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Original Article

Comparison of chlorhexidine impregnated dressing and standard dressing for the prevention of central-line associated blood stream infection and colonization in critically ill pediatric patients: A randomized controlled trial

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Abstract

***Background*:** The aim of this study was to compare chlorhexidine gluconate (CHG)-impregnated dressing and standard dressing with respect to the frequency of central-line-associated bloodstream infection (CLABSI), catheter-related bloodstream infection, primary bloodstream infection, and catheter colonization in critically ill pediatric patients with short-term central venous catheters.

***Methods*:** Children who were admitted to the pediatric intensive care unit of a tertiary institution between May 2018 and December 2019 and received placement of a short-term central venous catheter were included in this single-center randomized controlled trial. Patients were grouped according to the type of catheter fixation applied.

***Results*:** A total of 307 patients (151 CHG-impregnated dressing, 156 standard dressing), with 307 catheters (amounting to a collective total of 4,993 catheter days), were included in the study. The CHG-impregnated dressing did not significantly decrease the incidence of CLABSI (6.36 vs 7.59 per 1,000 catheter days; hazard ratio (HR): 0.93, $P = 0.76$), catheter related bloodstream infection (3.82 vs 4.18 per 1,000 catheter days; HR: 0.98; P = 0.98), and primary bloodstream infection (2.54 vs 3.42 catheter days; HR: 0.79; $P = 0.67$). The CHG-impregnated dressing significantly decreased the incidence of catheter colonization (3.82 vs 7.59 per 1,000 catheter days; HR: 0.40; $P = 0.04$). In both groups, the most frequent microorganisms isolated in CLABSI or catheter colonization were Gram-positive bacteria (the majority were coagulase-negative staphylococci).

***Conclusions*:** The use of CHG-impregnated dressing does not decrease CLABSI incidence in critically ill pediatric patients but it significantly reduced catheter colonization. Coagulase-negative staphylococci were the most common microorganisms causing CLABSI or catheter colonization.

Key words central line associated bloodstream infection, central venous catheter, chlorhexidine dressing, colonization, pediatric critical care.

Central venous catheters (CVCs) are instruments that enable long-term vascular access and can be used for a broad range of purposes, especially in intensive care units (ICU). Common indications for CVCs include their use for hemodynamic monitoring, intravenous administration of drugs, parenteral nutrition, fluids or blood products, and blood withdrawal.[1,2] Central venous catheters are placed due to various indications in more than 50% of children admitted to pediatric intensive care units (PICUs).[3]

Despite enabling reliable and safe vascular access in critically ill patients, these devices are associated with central line-associated bloodstream infections (CLABSIs) and catheter-related bloodstream infections (CRBSIs).[4–6] The frequency of CLABSI/CRBSI is reported to range from 0.20 to

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17.6 per 1,000 catheter days, and they have been associated with age, catheter type, insertion site, indications, indwelling time, and underlying disease.[7–10] A higher incidence of CLABSI/CRBSI development increases antibiotic use, prolongs length of hospital stay, and raises healthcare expense, as well as causing high mortality and morbidity.[11–13] Despite successful results with widespread implementation of catheter-care bundles, catheter infections remain an important cause of preventable nosocomial infections in patients requiring ICU management.[14] The practices proposed by catheter-care bundles, which are aimed at preventing CLABSI/CRBSI development, include hand hygiene, optimal catheter site selection, daily evaluation and removal of unnecessary catheters, standardization of procedures and care, maximum barrier precautions during the insertion process, and the use of antibiotic-antiseptic-impregnated CVCs.[15,16]

In recent years, the use of chlorhexidine gluconate (CHG) for catheter infection prevention has drawn interest among clinicians.[17] Chlorhexidine gluconate-impregnated dressings provide local antimicrobial effects through the constant release of CHG at the insertion site. Based on adult studies and meta-analyses, several randomized controlled trials (RCTs) have evaluated and reported the role of CHG-impregnated dressing as a prophylactic measure for CRBSIs and CLABSIs, and have revealed that the use of CHG-impregnated dressing can reduce the risk for catheter colonization and CRBSI/CLABSI.[17–23] However, there are very few studies that have assessed the efficacy of CHG-impregnated dressing in limited numbers of pediatric patients, which have yielded controversial results that appear to be in conflict with adult studies.[24–27] According to the "Guidelines for the Prevention of Intravascular Catheter-Related Infections" published by the Centers for Disease Control (CDC) and Prevention, the use of CHG-impregnated dressing is advised in those older than 18 years; however, its use has not been advised in those younger than 18 years due to the lack of conclusive evidence.[28]

The primary aim of this study was to conduct a randomized controlled study to compare CHG-impregnated dressing and standard dressing in terms of the incidence of CLABSI in critically ill pediatric patients admitted to the PICU who had received treatment with placement of short-term non-tunneled CVC. The secondary aims of the study were: (i) to compare the frequency of CRBSI, primary bloodstream infection (BSI) and catheter colonization in the two groups; (ii) to identify microorganisms causing CLABSI and colonization, and (iii) to determine adverse events (AEs) associated with the use of catheter dressing in this age group.

