iodine plus alcohol. Use of innovative devices extends the catheter complication-free dwell time.

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For the Chinese translation of the abstract see **Online** for appendix 1

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Introduction

Short-term peripheral venous catheters are the most commonly used invasive medical devices in hospitals; about 2 billion are sold annually worldwide.[1] Unfortunately, peripheral venous catheters often fail before the end of treatment due to mechanical, vascular, or infectious complications.[2] These complications—occlusion, infiltration, phlebitis, dislodgment, and local or bloodstream infections—lead to interruption of treatment, which can be detrimental to patients. Catheter replacement causes pain

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See **Online** for appendix 2

Research in context

Evidence before this study

Complications related to the use of short-term peripheral vascular catheters are common, leading to catheter failure in about half of patients before the end of treatment. Paradoxically, there are few recommendations on the modalities to prevent these complications. We searched PubMed for randomised-controlled and quasi-experimental trials and systematic reviews and meta-analyses assessing skin preparation before peripheral venous catheter insertion and choice of medical devices. We included trials published from Jan 1, 1980, to Dec 31, 2019, in French or in English, using the terms (short term peripheral venous catheter) AND (chlorhexidine) OR (iodine) OR (antiseptic) OR (failure) OR (occlusion) OR (dislodgment) OR (infiltration) OR (phlebitis) OR (accidental removal). We screened title and abstracts to retrieve full-text articles for assessment of eligibility and checked reference lists of relevant trials and reviews for additional references. Concerning skin preparation, we identified only one randomised small study showing the superiority of 2% chlorhexidine plus 70% isopropyl alcohol over 70% isopropyl alcohol in reducing catheter colonisation, and no study comparing chlorhexidine to povidone iodine. Concerning the type of devices, we identified only one randomised controlled trial showing the benefit of closed catheters over standard catheters and two quasi-experimental studies suggesting the benefit of using needleless connectors or disinfecting caps in reducing catheter-related infectious complications or catheter failure.

Added value of this study

We did an investigator-initiated, open-label, single centre, randomised-controlled, two-by-two factorial trial in Poitiers University Hospital, France, in which 1000 patients due to receive a short-term peripheral venous catheter were assigned to one of four groups according to skin disinfection and type of devices. Skin disinfection was a 30 s single application of 2% chlorhexidine plus 70% isopropyl alcohol or 5% povidone iodine plus 69% ethanol. Devices were closed integrated catheters and disinfecting caps with treatments administered through positive displacement needleless connectors preceded and followed by flushing with pre-filled saline syringes (innovation group) or open catheters with treatments administered through three-way stop cocks (standard group). Patients assigned to the chlorhexidine plus alcohol group had fewer local infections and fewer catheters colonised than did those assigned to the povidone iodine plus alcohol group. Use of innovative solutions in combination reduced the risk of catheter failure compared with standard devices and extended the median (IQR) time between catheter insertion and catheter failure.

Implications of all the available evidence

For skin preparation, 2% chlorhexidine plus alcohol should be preferred to 5% povidone iodine plus alcohol before the insertion of short-term peripheral venous catheters. Similarly, use of closed integrated catheters, positive displacement needleless connectors, prefilled flush syringes, and disinfecting caps should be recommended to increase catheters dwell time without complication. Whether all compounds of the combination should be recommended remains to be established.

and induces additional costs.[3] Additionally, bloodstream infections prolong hospitalisation and increase treatment costs and mortality.[4]

Prevention of these complications is therefore essential and is based on hygiene rules and use of biocompatible catheters. The choice of the most effective antiseptic solution for skin disinfection before catheter insertion is key. Although the use of alcoholic solutions is recommended by scientific societies,[5,6] the superiority of 2% chlorhexidine plus alcohol over 5% povidone iodine plus alcohol in preventing infectious complications has been shown only for short-term central venous and arterial catheters in patients who were critically ill.[7,8] Similarly, innovative solutions such as closed integrated catheters, positive displacement needleless-connectors, disinfecting caps, and single-use prefilled flush syringes are being marketed to maintain catheter patency over a longer time, but there is little scientific evidence to support their use in clinical practice[9–12] and no large-scale study has evaluated them when used in combination.

We hypothesised that skin preparation with 2% chlorhexidine plus 70% isopropanol (chlorhexidine plus alcohol) is more effective than a skin preparation with 5% povidone iodine plus 69% ethanol (povidone iodine plus alcohol) in preventing peripheral venous catheter-related infectious complications. We also hypothesised that use of closed integrated catheters, positive displacement needleless-connectors, disinfecting caps, and single-use prefilled flush syringes in combination extends the time elapsed between catheter placement and catheter failure compared with the use of open catheters and three-way stopcocks for treatment administration.

Methods

Study design and participants

CLEAN 3 is an investigator-initiated, open-label, single centre, randomised, two-by-two factorial, superiority trial done at Poitiers University Hospital, France. Patients were recruited at the emergency department, where the catheters were inserted, before being admitted to the medical wards. Patients were monitored daily for catheter-related complications for up to 48 h after catheter removal, or earlier if discharged from hospital. We enrolled adult patients (aged ≥18 years) who visited our emergency department and required placement of a single peripheral venous catheter for 48 h or longer before hospital admission in medical wards. Exclusion criteria were[13] known intolerance,

hypersensitivity or contraindication to chlorhexidine, povidone iodine, isopropanol or ethanol; suspicion of bloodstream infection; skin injury increasing the risk of catheter infection; presence of intravascular catheter in place within the last 2 days, or within the last 2 weeks and with local signs of catheter complication; suspicion of difficult catheter insertion; surgery required; and previous participation in this study. We obtained written informed consent before study inclusion. The study protocol was approved by the French Southwest and Overseas Ethics Committee and the French Drug Safety Agency, and was published elsewhere.[13] The study was carried out in accordance with the principles of the Declaration of Helsinki and the Clinical Trials Directive 2001/20/EC and 2005/28/EC of the European Parliament.

