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Needleless connector decontamination for prevention of central venous access device infection: a pilot randomized controlled trial

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SUMMARY

Pilot randomized controlled trial (180 patients) of needleless connector decontamination. Central line-associated bloodstream infection occurred in 2% (1/61) of 70% isopropyl alcohol (IPA) wipe, 2% (1/59) of 70% IPA cap, and zero (0/58) infections in 2% chlorhexidine gluconate in 70% IPA wipe patients. Larger definitive trials are feasible and needed.

KEY WORDS: Randomized controlled trial; Catheterization, Central Venous; Catheter Related Infections; Bacteremia; Chlorhexidine Gluconate; Isopropyl Alcohol

BACKGROUND

Central venous access devices (CVADs) risk central line-associated bloodstream infection (CLABSI) which increase costs, morbidity and mortality.[1] The intraluminal infection source can be minimized by needleless connector (NC) decontamination prior to each use using chlorhexidine gluconate (CHG), povidone-iodine, or 70% isopropyl alcohol (IPA).[1] The optimal antiseptic is unknown, although povidone-iodine's slow dry-time presents challenges in clinical practice.[2] Combination CHG/IPA wipes,[3, 4] or IPA in a cap format[5, 6] may be superior to traditional intermittent 70% IPA wipes, but no randomized controlled trials (RCTs) have been completed. Our aim was to generate feasibility and pilot data comparing 70% IPA wipes, 2% CHG in 70% IPA wipes, and 70% IPA caps.

MATERIALS AND METHODS

Setting and study design: Three-arm pilot RCT at the Royal Brisbane and Women's Hospital and Gold Coast University Hospital in Australia. We had University and Hospital Ethics Committees approval (2016/410; HREC/15/QRBW/553) and Australian New Zealand Clinical Trials Registry registration: 12615001120561. The four-week intervention had follow-up until 48 hours post study completion, hospital discharge or device removal. We surveyed registered nurses (RNs) for protocol compliance and satisfaction.

Participants and sample size: Eligibility criteria: ≥18 years of age; CVAD (peripherally inserted central catheter [PICC] or tunneled, cuffed CVAD) inserted <24 hours; CVAD required for ≥7 days; and written consent. Exclusions: baseline bloodstream infection, non-English speaking without interpreter, or previous enrolment. Research nurses (ReNs) screened daily,

gave trial information, and obtained consent. The target was 60 per group (one CVAD per patient) with recruitment 31 July 2017 to 5 April 2019.[7]

Randomization and blinding: Centralized, computer-generated randomization (https://randomisation.griffith.edu.au) using randomly varying permuted blocks of 3 and 6 (1:1:1 ratio): (i) 70% IPA wipes, (ii) 2% CHG in 70% IPA wipes, or (iii) 70% IPA caps. Clinical outcome assessors and data analysts were masked.

Interventions:

- 70% IPA wipes: 0.6 ml *Alcohol Prep Pads* (Reynard, New Zealand) applied vigorously to NC for 5 seconds (manufacturer recommended and hospital policy), visibly dry prior to CVAD access;
- 2% CHG in 70% IPA wipes: 0.6 ml *Alcohol and CHG Prep Pads* (Reynard, New Zealand), applied vigorously to NC for 15 seconds (guideline recommendation[8]), visibly dry prior to CVAD access;
- 70% IPA cap*: Luer access valve cap Swabcap*® (ICU Medical, San Clemente) screwed onto NCs for minimum 5 minutes (manufacturer-recommended) prior to each access, then replaced with a new cap.

NCs were Smartsite® Needle-Free Valve or Max Plus® (both Carefusion/BD, San Diego), attached to the CVAD hubs and all entry points of infusion systems.

ReNs provided education (clinical staff undertook the intervention) and visited twice weekly to collect data, supply products, and reinforce the protocol. Decisions to culture blood/CVAD tips, or remove CVADs were made by medical staff (not investigators).