Methods

Ethics statement

The study was approved by Istanbul Medeniyet University Goztepe Training and Research Hospital Clinical Research Ethics Committee (clinical registry registration 2018/0203). Written informed consent was received from the parents or legal guardians of all study subjects. The study was registered at ClinicalTrials.gov (NCT04794231).

Study design

We used a single-center, randomized controlled and single-blinded study design to compare two types of transparent dressing: (i) standard dressing group (SDG): a standard breathable, hypoallergenic, transparent dressing (Tegaderm™ 1635, 8.5 × 10.5 cm, or 1633, 7 × 8.5 cm depending on patient size; 3 M, Neuss, Germany), and (ii) CHG-impregnated dressing group (CIDG): a CHG-gel impregnated transparent dressing (Tegaderm™ CHG 1660R, 7 × 8.5 cm, or 11.5 × 8.5 cm, depending on patient size; 3 M, Neuss, Germany). The laboratory microbiologist was blinded to the study groups. The two dressings were visibly different and, consequently, it was not possible to blind the patients, PICU staff, or the investigators who collected data in the PICU. If a blood culture or catheter tip culture was positive, another investigator, blinded to the study groups, reviewed the medical records to determine whether the findings could be classified as CLABSI, CRBSI, or catheter colonization.

Study group and randomization

From May 2018 until December 2019, we recruited pediatric patients (1 month to 18 years of age) admitted to our PICU who were expected to require short-term, nontunneled catheterization for at least 48 h. Patients were randomly assigned to one of two dressings, both of which were being used actively as part of standard care. A researcher who had no knowledge of recruiting status, which was independently assessed by the recruiting nurse, prepared a computer-generated randomization table (1:1 ratio), which stratified patients by matching characteristics using a block size of four or eight (random).

Population and setting

Eligibility criteria were being aged age <18 years old, providing informed consent to participate in the study, and requiring the insertion of a short term nontunneled, percutaneously inserted CVC (jugular, subclavian, or femoral) that would remain in place for >48 h during PICU admission. Patients were excluded if they had known allergies to CHG-impregnated or standard dressing, would receive insertion of any other type of CVC device (e.g., peripherally inserted CVC, tunneled CVC), were included in the study previously, had a current BSI (positive blood culture within 48 h), and had received CVC insertion within the 30 days prior to PICU admission. We also excluded patients in which catheterization had not been performed by the PICU specialist, those that were discharged from the PICU with indwelling CVC, patients who received extracorporeal membrane oxygenation, and individuals in which the following events were recorded: accidental catheter removal, CVC removal before 48 h, and death

within 48 h after CVC insertion. In the event that a patient required CVC reinsertion after the initial catheter was removed (for any reason), only the first application was included in the study – given that any other exclusion criteria did not exclude the patient. Finally, if a patient required catheter reinsertion before the completion of the 48 h catheter-infection monitoring of the initial application, the first catheterization was excluded from the study.

Catheters and procedures

Before beginning the study, care bundles and checklists for catheter use and management were prepared according to various guidelines.[6,29] The practices employed as part of the care bundle were as follows: (i) "standards for medication administration through CVCs"; (ii) "management and replacement of infusion sets"; and (iii) "CVC exit site management." Staff training on the care bundle and the use of checklists was conducted prior to study implementation with all nursing staff for a duration of 1 month.

The insertion of the CVC was performed according to the recommendations of the CDC, and maximal sterile barrier precautions were taken by the clinician who performed the procedure (use of cap, mask, sterile gloves, large sterile drape, gown, and surgical hand antisepsis).[6] In line with hospital policy, the CVC insertion site was cleaned with 2% CHG in 70% isopropyl alcohol (Opakjel 2-70, Istanbul, Turkey), and was allowed to dry before insertion.

Short-term nontunneled CVC sizes were based on patient weight and age. We used 4 Fr double lumen or 5.5 Fr triple lumen or 7 Fr triple lumen catheters (Alifatic polyuretane catheter, Plastimed, Seldiflex, 5 Fr - 2 Lumen/5,5 Fr - 3 Lumen/7 Fr – 3 Lumen, Le Plessis Bouchard, France). Antiseptic- or antibiotic-impregnated catheters were not used in any of the patients. Dressings were changed 24 h after catheter insertion (Day 1) then every 7 days according to standard practice in our PICU. Leaking, soiled, loosened and damp dressings were changed immediately. During dressing changes, the catheter insertion site was cleaned using a sterile gauze and a 2% CHG-alcohol preparation.