Randomisation and blinding

Randomisation was carried out by the emergency department physician through a secure web-based randomisation system. A statistician not involved in either screening patients or assessing outcomes provided a computer-generated numbered list. Patients were randomly assigned (1:1:1:1, in permuted blocks with varying block sizes from four to 12) to one of the four treatment groups based on skin preparation (chlorhexidine plus alcohol or povidone iodine plus alcohol) and devices used for the venous line (innovation group or standard group). Masking of the participants and medical staff was not feasible due to the nature of the interventions. However, the microbiologists who tested the catheters and blood samples and the statisticians (JP and DF) were masked to the group assignment.

Procedures

The peripheral venous catheters were inserted by 39 nurses working in the emergency department. To participate in the study, nurses were required to have previously inserted at least 50 open peripheral venous catheters. They also were required to follow French recommendations,[5] similar to US Centers for Disease Control and Prevention recommendations,[14] for catheter insertion and care. Hair was removed only if required with a clipper (no shaving) before catheter insertion. Hands of nurses were disinfected with hydro-alcoholic solution and the nurses wore non-sterile gloves.

Skin was disinfected with either 2% (weight devided by volume) chlorhexidine and 70% (volume divided by volume) isopropyl alcohol (ChloraPrep, Becton Dickinson, Le Pont de Claix, France) or 5% (weight divided by volume) povidone iodine and 69% (volume divided by volume) ethanol (Bétadine alcoolique, Mylan Medical SAS, Merignac, France). The assigned antiseptic solution was applied by moving back and forth using prefilled applicators (chlorhexidine plus alcohol) or by circular movements using sterile gauzes soaked with the antiseptic (povidone iodine plus alcohol) for at least 30 s, starting at the catheter insertion site and then extending to the entire work area. Assigned peripheral venous catheters were inserted once the work area was dry and taped with Tegaderm 1626W transparent film dressing (3M, St Paul, MIN, USA). No ultrasound guidance was allowed during the study.

In the innovation group, peripheral venous catheters were the Nexiva single port catheter (Becton Dickinson). Intravenous fluids or drugs were administered through a positive displacement needleless-connector (MaxZero [Becton Dickinson]), after removal of the disinfecting cap covering the needle-free luer connector (PureHub™ [Becton Dickinson]). Before and after each drug administration, a pulse flushing technique with 5 mL of sterile saline solution in prefilled syringe (Becton Dickinson) was used to flush the catheter and its extension, followed by administering positive pressure to seal the tube (by pushing the flushing solution while simultaneously clamping the extension tubing). Pulse flushing consists of alternately pushing and pausing in flushing with saline solution, creating a small vortex within the catheter. Recapping of the needle-free luer connector with a new disinfecting cap was systematic. Intravenous fluids were infused only if the patient needed them, not so as to avoid catheter occlusion, and usually discontinuously.

In the standard group, peripheral venous catheters were the Insyte Autoguard Blood Control Winged (Becton Dickinson). Intravenous fluids and drugs were administered through a three-way stop cock (Becton Dickinson), after disinfecting the administration site with sterile gauzes soaked with an alcohol-based antiseptic, peripheral venous catheters were continuously infused with saline or polyionic solution, by gravity, to prevent catheter occlusion, until catheter removal.

Nurses' hands were decontaminated before any contact with the peripheral venous catheter or injection sites, using an alcohol-based hand rub. No restriction on the products administered through the peripheral venous catheters was placed. Dressings were not changed except if soiled or loose. The same antiseptic procedure was used at each dressing change.

Catheters were removed only for completion of treatment, phlebitis, infiltration, occlusion, dislodgment, or suspected infection, and usually not later than day 4. However, the decision to remove the catheter was made solely by the physicians in charge of the patients. Catheter tips were cultured with a simplified quantitative broth dilution technique.[15] Nurses training and study monitoring is summarised in appendix 2 (p 4).

We defined catheter colonisation as a catheter culture growing more than 1000 CFU of a pathogen per mL.

We defined local infection as organisms growing from purulent discharge with no evidence of associated bloodstream infection. Definition of catheter-related bloodstream infection and all-cause bloodstream infection are provided in the appendix 2 (p 5).