Primary outcome(s): Protocol feasibility was assessed as: (i) eligibility, (ii) retention and attrition, (iii) protocol adherence, (iv) missing data, and (v) RN satisfaction.

Secondary outcome(s):

(i) *Central line-associated bloodstream infection (CLABSI)*[9] (2018 National Health and Safety Network definition) assessed by masked infectious diseases specialist (EGP);

(ii) *Mortality* (all-cause) during trial;

(iii) *Primary bloodstream infection* (laboratory confirmed bloodstream infection);[9]

(iv) *CVAD (tip) colonization* (≥15 colony-forming units, semi-quantitative culture).[1]

Adverse events: We captured all potentially intervention-related events, and all-cause intensive care unit (ICU) admission (serious adverse event).

Statistical analysis: Research Electronic Data Capture (REDCap, Nashville, TN) and Stata 15 (College Station, TX) were used. Feasibility outcomes were analyzed against predetermined criteria (>80% of screened patients eligible and >80% eligible patients recruited; ≥95% retention and attrition (not withdrawn/lost to follow-up); >90% study visits with correct products in use, and self-reported RN adherence to application/dry times; 5% missing data (CLABSI endpoint); RN satisfaction on 1-10 numerical rating scale.

Clinical outcomes were compared using Fisher's exact and log-rank tests, incidence rates and Kaplan-Meier survival estimates ($p<0.05$ statistically significant; patients censored at discharge). A modified intention-to-treat analysis excluded only randomized patients who never received a CVAD.

RESULTS

Patient/device characteristics are presented in Table 1 and supplementary Table 1. Average CVAD dwell-times were 11.3, 9.3, and 7.4 days in the 70% IPA, 2% CHG in 70% IPA, and 70% IPA cap groups respectively.

Table 1. Participant (N=180) and device (N=178) characteristics at baseline

	70% IPA	2% CHG in 70% IPA	70% IPA cap	Total
Participants per study groups[a]	61 (34)	59 (33)	60 (33)	180 (100)
Age (years)[b]	61 (50-67)	60 (47-67)	63 (50-72)	61 (50-70)
Sex: male	31 (51)	28 (47)	37 (62)	96 (53)
Cancer treatment[c]	19 (31)	18 (31)	17 (28)	54 (30)
Admission type:				
- surgical	47 (77)	46 (78)	49 (82)	142 (79)
- haematology	12 (20)	10 (17)	10 (17)	32 (18)
- medical	1 (2)	3 (5)	1 (2)	5 (3)
- medical oncology	1 (2)	0 (0)	0 (0)	1 (1)
Comorbidities:				
- nil or one	17 (28)	17 (29)	16 (27)	50 (28)
- two or three	20 (33)	16 (27)	20 (33)	56 (31)
- four or more	24 (39)	26 (44)	24 (40)	74 (41)
Leucocytes[d] <500/µl (n=179)	5 (8)	5 (9)	5 (8)	15 (8)
Pre-existing infection	27 (44)	32 (54)	34 (57)	93 (52)

	70% IPA	2% CHG in 70% IPA	70% IPA cap	Total
Devices by study groups[a]	61 (34)	58 (33)	59 (33)	178 (100)
Device type:				
- PICC	57 (93)	54 (93)	56 (95)	167 (94)
- TC	4 (7)	4 (7)	3 (5)	11 (6)
No. of lumens:				
- one	16 (26)	21 (36)	20 (34)	57 (32)
- two	45 (74)	37 (64)	39 (66)	121 (68)
Location:				
- upper arm	57 (93)	54 (93)	56 (95)	167 (94)
- chest	4 (7)	4 (7)	3 (5)	11 (6)
IV Medications:				
- antibiotics	43 (70)	39 (67)	42 (71)	124 (75)
- fluids	24 (39)	25 (43)	21 (36)	70 (39)
- blood product	9 (15)	13 (22)	5 (8)	27 (15)
- antiemetic	9 (15)	7 (12)	9 (15)	25 (14)
- parenteral nutrition	12 (20)	6 (10)	6 (10)	24 (13)
- potassium chloride	6 (10)	6 (10)	4 (7)	16 (9)
- chemotherapy	4 (7)	5 (9)	5 (8)	14 8)
- antifungal/antiviral	4 (7)	1 (2)	2 (3)	7 (4)
- other medication	29 (48)	25 (43)	17 (29)	71 (40)
No medications (fluids only)	5 (8)	6 (10)	7 (12)	18 (10)