Patients were followed until 48 h after PICU discharge. Catheters were removed if there was no further need for catheterization, in the event that the patient had infection-related findings, given that any source other than the catheter could not be identified, in the presence of findings associated with exit-site infection, and in the event of discharge from the hospital or death.

Culture assessment

When a patient was suspected to have CLABSI or CRBSI, two samples for blood culture were withdrawn simultaneously from the catheter and a peripheric vein. The volume of blood to be withdrawn from each patient was based on the age-appropriate values described by the Infectious Diseases Society of America (IDSA).[30] Peripheral venous and catheter samples were inoculated into BACT/ALERT® PF/FA Plus (bioMerieux, Inc., Durham, USA) blood culture bottles and sent to the microbiology laboratory in a fashion that ensured blinded evaluation by the microbiology specialist. In the presence of recurring fever peaks, samples for blood culture were obtained on at least two separate occasions within 24 h. If there was growth in the blood cultures, we assessed the timing of growth signals in the catheter sample and the peripheric blood sample. In patients where the catheter was scheduled for removal, two sets of blood culture samples, one from a peripheral site and one from the catheter, were obtained immediately before removal. After the skin was cleaned with 2% CHG-alcohol to prevent contamination of the catheter tip by microorganisms on the skin, the 2 cm tip of the catheter was removed and sent to the microbiology laboratory along with the blood samples.

Data collection

The following patient data were collected: demographics, Pediatric Risk of Mortality III (PRISM III) score, percentage predicted death rate (%PDR), primary reason for PICU admission, presence of comorbidity and/or immunosuppression, need for mechanical ventilation (MV), steroid use, hemodialysis catheter use, renal replacement and/or plasmapheresis treatment, length of stay (LOS) at PICU, and survival.

The following data about catheter characteristics were collected: total duration of catheter days, time in place, catheter insertion time, transport out of the PICU with catheter in place, use of antimicrobial treatment at catheter insertion, catheterization site and lumen count, medications applied via the catheter (vasopressor, parenteral nutrition, blood product transfusion, heparin), number of dressing changes, number of unplanned dressing changes, and reasons for catheter removal. Finally, we also recorded infection-related data (CLABSI, CRBSI, primary BSI, catheter colonization, and microbiological results) and catheter-related AEs.

Definitions and outcome measures

The primary outcome measure was the incidence of CLABSI, CRBSI, primary BSI, and catheter colonization for CHG-impregnated dressing versus standard dressing. Microbiological results and AEs were the secondary outcome criteria compared between CHG-impregnated dressings and standard dressings. These incidences were defined per 1,000 catheter days. Catheter infections including CLABSI, CRBSI, primary BSI, and catheter colonization were identified according to National Healthcare Safety Network (NHSN) and IDSA criteria.[4,5] For this study, the definitions of catheter-related infections were assessed and categorized as follows:

1. Catheter related bloodstream infection was defined as bacteremia/fungemia in a patient with an intravascular catheter with at least 1 positive blood culture obtained from a peripheral vein sampled immediately before or within

48 h after catheter removal, clinical manifestations of infections (i.e., fever, chills, and/or hypotension), and no apparent source for the BSI except the catheter given that at least one of the following was present: (i) a positive semiquantitative (>15 colony forming unit (CFU)/catheter segment) or quantitative ($>10^3$ CFU/catheter segment) culture whereby the same organism (species and antibiogram) is isolated from the catheter segment and peripheral blood; (ii) simultaneous quantitative blood cultures with a ≥ 5:1 ratio (CVC versus peripheral); or (iii) differential period of at least 2 h between CVC culture versus peripheral blood culture positivity. If a patient had blood culture positivity for coagulase-negative staphylococci, the identification of the same pulsotype in the CVC and peripheric blood culture samples was required for diagnosis.[4]

2. Central-line-associated bloodstream infection was defined as the presence of either CRBSI or primary BSI.[5]
3. Primary BSI was defined as the presence of a patient with CVC who had (i) at least one positive blood culture, (ii) clinical manifestation of infection (i.e., fever, chills, and/or hypotension), (iii) no apparent source for the BSI except the catheter, and (iv) no positivity in the catheter culture.[5]
4. Catheter colonization was defined as the growth of >15 CFU in catheter tip cultures in the absence of local or systemic signs of infection or lack of growth in the two blood samples, or in the event that the two cultures showed growth of the same microorganism, which was different from the microorganism isolated in the culture of the catheter tip.[4]