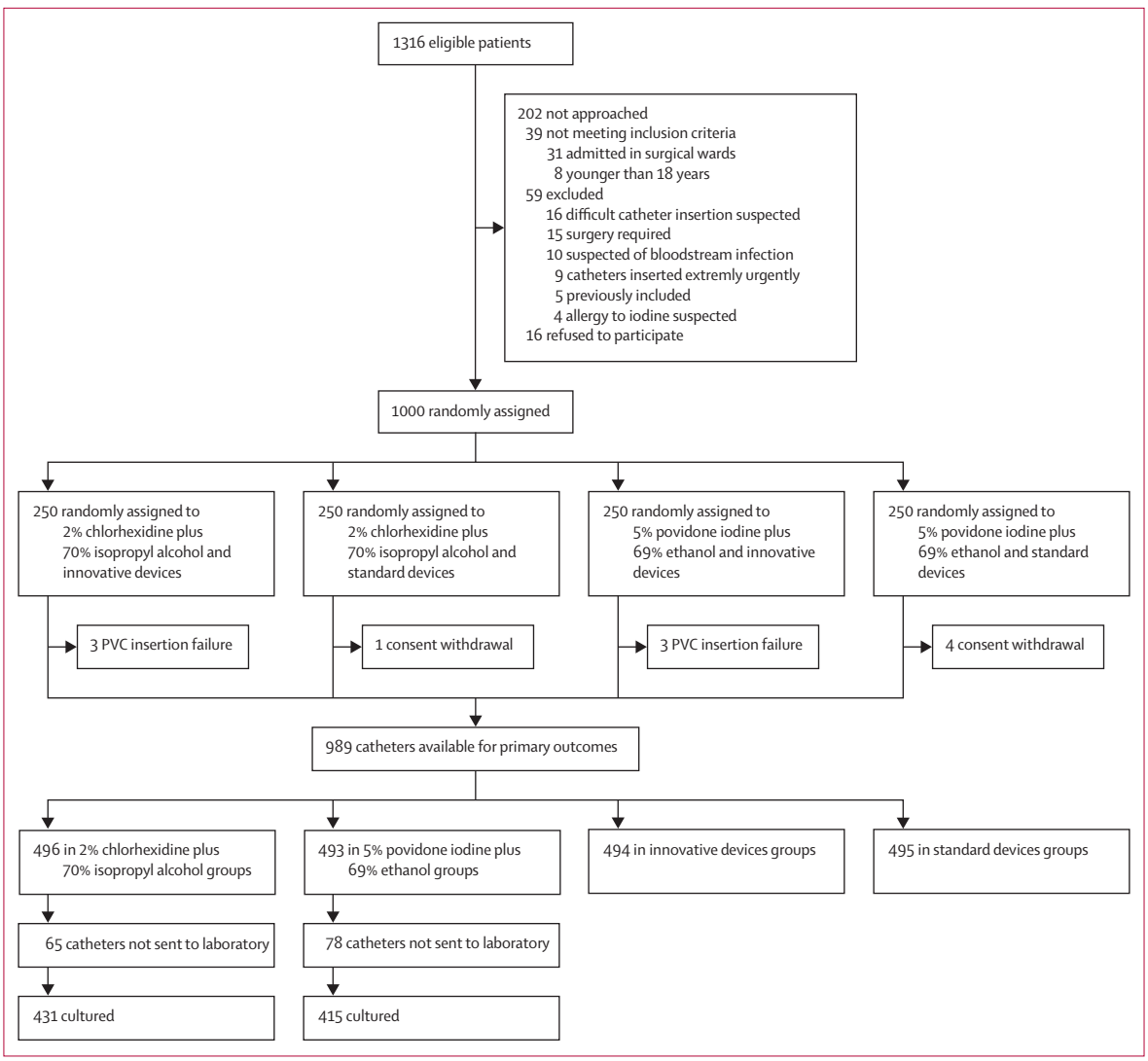

Figure 1: **Trial profile**
PVC=peripheral venous catheters.

We defined phlebitis as two or more of the following present simultaneously: patient-reported pain or tenderness (on questioning, followed by palpation by the research nurse) with severity of two or more on a ten-point scale; erythema extending at least 1 cm from the insertion site; swelling, extending at least 1 cm from the insertion site; purulent discharge; and palpable venous cord beyond the intravenous catheter tip.

We defined infiltration as the infusion of non-blistering drug leaking through the normal vascular channel and resulting in the swelling of tissue peripheral to the puncture site.

We defined occlusion as the inability of the catheter to flush (not able to intravenously inject 1 mL of normal saline within 30 s). We defined dislodgment as any situation leading to a catheter being outside the vein.

Outcomes

The first primary outcome was the incidence of catheter-related infectious complications, and included local infection, catheter colonisation, and catheter-related bloodstream infection. The second primary outcome was the time between catheter insertion, and catheter failure. Catheter failure was defined as any premature removal of peripheral venous catheters before end of treatment, other than for routine replacement, and included phlebitis, infiltration, occlusion, dislodgment, local infection and catheter-related bloodstream infection (whichever occurred first). French guidelines recommend changing peripheral venous catheters every 4 days, a time frame that can be extended by decision of the attending physician. Additional prespecified secondary outcomes were: incidence of local infection, catheter colonisation, catheter-related bloodstream infection, and of all-cause bloodstream infection,

	Entire population (n=995)	Antiseptic groups		Device groups	
		CHG group (n=499)	PVI group (n=496)	Innovation group (n=500)	Standard group (n=495)
Age, years	76 (62–86)	78 (62–87)	76 (61–85)	77 (62–87)	76 (61–86)
Men	503 (51%)	243 (49%)	260 (52%)	259 (52%)	244 (49%)
Body-mass index, kg/m^2	25 (22–29)	25 (22–29)	25 (22–29)	25 (23–29)	25 (22–29)
Smoker	137 (14%)	63 (13%)	74 (15%)	61 (12%)	76 (15%)
At least one chronic disease	667 (67%)	332 (67%)	335 (68%)	350 (70%)	317 (64%)
Diabetes	204 (21%)	105 (21%)	99 (20%)	113 (23%)	91 (18%)
Dyslipidemia	209 (21%)	92 (18%)	117 (24%)	105 (21%)	104 (21%)
Chronic obstructive pulmonary disease	92 (9%)	48 (10%)	44 (9%)	58 (12%)	34 (7%)
Chronic heart failure	180 (18%)	78 (16%)	102 (21%)	101 (20%)	79 (16%)
Chronic renal failure	72 (7%)	25 (5%)	47 (9%)	44 (9%)	28 (6%)
Long-term corticosteroids	30 (3%)	15 (3%)	15 (3%)	16 (3%)	14 (3%)
Immune deficiency	47 (5%)	19 (4%)	28 (6%)	24 (5%)	23 (5%)
Haematological malignancy	25 (3%)	14 (3%)	11 (2%)	14 (3%)	11 (2%)
Antibiotics in the last 15 days	75 (8%)	40 (8%)	35 (7%)	38 (8%)	37 (7%)
Anticoagulant therapy	215 (22%)	109 (22%)	106 (21%)	122 (24%)	93 (19%)
Antiplatelet aggregation therapy	263 (26%)	122 (24%)	141 (28%)	138 (28%)	125 (25%)

Data are median (IQR) or n (%). CHG=2% alcoholic chlorhexidine. PVI=5% alcoholic povidone iodine. Patients are described twice, once in the antiseptic groups columns and once in the device groups columns.