frequencies and column percentages shown unless otherwise noted; [a] row percentage shown; [b] median and inter-quartile range (25th and 75th percentiles) shown; [c] in previous 6 months; [d] absolute, within 72 hours of trial entry.

Primary outcomes: Seventy percent (211/303) of screened patients were eligible and 85% (180/211) were randomized (31 declined, missed, or had CHG allergy; figure 1). Two patients were excluded post-randomization due to CVAD insertion failure. There was 100% retention, 0% attrition, and 0% missing CLABSI endpoints (figure 1). Thus, 178 patients were analyzed.

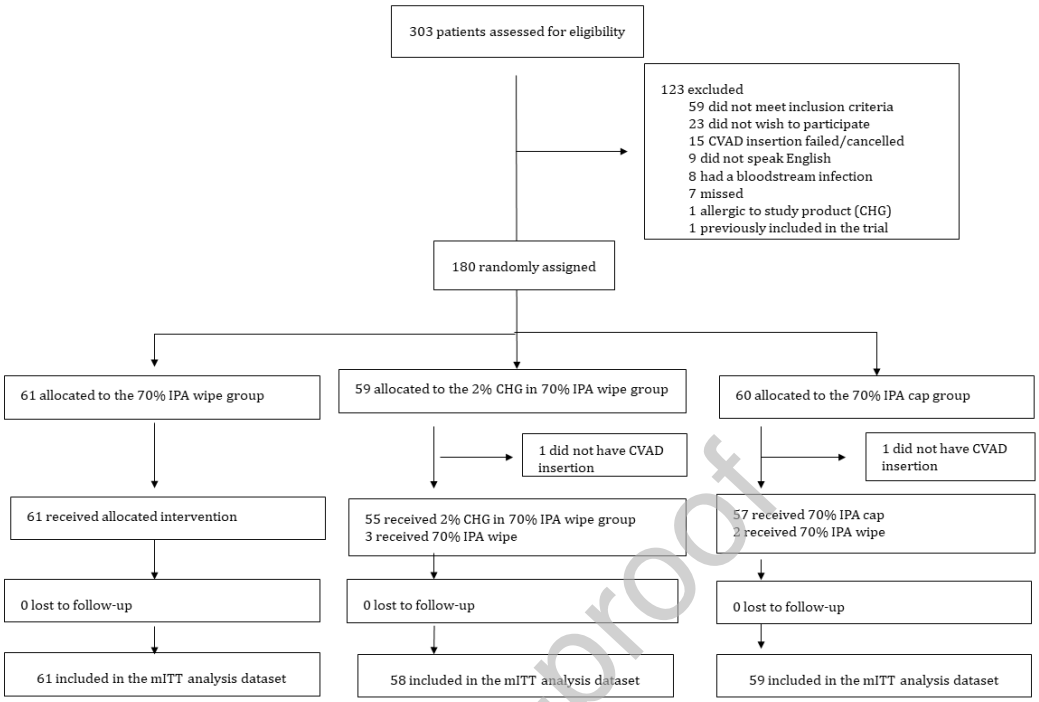

Figure 1. CONSORT flowchart (CVAD = central venous access device, CHG = chlorhexidine gluconate, IPA = isopropyl alcohol, mITT = modified intention-to-treat).

Observed protocol adherence was 98% (174/178); all but three 2% CHG in 70% IPA wipe and two 70% IPA cap patients commenced the correct intervention. 70% IPA wipe patients had no protocol deviations. At least one incorrect product use occurred in 5% (3/58) 2% CHG in 70% IPA, and 10% (6/59) 70% IPA cap patients.