Adverse events were classified as systemic and local reactions. Local AEs were described on a standardized form at each dressing change and at catheter removal by a nurse in charge of the patient. The form was based on a dermatitis scoring system developed by the International Contact Dermatitis Research Group.[31]

Statistical analysis

Characteristics of patients, catheters and dressings are described as frequency and percentage or median (interquartile range, IQR) for categorical and continuous variables, respectively, and were compared among treatment groups using the Pearson χ^2 or Mann–Whitney tests, respectively. Categorical variables were assessed by the Fisher's exact test when the expected values were <5. The Kaplan–Meier curves of the risks of CLABSI, CRBSI, primary BSI and catheter colonization were plotted for each treatment group. The design of this factorial study assumed that the two interventions did not interact. This assumption was confirmed by testing for a treatment interaction in the cox model. Analyses were performed using SPSS (IBM Corp., IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY) and R Version 3.6 (R Foundation for Statistical Computing, Version 3.6; Vienna, Austria). $P \leq 0.05$ was considered to demonstrate statistical significance.

Power analysis

Post-hoc power analysis was performed using Power Analysis Sample Size for Windows (PASS) (NCSS Corp. Released 2011, Version 11.0, Utah, USA). The alpha significance level was taken as 5% ($P = 0.05$). The power analysis was calculated based on the frequency of CLABSI in the two groups including 151 patients with CHG-impregnated dressing and 156 patients with standard dressing. The frequency was 5.8% in the CHG-impregnated group and 7.6% in the SDG. As a result of the power analysis calculated in line with these ratios, it was observed that the power of the study was 90%.

Results

Patients and catheter characteristics

A total of 373 patients (out of an eligible count of 430 patients) with non-tunneled CVCs were randomly assigned and allocated. Through the randomization procedure, a total of 185 patients were allocated to the CIDG and 188 patients were allocated to the SDG. Among these, 34 patients from the CIDG and 32 from the SDG were excluded according to exclusion criteria. A final total of 307 patients (151 in the CHG-impregnated dressing group, 156 in the SDG) were available for inclusion in the intention-to-treat analysis with a total of 307 catheters and 4,993 catheter days (Fig. 1). The groups did not differ with regard to patient or CVC characteristics (Tables 1 and 2).

Dressing impregnated with CHG versus standard dressing

The overall CLABSI rate was 11% (35 events, 7.01 per 1,000 catheter-days), the CRBSI rate was 6.3% (20 events, 4.01 per 1,000 catheter days), the primary BSI rate was 4.7% (15 events, 3.00 per 1,000 catheter days), and catheter colonization rate was 9.1% (29 events, 5.81 per 1,000 catheter-days) (Table 3).

The CLABSI rates were 6.36 per 1,000 catheter days in the CIDG and 7.59 per 1,000 catheter days in the SDG. The CLABSI incidence was not different between groups (HR: 0.930; 95% CI: 0.459–1.776; $P = 0.767$) (Fig. 2a).

The CRBSI incidence was 3.82 per 1,000 catheter days in the CIDG and 4.18 per 1,000 catheter days in the SDG. Primary BSI rates were 2.54 per 1,000 catheter days in CHG-impregnated group and 3.42 per 1,000 catheter days in the SDG. There was no statistically significant difference in CRBSI and primary BSI rates between the CHG-impregnated dressing and the SDGs (HR: 0.989; 95% CI: 0.405–2.415; $P = 0.981$ and HR: 0.799; 95% CI: 0.282–2.261; $P = 0.672$, respectively) (Fig. 2b,c).