Table 1: **Patient characteristics of the modified intention-to-treat population**

phlebitis, infiltration, catheter occlusion, and catheter dislodgment; and length of first hospital stay censored at day 28. Prespecified secondary safety outcomes were: daily skin status assessed using the International Contact Dermatitis Research Group scale; pain at catheter insertion using the 10-cm visual analogue scale (appendix 2 p 6); patient satisfaction at catheter removal using the visual analogue scale; and effect of venous line on patient's mobility at catheter removal using the visual analogue scale. The International Contact Dermatitis Research Group scale includes four stages of increasing severity: faint erythema only; non-vesicular erythema, infiltration, possibly papules; vesicular erythema, infiltration, and papules; and intense erythema and infiltration, coalescing vesicles, bullous reaction. The first two stages are considered minor reactions; the last two stages are considered severe reactions.

Each participant remained in the study until 48 h after catheter removal or until they decided to stop participating in the study.

Statistical analysis

Assuming a 12% infectious complication rate in the povidone iodine plus alcohol group,[16] 712 patients were required to detect a 50% reduction of peripheral venous catheter infectious complications with the use of chlorhexidine plus alcohol,[11] with two-tailed α (type-I error) of 5% and a power of 80%. We enrolled 1000 patients to better rule out a potential interaction between the two strategies (+30%) and a maximum catheter culture loss of 10%.

The analyses were done by two-by-two factorial design on a modified intention-to-treat-basis (all patients except those who withdrew consent).[17] No interim analysis was planned.

Demographic data and catheter characteristics were described as number and percentage or median and IQR. For analysis of the primary outcomes, the interaction between two study interventions (antiseptic agent and type of device) was sought first using multivariable logistic regression models. Treatment effects (antiseptics comparison or devices comparison) were then assessed with competing risks regression, taking into account catheters removed without having developed a complication (competing risk) and with adjustment for other intervention (device groups for antiseptics comparison or antiseptic groups for devices comparison). The proportional hazards assumption was assessed with Schonfeld's residuals. To make inferences about the effect of treatments, adjusted subdistribution hazard ratios (HRs) and 95% CI were determined, and average marginal effects were calculated as adjusted probability of events. Sensitivity analyses were done to account for patients excluded from the analyses for catheter insertion failures and for consent withdrawals. Excluded catheters were considered to have infectious complications in the chlorhexidine plus alcohol group or having failed in the innovation group, and free of complications in the povidone iodine plus alcohol and standard groups.

Secondary outcomes were described as number and percentage or median and IQR and compared with

	Entire population (n=989)	Antiseptic groups		Device groups	
		CHG group (n=496)	PVI group (n=493)	Innovation group (n=494)	Standard group (n=495)
Catheter size					
22 gauge	12 (1%)	7 (1%)	5 (1%)	5 (1%)	7 (1%)
20 gauge	281 (28%)	136 (27%)	145 (29%)	146 (30%)	135 (27%)
18 gauge	691 (70%)	351 (71%)	340 (69%)	340 (69%)	351 (71%)
16 gauge	1 (0%)	0	1 (0%)	1 (0%)	0
14 gauge	1 (0%)	0	1 (0%)	0	1 (0%)
Missing	3 (0%)	2 (0%)	1 (0%)	2 (0%)	1 (0%)
Insertion site					
Hand	143 (14%)	78 (16%)	65 (13%)	61 (12%)	82 (17%)
Wrist	117 (12%)	50 (10%)	67 (14%)	52 (11%)	65 (13%)
Outer face forearm	198 (20%)	90 (18%)	108 (22%)	97 (20%)	101 (20%)
Inner face forearm	174 18%)	90 (18%)	84 (17%)	91 (18%)	83 (17%)
Cubital fossa	306 (31%)	164 (33%)	142 (29%)	169 (34%)	137 (28%)
Arm	23 (2%)	11 (2%)	12 (2%)	9 (2%)	14 (3%)
Missing	28 (3%)	13 (3%)	15 (3%)	15 (3%)	13 (3%)
Insertion side					
Right	510 (52%)	247 (50%)	263 (53%)	252 (51%)	258 (52%)
Left	476 (48%)	247 (50%)	229 (46%)	240 (49%)	236 (48%)
Missing	3 (0%)	2 (0%)	1 (0%)	2 (0%)	1 (0%)
Insertion attempt					
1	805 (81%)	402 (81%)	403 (82%)	391 (79%)	414 (84%)
2	128 (13%)	64 (13%)	64 (13%)	69 (14%)	59 (12%)
3	40 (4%)	20 (4%)	20 (4%)	25 (5%)	15 (3%)
>3	13 (1%)	8 (2%)	5 (1%)	7 (1%)	6 (1%)
Missing	3 (0%)	2 (0%)	1 (0%)	2 (0%)	1 (0%)
Operator change	51 (5%)	24 (5%)	27 (5%)	28 (6%)	23 (5%)
Catheter usage					
Hydratation	654 (66%)	329 (66%)	325 (66%)	319 (64%)	335 (68%)
Antibiotic	130 (13%)	62 (12%)	68 (14%)	68 (14%)	62 (13%)
Heparin	8 (1%)	5 (1%)	3 (1%)	7 (1%)	1 (0%)
Potassium	15 (2%)	6 (1%)	9 (2%)	10 (2%)	5 (1%)
Corticosteroids	18 (2%)	5 (1%)	13 (3%)	9 (2%)	9 (2%)
Other drugs	511 (52%)	247 (49%)	264 (54%)	266 (54%)	245 (49%)
Blood products	40 (4%)	24 (5%)	16 (3%)	22 (4%)	18 (4%)
Dressing changes	81 (8%)	40 (8%)	41 (8%)	47 (10%)	34 (7%)
Time with catheter in place, hrs	39 (20–65)	39 (21–63)	41 (20–67)	43 (21–69)	36 (19–57)