Of 35 RNs (40 surveyed, response rate 88%), protocol-adherent scrub times were reported by 31 (89%) for 70% IPA wipe, and 26 (74%) for 2% CHG in 70% IPA wipe. Median satisfaction was

9 (interquartile range: 2), 10 (2), and 9 (2) for 70% IPA wipes, 2% CHG in 70% IPA wipes, and 70% IPA caps, respectively (N=22 for 70% IPA caps; not all RNs had used these).

Secondary outcomes:

CLABSI occurred in 1/61 (2%) 70% IPA wipe, 0/58 (0%) 2% CHG in 70% IPA wipe, and 1/59 (2%) 70% IPA cap patients (p=1.0, figure 2). CLABSI incidence per 1,000 catheter-days was 1.38 (95% confidence interval [CI]: 0.19–9.81), nil (no outcomes), and 1.70 (95% CI: 0.24–12.1) for 70% IPA wipes, 2% CHG in 70% IPA wipes, and 70% IPA caps respectively (p=0.637).

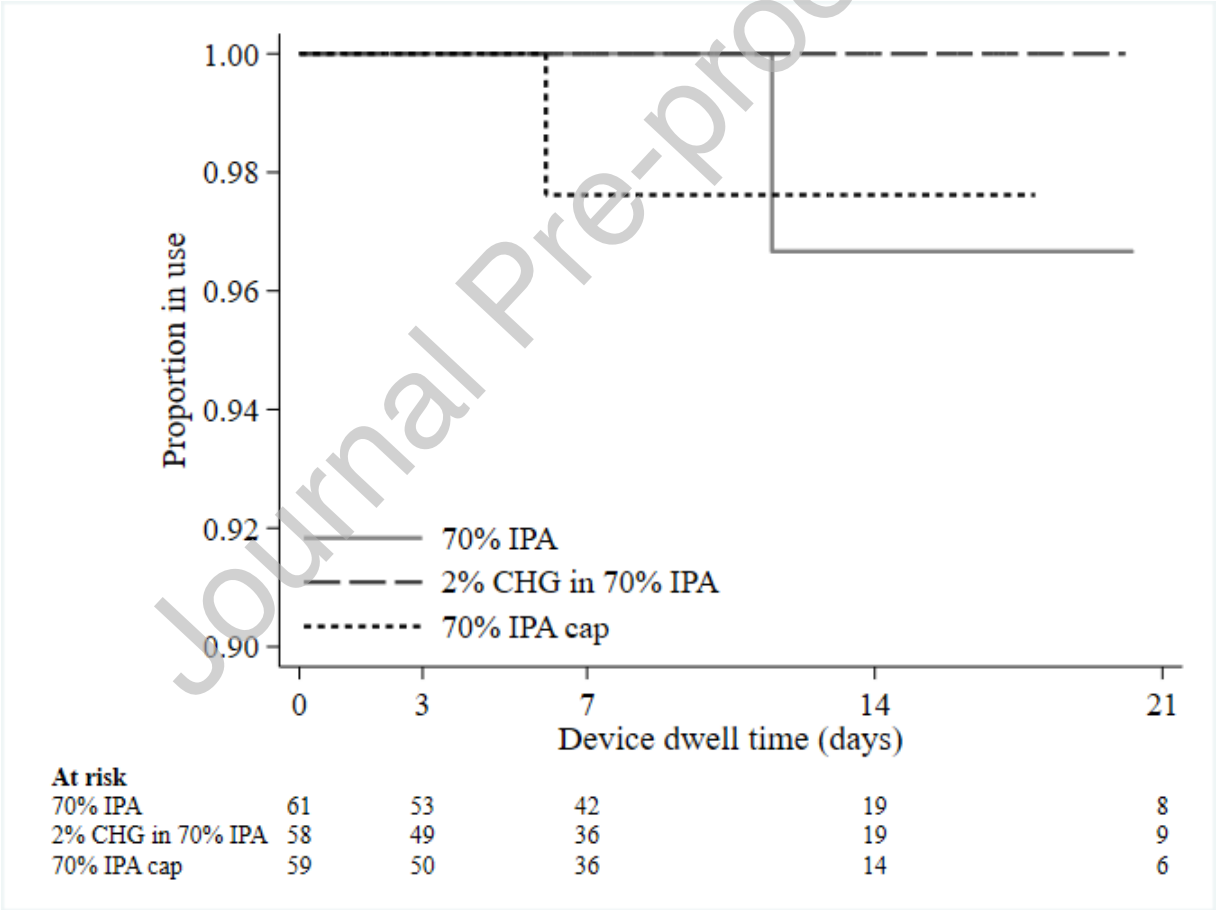

Figure 2. Kaplan-Meier survival estimates for central line-associated bloodstream infection by study groups (A = 70% IPA wipe group, B = 2% CHG in 70% IPA wipe group, C = 70% IPA cap group)

Primary bloodstream infections occurred in 2/61 (3%) 70% IPA wipe, 2/58 (3%) CHG in 70% IPA wipe (one of these was a mucosal barrier infection), and 1/59 (2%) 70% IPA cap patients. There were no deaths and no positive catheter tips (N=10 cultured).

Adverse events: Two 70% IPA cap NCs became opaque (IPA appeared to seep between the rubber inner and outer plastic, denaturing the plastic but with no effect on patients). Four patients required transfer to ICU for unrelated reasons (n=3, 70% IPA wipe; n=1 70% IPA cap).

DISCUSSION

NC decontamination is a high-volume, high-value practice that urgently needs high-quality evidence to prevent CLABSI. This pilot RCT confirms the feasibility of large RCTs, with acceptable recruitment, protocol adherence, and RN satisfaction, as well as high retention, low attrition and no missing data. Eligibility at 70% could be improved with amplified research nurse availability at device insertion to promote recruitment.