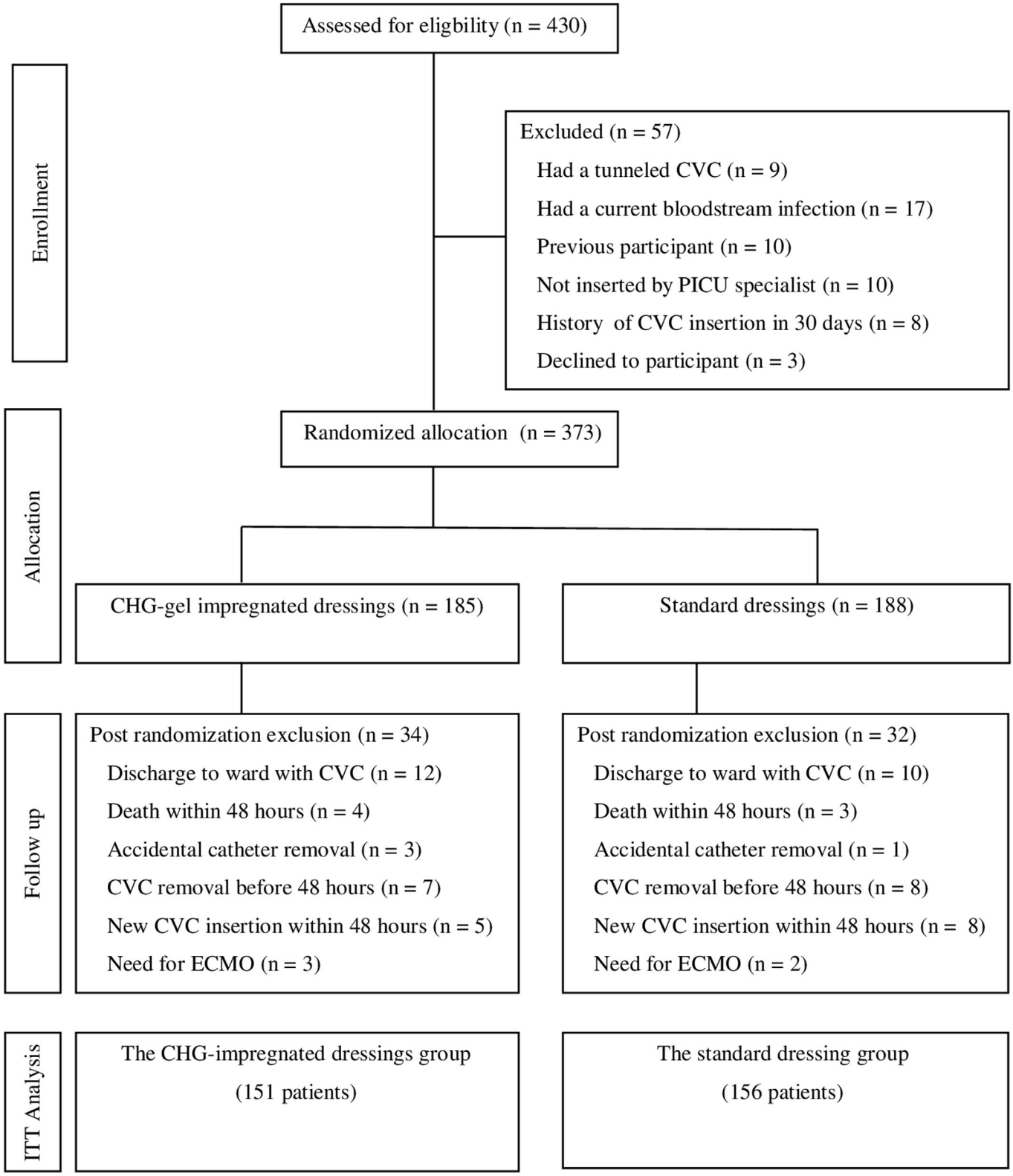

Fig. 1 Flow chart of the study. CVC, central venous catheter; CHG, chlorhexidine gluconate; ECMO, extra corporeal membrane oxygenation; ITT, intention-to-treat; PICU, pediatric intensive care unit.

Table 1 Patient characteristics

Characteristics	All patients (intention to treat) (n = 307)	CHG-impregnated dressing (n = 151)	Standard dressing (n = 156)	P
Age (year), median (IQR)	2.0 (0.8–7.9)	1.7 (0.7–6.8)	2.3 (0.9–8.5)	0.072
Male, n (%)	173 (56.4)	87 (57.6)	86 (55.1)	0.939
PRISM III score, median (IQR)	18.0 (14.0–23.0)	19.0 (14.0–23.0)	18.0 (12.0–24.0)	0.603
% PDR, median (IQR)	25.8 (13.2–49.5)	25.8 (13.2–44.3)	25.8 (9.1–54.6)	0.682
Primary reason for PICU admission, n (%)				
Respiratory disease/failure	92 (30.0)	41 (27.2)	51 (32.7)	0.297
Trauma	52 (16.9)	25 (16.6)	27 (17.3)	0.782
Shock	40 (13.0)	22 (14.6)	18 (11.5)	0.527
Metabolic disease	15 (4.9)	6 (4.0)	9 (5.8)	0.439
Liver failure	6 (2.0)	3 (2.0)	3 (1.9)	1.000
Renal failure	13 (4.2)	8 (5.3)	5 (3.2)	0.405
Poisoning	7 (2.3)	4 (2.6)	3 (1.9)	0.705
Central nervous system disease	51 (16.6)	26 (17.2)	25 (16.0)	0.889
Cardiac disease	6 (2.0)	3 (2.0)	3 (1.9)	1.000
Malignancy	10 (3.3)	5 (3.3)	5 (3.2)	1.000
Postoperative	7 (2.3)	4 (2.6)	3 (1.9)	0.705
Others	8 (2.6)	4 (2.6)	4 (2.6)	1.000
Presence of comorbidity, n (%)	69 (22.5)	29 (19.2)	40 (25.6)	0.185
Presence of immunosuppression, n (%)	19 (6.2)	7 (4.6)	12 (7.7)	0.251
Use of parenteral steroid, n (%)	46 (15.0)	19 (12.6)	27 (17.3)	0.238
Mechanical ventilation, n (%)	202 (65.8)	98 (64.9)	104 (66.7)	0.673
Use of hemodialysis catheter, n (%)	60 (19.5)	28 (18.5)	32 (20.5)	0.606
Renal replacement treatment, n (%)	44 (14.3)	22 (14.6)	22 (14.1)	1.000
Plasmapheresis, n (%)	52 (16.9)	21 (13.9)	31 (19.9)	0.166
Length of PICU stay (days), median (IQR)	12.0 (8.0–22.0)	11.0 (7.0–19.0)	13.0 (8.0–27.0)	0.067
Death within PICU, n (%)	29 (9.4)	13 (8.6)	16 (10.3)	0.577