Data median (IQR) or n (%). CHG=2% alcoholic chlorhexidine. PVI=5% alcoholic povidone iodine. Catheters are described twice, once in the antiseptic groups columns and once in the device groups columns.

Table 2: **Characteristics of the catheters**

logistic regression or multiple linear regression, according to the type of variable, to allow interactions terms as for primary outcomes; treatment effects are presented as adjusted relative risk (RR) or adjusted mean difference.

All of the tests are two-tailed with no adjustment for multiple testing. Analyses were done with SAS (version 9.4) and R software (3.63). The analysis report is presented in accordance with the CONSORT statement.[18]

This study is registered with ClinicalTrials.gov, NCT03757143, and is closed to new participants.

Role of the funding source

The sponsor and Becton Dickinson had no role in trial initiation, study design, choice of antiseptic products, data collection, data analysis, data interpretation, writing of the report, or the decision to submit. The corresponding author and JG had full access to all of the data and had final responsibility for the decision to submit for publication.

Results

Between Jan 7, 2019, and Sept 6, 2019, of the 1316 patients eligible to participate in the study, we

	Entire population (n=989)	Antiseptic groups		Adjusted relative risk	Device groups		Adjusted relative risk
		CHG group (n=496)	PVI group (n=493)		Innovation group (n=494)	Standard group (n=495)	
Infectious complications							
Catheter colonisation*	74/846 (9%)	4/431 (1%)	70/415 (17%)	0·06 (0·05 to 0·06)	42/431 (10%)	32/415 (8%)	1·11 (0·77 to1·67)
Local infection	6 (1%)	0	6 (1%)	0·45 (0·26 to 0·99)	2 (<1%)	4 (1%)	0·48 (0·34 to 1·43)
Catheter-related bloodstream infections	0	0	0	..	0	0	..
All-causes bloodstream infections	21 (2%)	8 (2%)	13 (3%)	0·59 (0·40 to 1·07)	9 (2%)	12 (2%)	0·71 (0·48 to 1·43)
Non-infectious complications							
Infiltration	153 (16%)	79 (16%)	74 (15%)	1·07 (0·83 to 1·43)	71 (14%)	82 (17%)	0·71 (0·50 to 1·43)
Occlusion	64 (7%)	36 (7%)	28 (6%)	1·11 (0·48 to1·91)	20 (4%)	44 (9%)	0·48 (0·32 to 0·98)
Dislodgment	161 (16%)	73 (15%)	88 (18%)	0·83 (0·67 to 1·67)	67 (14%)	94 (19%)	0·63 (0·53 to 0·91)
Phlebitis	23 (2%)	8 (2%)	15 (3%)	0·48 (0·34 to 1·03)	12 (2%)	11 (2%)	1·01 (0·45 to 2·33)
Patient-related outcomes							
Pain at catheter insertion	0 (0 to 2)	0 (0 to 2)	0 (0 to 2)	..	0 (0 to 2)	0 (0 to 2)	..
Effect of venous line on mobility	0 (0 to 2)	0 (0 to 2)	0 (0 to 2)	..	0 (0 to 2)	0 (0 to 2)	..
Satisfaction at catheter removal	9 (8 to 10)	9 (8 to 10)	10 (8 to 10)	–1 (–2 to 0)†	10 (8 to 10)	9 (8 to 10)	1 (0 to 1)†
Skin adverse events							
Minor	16 (2%)	9 (2%)	7 (1%)	1·06 (0·77 to 1·35)	8 (2%)	8 (2%)	0·91 (0·83 to 1·11)
Severe	0	0	0	..	0	0	..
Hospital stay length, days	6 (3 to 11)	6 (3 to 11)	6 (3 to 10)	0 (–1 to 0)†	6 (3 to 11)	6 (3 to 11)	0 (–1 to 0)†

Data are median (IQR), n (%), n/N (%), or [95% CI]. CHG=2% alcoholic chlorhexidine. PVI=5% alcoholic povidone iodine. Complications are described twice, once in the antiseptic groups columns and once in the device groups columns. *Only 846 catheter tips were cultured. †These are adjusted mean difference.

Table 3: **Secondary outcomes**

enrolled 1000 (figure 1). 250 patients were randomly assigned to each study group. Five patients (one [<1%] in the chlorhexidine plus alcohol and standard device group and four [2%] in the povidone iodine plus alcohol and standard device group) withdrew consent and were excluded from the analyses. Baseline characteristics of the remaining 995 patients (250 in the chlorhexidine plus alcohol and innovation devices group, 249 in the chlorhexidine plus alcohol and standard devices group, 250 in the povidone iodine plus alcohol and innovation devices group and 246 in the povidone iodine plus alcohol and standard devices group) were similar in the four study groups (table 1; appendix 2 p 7). Failure to insert peripheral venous catheters was observed in six patients (three [1%] in the chlorhexidine plus alcohol and innovation devices group and three [1%] in the povidone iodine plus alcohol and innovation devices group). In total, 989 peripheral venous catheters were available to assess primary outcomes. Characteristics of catheters were similar for the four study groups (table 2). We cultured 846 (86%) of the 989 catheters. 756 (76%) patients had their follow-up visit 24 h after catheter removal and 677 (69%) at 48 h. None of the patients who were not fully followed up revisited the emergency department for a catheter-related complication.