CLABSI incidence was low in both groups using 70% IPA, and zero when this antiseptic was combined with CHG. These results are consistent with laboratory data ,[3] and a large RCT on pre-CVAD insertion skin decontamination which both favoured combination CHG and IPA[10]]; a larger RCT would be needed to substantiate these findings in NCs. Although scrub times differed (15 seconds for 2% CHG in 70% IPA wipe as per guidelines[8], and 5 seconds for 70% IPA wipes as per manufacturers and hospital policy), recent data indicates no difference in effectiveness with 5, 10, or 15 second scrub times.[4]

CLABSI was infrequent, however as >50% were patients were discharged during follow-up, future RCTs should study the entire CVAD dwell (including home care) to ensure adequate sample size to test hypotheses and generalizability. Nevertheless, our CLABSI of approximately 1 per 1,000 catheter-days, is similar to reported USA rates, but may not be generalizable where rates are higher.[11] Despite low frequency, CLABSI remains the most appropriate outcome to assess NC disinfection efficacy. Other methods such as routine CVAD tip culture have poor positive predictive value.[12]

Insertion bundles have reduced CLABSI, with focus now needed on techniques to prevent post-insertion, intra-luminal bacterial entry. Currently, 70% IPA wipes are dominant due to low cost, availability and rapid drying[2] however the addition of CHG likely increases efficacy,[3, 4] and non-randomized studies support 70% IPA caps.[5, 6] Pilot RCTs are not designed to test statistical differences in outcomes or for the effect of potential confounders or covariates such as NC/device type or patient factors. Large RCTs are needed to examine various modes and strengths of antiseptics, NC materials/designs, and monitor possible new adverse events as solutions are exposed to NCs and potentially the bloodstream.

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FIGURE LEGEND

Figure 1. CONSORT flowchart (CVAD = central venous access device, CHG = chlorhexidine gluconate, IPA = isopropyl alcohol, mITT = modified intention-to-treat)

Figure 2. Kaplan-Meier survival estimates for central line-associated bloodstream infection by study groups (A = 70% IPA wipe group, B = 2% CHG in 70% IPA wipe group, C = 70% IPA cap group)