CHG, chlorhexidine gluconat; IQR, interquartile range; PDR, predictive death rate; PICU, pediatric intensive care unit; PRISM, pediatric risk of mortality.

The rate of catheter colonization was 5.7% (9 events, 3.82 per 1,000 catheter-days) in the CIDG and 12.4% (20 events, 7.59 per 1,000 catheter-days) in the SDG. Use of CHG-impregnated dressing significantly decreased the incidence of catheter colonization (HR: 0.407; 95% CI: 0.171–0.965; P = 0.041) (Fig. 2d).

Distribution of microorganisms in CHG-impregnated dressing versus standard dressing

The distribution of microorganisms causing CLABSI and catheter colonization are depicted in Table 4. There were no differences between the CIDG and the SDG in terms of the distribution of microorganisms causing CLABSI or catheter colonization.

In both groups, the most frequent microorganisms isolated in cases with CLABSI or catheter colonization were Gram positive, with the majority being coagulase-negative staphylococci.

Adverse events

The distribution of AEs with respect to groups is given in Table 5. No systemic adverse reactions were observed in the study groups. Severe local AEs leading to permanent removal of dressing did not occur. In the CHG-impregnated dressing group, 11 local AEs (7.0 per 100 catheters) occurred, while in the SDG, 7 local AEs (4.3 per 100 catheters) occurred. The frequency of local AEs were similar in both study groups (P = 0.346).

Discussion

The majority of studies evaluating the efficacy of CHG-impregnated dressing on CLABSI/CRBSI frequency have been conducted in the adult population. Most of these studies have demonstrated that CHG-impregnated dressing decreases the frequency of CLABSI/CRBSI in short-term nontunneled CVCs.[17–19,21,22,32–34] There are two extensive meta-analyses that have drawn most of their data from recent RCT studies focused on the effects of CHG-impregnated dressing on CLABSI/CRBSI frequency in adults. In both the 2014 study, which included nine RCTs (6,067 patients), and the 2019 study, which included 12 RCTs (6,028 patients), it was concluded that CHG-impregnated dressing significantly reduced CRBSI frequency.[17,23] As a result of this extensive research, the CDC recommended the use of CHG-impregnated dressing for adults in 2017.[28]

In contrast with the wealth of data in adults, there are few studies focused on this topic in the pediatric age group.[24–27,35]