The OR of the interaction term between the two study interventions (antiseptic agent and type of device) and incidence of infectious complications or complications leading to catheter failure was 1·69 (95% CI 0·90–3·20). The results for comparison between the two antiseptics were not affected by the type of devices, nor were the results for comparison between standard and innovative devices affected by the type of antiseptic.

We identified six local infections and 74 (9%) colonised catheters. Local infection and catheter colonisation occurred in four cases in the same patient. Local infections (0 [0%] of 496 patients *vs* six [1%] of 493 patients; table 3; appendix 2 p 8) and catheter colonisation (four [1%] of 431 patients *vs* 70 [17%] of 415 patients among the 846 catheters cultured; table 3; appendix 2 p 8) occurred less frequently with chlorhexidine plus alcohol than with povidone iodine

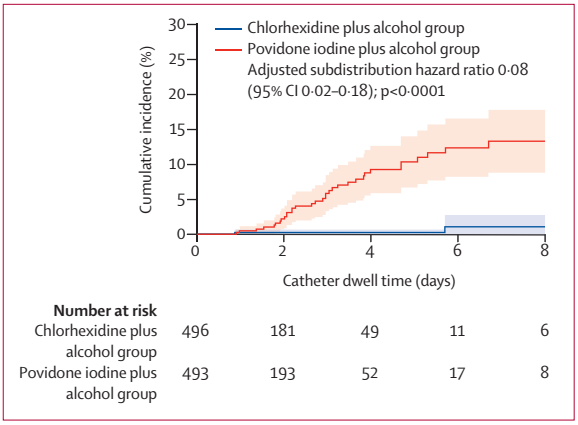

Figure 2: **Cumulative incidence and adjusted subdistribution hazard ratio for catheter-related infectious complications by antiseptic group allocation**

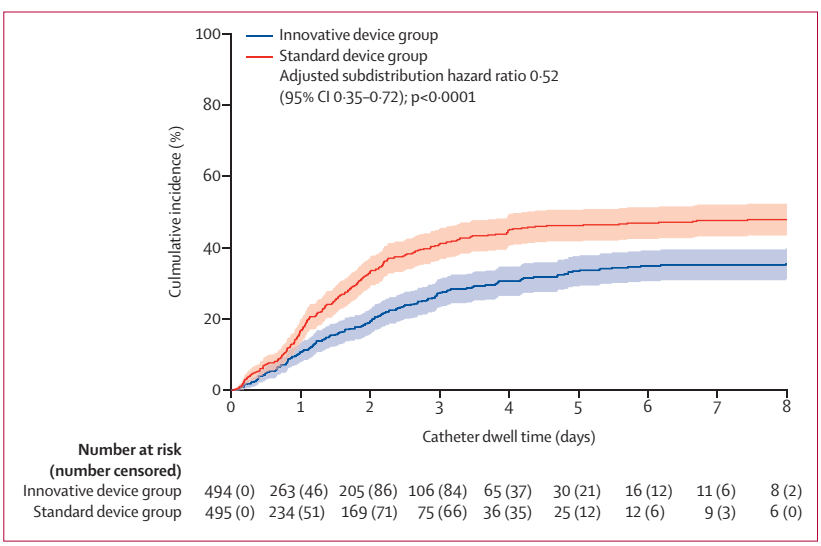

Figure 3: **Cumulative incidence and adjusted subdistribution hazard ratio for catheter removal due to catheter failure by device group allocation**

plus alcohol (adjusted subdistribution HR 0·08 [95% CI 0·02–0·18]; figure 2), with similar effects on Gram-positive and Gram-negative organisms (appendix 2 p 9). Adjusted probability of catheter-related infectious complications for the four study groups provided similar findings (appendix 2 p 10). No catheter-related bloodstream infection was reported in either of the two antiseptic groups.

407 catheters (41%) failed before the end of treatment. Catheter failure occurred less frequently in the innovation group than in the standard group (172 [35%] of 494 catheters *vs* 235 [48%] of 495 catheters; absolute risk difference –12·7% [95% CI –18·7 to –6·6%]; adjusted subdistribution HR 0·52 [95% CI 0·35 to 0·72]; figure 3). Use of innovative devices reduced catheter occlusion (20 [4%] *vs* 44 [9%]) and dislodgment (67 [14%] *vs* 94 [19%]), but not infiltration (71 [14%] *vs* 82 [17%]), phlebitis (12 [2%] *vs* 12 [2%]), and local infection (two [<1%] *vs* four [1%]; table 3; appendix 2 p 11). Adjusted probability of catheter failure for the four study groups provided similar findings (appendix 2 p 10). Median [IQR] time between catheter insertion and catheter failure (50·4 [29·6 to 69·4] *vs* 30·0 [16·6 to 52·6] h; p=0·0017) was longer in patients assigned to the innovative group compared with those assigned to the standard group.

Incidence of all-causes bloodstream infections and length of stay in hospital were not affected by the choice of antiseptic agent or type of device (table 3). Effect of the venous line on mobility was rated as low by patients and their overall satisfaction upon catheter removal was very high, both of which were also unaffected by the choice of antiseptic agent or type of device (table 3).

No systemic or severe local adverse reactions to any antiseptic solution occurred. Minor skin reactions were uncommon (16 [2%] events), without any significant difference between chlorhexidine plus alcohol and povidone iodine plus alcohol (table 3). No adverse reactions related to the use of medical devices were reported.