Table 2 Catheter and treatment characteristics

Characteristics	All catheters (n = 307)	CHG-impregnated dressing (n = 151)	Standard dressing (n = 156)	P
Total catheter days (day)	4,993	2,359	2,634	NA
Internal jugular vein	2,904 (58.1)	1,377 (58.4)	1,527 (58.0)	NA
Femoral vein	1,631 (32.7)	820 (34.8)	811 (30.8)	
Subclavian vein	458 (9.2)	162 (6.8)	296 (11.2)	
Time in place (days), median (IQR)	10.0 (7.0–18.0)	10.0 (6.75–15.25)	9.0 (7.0–20.5)	0.709
Catheter insertion time (days), median (IQR)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	1.000
Transport out of the PICU with catheter in place, n (%)				
No	207 (67.4)	103 (68.2)	104 (66.7)	0.819
Once	63 (20.5)	29 (19.2)	34 (21.8)	
More than once	37 (12.1)	19 (12.6)	18 (11.5)	
Antimicrobials at catheter insertion, n (%)	272 (88.6)	140 (92.7)	132 (84.6)	0.114
Catheterization site, n (%)				
Internal jugular vein	193 (62.9)	89 (58.9)	104 (66.7)	0.218
Femoral vein	91 (29.6)	52 (34.4)	39 (25.0)	
Subclavian vein	23 (7.5)	10 (6.7)	13 (8.3)	
No. of lumens, n (%)				
2	151 (49.2)	76 (50.3)	75 (48.1)	0.655
3	156 (50.8)	75 (49.7)	81 (51.9)	
Vasopressor use	87 (28.3)	44 (29.1)	43 (27.6)	0.900
Parenteral nutrition use	53 (17.3)	22 (14.6)	31 (19.9)	0.230
Heparin use	182 (59.3)	92 (60.9)	90 (57.7)	0.910
Blood product transfusion	159 (51.8)	82 (54.3)	77 (49.3)	0.502
No. of dressing changes per catheter, median (IQR)	3.0 (2.0–5.0)	3.0 (2.0–5.0)	3.0 (2.0–5.0)	1.000
No. of unplanned dressing changes per catheter, median (IQR)	1.0 (0.0–2.0)	1.0 (0.0–2.0)	1.0 (0.0–2.0)	1.000
Percentage of unplanned dressing change/total dressing change				
<50%	228 (74.3)	113 (74.8)	115 (73.7)	0.796
≥50%	79 (25.7)	38 (25.2)	41 (26.3)	
Reasons for CVC removal, n (%)				
No longer indicated	217 (70.7)	107 (70.8)	110 (70.5)	0.973
Suspected infection[†]	51 (16.6)	25 (16.6)	26 (16.7)	
Malfunction	11 (3.6)	6 (4.0)	5 (3.2)	
Death	28 (9.1)	13 (8.6)	15 (9.6)	

[†]Suspected infection: central line associated bloodstream infection, NA, not applicable.

Table 3 Comparisons of CLABSI, CRBSI, primary BSI and catheter colonization rates in the intention-to-treat analysis group

Variable	All catheters (n = 307) 4,993 catheter days	CHG-impregnated dressing (n = 151) 2,359 catheter days	Standard dressing (n = 156) 2,634 catheter days	HR (95% CI)	P
CLABSI rate, n (%)	35 (11.4)	15 (9.9)	20 (12.8)		
Incidence density of CLABSI (95% CI)	7.01	6.36	7.59	0.930 (0.459–1.776)	0.767
CRBSI rate, n (%)	20 (6.5)	9 (5.9)	11 (7.0)		
Incidence density of CRBSI (95% CI)	4.01	3.82	4.18	0.989 (0.405–2.415)	0.981
Primary BSI rate, n (%)	15 (4.9)	6 (3.9)	9 (5.7)		
Incidence density of BSI (95% CI)	3.00	2.54	3.42	0.799 (0.282–2.261)	0.672
Catheter colonization rate, n (%)	29 (9.4)	9 (5.9)	20 (12.8)		
Incidence density of catheter colonization (95% CI)	5.81	3.82	7.59	0.407 (0.171–0.965)	0.041

Incidence density values correspond to episodes per 1,000 catheter-days.

BSI, bloodstream infection; CHG, chlorhexidine gluconate; CI, confidence interval; CLABSI, central line associated bloodstream infection; CRBSI, catheter related bloodstream infection; HR, hazard ratio.