When excluded patients of the chlorhexidine plus alcohol group (four [1%]) were considered to have catheter-related infectious complications and those of the povidone iodine plus alcohol group (seven [1%]) were not, the risk of infectious complications (eight [2%] of 500 *vs* 72 [14%] of 500 catheters, absolute difference –12·8% [95% CI –16·1% to –9·5%]) remained lower in patients assigned to the chlorhexidine plus alcohol group than in patients assigned to the povidone iodine plus alcohol group. Similarly, when excluded patients of the innovation group (six [1%]) were considered to have catheter failure and those of the standard group (five [1%]) were not, the risk of catheter failure (178 [36%] of 500 *vs* 235 [47%] of 500 catheters, absolute difference –11·4% [95% CI –17·5% to –5·3%]) remained lower in patients assigned to the innovation group than in patients assigned to the standard group.

Discussion

We report the first large-scale study comparing the efficacy of two antiseptics for the prevention of infectious complications related to the use of peripheral venous catheters, and two types of venous lines for the prevention of complications leading to catheter failure. Use of 2% chlorhexidine plus alcohol for skin antisepsis instead of 5% povidone iodine plus alcohol reduced the risk of catheter colonisation and local infection. Use of innovative solutions including closed integrated catheters, positive displacement needleless-connectors, disinfecting caps and prefilled syringes for flushing extended the catheters complication-free dwell time. Tolerance to antiseptics was excellent, with only rare minor skin reactions reported, without any difference between the two solutions.

We chose a composite criterion combining catheter colonisation, local infection, and catheter-related bloodstream

infection to compare the efficacy of antiseptics in preventing infectious complications. Incidence of catheter-related bloodstream infection alone might have been a more clinically relevant outcome, but it is so rare, equal to 0·18% among 85 063 peripheral venous catheters from the available literature,[19] that several thousand catheters would have been required to show a benefit. No catheter-related bloodstream infection was reported in our study despite the inclusion of nearly 1000 catheters. Catheter colonisation, which precedes catheter infection, is more frequent and has long been considered an acceptable substitute for catheter-related bloodstream infection,[20] although this has been questioned recently for central venous catheters.[21] The inclusion of local infections, a more frequent event than catheter-related bloodstream infection, reinforces the clinical relevance of our composite criterion.

Very few studies have focused on the choice of the best antiseptic for skin preparation before peripheral venous catheter insertion. Although the benefit of combining chlorhexidine with alcohol over alcohol alone has been suggested by one small-scale study,[22] the best compound to combine with alcohol remained unknown before our study was started. French[5] and English[6] recommendations in favour of 2% chlorhexidine plus alcohol were based on findings of the CLEAN study carried out on central venous and arterial catheters in critically ill patients.[7] Our study confirms the superiority of chlorhexidine plus alcohol over povidone iodine plus alcohol in reducing both catheter colonisation and local infection, and warrants recommendation of 2% chlorhexidine plus alcohol as the preferred antiseptic for short-term peripheral venous catheter insertion and care. The superiority of chlorhexidine plus alcohol has been associated with long-term antimicrobial suppressive activity of chlorhexidine and the inactivation of povidone iodine by blood and other protein-rich biomaterials present on skin,[23,24] even though the latter point has been challenged.[25]

The high incidence and clinical and economic consequences of catheter failure warranted the addition of a second primary outcome. 41% of catheters in our study failed before the end of treatment, which is in agreement with the 43% of catheter failures reported in previous randomised-controlled trials.[2] Although some events (dislodgment and occlusion) have a universal definition, others (phlebitis and infiltration) have a non-universal definition, rendering comparison between studies problematic sometimes. The number of catheter dislodgments observed in our study was two-times higher compared with previous studies.[2] This result might be due to some extent to the inclusion of an older population at high risk of developing neurological disorders during hospitalisation.

Innovative devices have been developed recently to decrease catheter complications and increase functional dwell time, but few studies have evaluated their benefit in clinical situations. One randomised trial compared 584 integrated peripheral venous catheters (preassembled systems containing the catheter and extension tubing incorporated as one piece, and with a flatter hub profile resting against the skin surface) with 599 standard peripheral venous catheters (separate components needing to be attached, with a rounded hub profile against the skin).[9] The integrated group had fewer non-infectious complications (RR 0·64; 95% CI 0·47–0·88), leading to longer median functional dwell time and substantially reduced associated costs. In one quasi-experimental monocentre study, phlebitis rate (7% *vs* 60%; p<0·001) was lower in 169 peripheral venous catheters after introduction of needleless-connectors than in 620 peripheral venous catheters using regular caps.[26] Absence of randomisation and an unusually high rate of phlebitis in the baseline period make the findings questionable. Another quasi-experimental monocentre study showed a 43% reduction in bloodstream infections after introduction of disinfecting caps in a hospital with 630 beds.[10] The absence of randomisation and of significant statistical difference despite the long duration of the two study periods (21 months) precludes any conclusion. Although flushing peripheral venous catheters with saline solutions has the capacity to maintain catheter patency longer, use of manually filled syringes could be a barrier to regular flushing. In one quasi-experimental multicentre study involving 3853 peripheral venous catheters, introduction of pre-filled flushing syringes was associated with a decrease in peripheral venous catheter failure rate (57% *vs* 43%; p<0·0001).[11] Absence of randomisation and change in the catheter type used in a participating hospital between the two study periods can make the study hard to interpret.

Our randomised study is the first adequately designed to evaluate different innovative devices that have shown potential benefit in reducing catheter failure. Compared with standard devices, use of innovative devices in combination reduced the RR of catheter failure by 27%, resulting in longer catheter dwell time without complications. The benefit of the combination became clear from the second day of use (figure 3), suggesting that these devices should be restricted to patients requiring a vascular access for more than 24 h. This advantage was significant on catheter occlusion and catheter dislodgment, but not on infiltration and phlebitis. These latter results could be explained by an absence of power of the study, but also by the fact that almost all dislodgments were accidental catheter removal by the patients. Of note, the number of catheter occlusions was lower in the innovation group despite the fact that only catheters in the standard group were routinely continuously infused.

Reasons for the superiority of the combination of innovative devices are probably multifactorial. Integrated peripheral venous catheters reduce pressures on the vein and movement of the catheter body against the inner wall of the vein, which occurs when nurses manipulate the

catheter, or when additional fluid tubing or direct injections are made through the dedicated port.[27] Decreasing pressure on the vein and catheter movements is key to reducing irritation of the tunica intima of the vessels, which in turn can reduce infiltration, occlusion, or phlebitis. Flushing the catheter before and after drug administration contributes to maintaining the catheter patency in several ways: reduction of contact between incompatible drugs or fluids, limitation of the risk of thrombosis and phlebitis, and reduction of fibrin accumulation in the internal lumen of the catheter, reducing the risk of thrombosis, and bacterial colonisation.[11] Use of pre-filled syringes has the advantage of increasing flushing compliance by making it easier to administer to patients, which saves nursing time and reduces the risk of bacterial contamination.

Adverse events of both antiseptic solutions were rare and similar in both frequency and severity in our study. Minor skin reactions occurred in nine [2%] of 496 of patients assigned to chlorhexidine plus alcohol and in seven [1%] of 493 patients assigned to povidone iodine plus alcohol, ten-times lower than those reported with the same antiseptics in patients who were critically ill.[7] No severe skin reaction was reported in our study, although the complication was noted in 3% of patients assigned to chlorhexidine plus alcohol and in 1% of patients assigned to povidone iodine plus alcohol in critically ill patients.[7] Greater severity of the disease and a three-times longer duration of exposure of the skin to antiseptics in patients who were critically ill might explain these differences. No adverse event related to use of the devices was reported. Six [1%] closed integrated catheter insertions failed. Limited acquisition of the insertion technique notwithstanding training of the teams before starting the study could explain these observations, as suggested by the time of occurrence, all during the first half of the study.

Patient satisfaction was high overall, with no differences between study groups. These observations might be explained by the inclusion of patients at the beginning of hospitalisation, a period during which patients have little mobility due to their health condition, and by their difficulty in perceiving the benefit of the innovative approach in the absence of a concomitant standard approach.

Our study had several limitations. First, not all eligible patients were enrolled in the trial; indeed, emergency departments had strain periods not suitable for the inclusion of patients in studies. Second, blinding was not possible because the two antiseptics differed in colour and the medical devices were easily recognisable. However, the microbiologists and statisticians were masked from the treatment group, and outcomes were based on strict definitions. Third, patients requiring surgery were excluded from the study to limit biases related to the higher risk of complications during patient transfers to the operating room. Fourth, results were not adjusted for nurses who inserted the catheters. However, only nurses with experience (≥50 peripheral venous catheter insertions) participated in the trial. Fifth, as assumed, no significant interaction was found between the the two study interventions (antiseptics comparisons and devices comparisons). Despite the relatively high number of catheters included, including the 30% increase in their estimated amount, an influence of the type of antiseptic solution used on the comparison of devices, or of the type of devices used on the comparison of skin antiseptics cannot be totally excluded. Sixth, despite the daily presence of research nurses in the wards, it was not possible to ensure full compliance with the protocol. Nevertheless, any mistake, such as the no flushing before or after each fluid or medication administration, would have rather disadvantaged the innovation group. Seventh, because the innovation group was analysed as a whole, it is impossible to know whether all components of the combination are useful or not. We have chosen to compare the approach currently recommended in France to a set of innovations for which a synergistic benefit might be anticipated. Finally, it is not clear from the study whether the use of innovative devices is cost-effective. A study should be carried out to compare the additional costs of innovative devices with those related to the treatment of catheter complications and catheter replacement.

The strengths of our study include the participation of nearly all medical wards of our hospital, the study design, including randomisation, the high number of catheters included, the training of all health-care personnel in the use of medical devices before initiating inclusion, and the availability of clinical research nurses to ensure compliance with the protocol 7 days a week. Most medical patients requiring admission in the wards were included. Patients requiring catheter placement in extreme emergency were excluded given the risk of non-compliance with recommended hygiene procedures. Therefore, we believe that our results can be extrapolated to all adult patients admitted to a medical ward and requiring peripheral venous catheter placement and, by extrapolation, to those admitted to a surgical ward.

In conclusion, use of 2% alcoholic chlorhexidine should become the first-line antiseptic for skin disinfection before insertion of a short-term peripheral venous catheter. Use of closed integrated catheters, positive displacement needleless-connectors, disinfecting caps, and pre-filled flush syringes should be the rule when expected catheter dwell time exceeds 24 h. Further studies are needed to identify the most cost-effective components of the combination.

Contributors

JG, BD, RON, and OM led the trial. All the investigators mentioned as coauthors collected the data. JP and DF did the statistical analysis and were masked for group assignment. OM, JG, and DF wrote the Article.

Declaration of interests

OM received funding for congress attendance, and research funding from Becton Dickinson. MB received personal fees from Becton Dickinson. All other investigators declare no competing interests.

Data sharing

Individual participant data will not be available directly to external users but will be available after de-identification to researchers who provide a methodologically sound proposal, 3 months following article publication and up to 5 years later. Proposals should be sent to olivier.mimoz@chu-poitiers.fr.

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