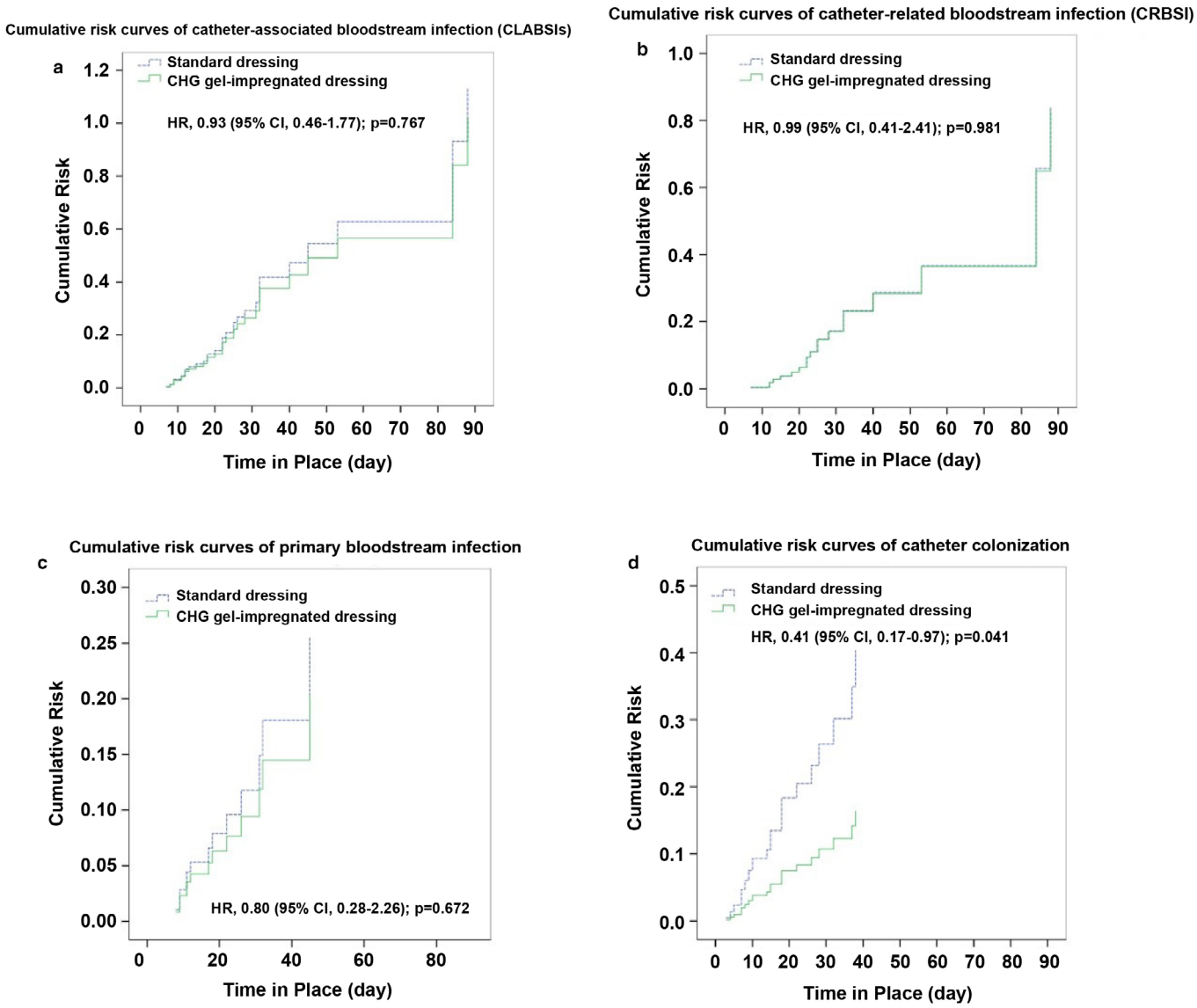

Fig. 2 Cumulative risk of (a) central-line-associated bloodstream infection (CLABSI), (b) catheter-related infection (CRBSI), (c) primary bloodstream infection (BSI), and (d) catheter colonization with chlorhexidine (CHG)-impregnated gel dressing versus standard dressing. CI, confidence interval; HR, hazard ratio.

Garland *et al*., in their study including 705 patients, managed in the neonatal ICU, reported that the use of CHG-impregnated disks on the insertion site of non-tunneled catheters did not reduce CRBSI or primary BSI frequency.[25] Similar outcomes were observed by Levy *et al*. in 145 cardiac PICU patients and by Duzkaya *et al*. in 100 PICU patients.[24,27] A recent study involving 192 pediatric patients with non-tunneled CVC reported a CLABSI incidence of 7.9 per 1,000 catheter days and found no benefit with the use of CHG-impregnated dressing,[35] similar to our findings. It has also been shown that a CHG-impregnated dressing was not effective in reducing catheter infection frequency in tunneled long-term catheters.[26]

The most common mechanism of catheter infection is considered to be the migration of microorganisms through the cutaneous catheter tract, leading to catheter colonization and subsequent catheter infection.[6] Prevention of colonization might therefore be thought to be the most rational step to prevent CLABSI.[18] The use of CHG-impregnated dressing has been proved to reduce catheter colonization in the adult population.[17–19,21,22,32–34] In these studies, the effect of CHG-impregnated dressing on colonization frequency and CLABSI/CRBSI frequency have been shown to be strongly correlated. Both of the two extensive meta-analyses have demonstrated a reduction in catheter colonization with the use of CHG-impregnated dressing.[17,23] The effect of CHG-impregnated dressing on catheter colonization is controversial in the pediatric age group; moreover, there is often no correlation between colonization and CLABSI frequency. The present study found that the frequency of catheter colonization was

Table 4 Distribution of microorganisms causing CLABSI and catheter colonization between study groups

Variable, *n* (%)	All catheters (*n* = 307)	CHG-impregnated dressing (*n* = 151)	Standard dressing (*n* = 156)	*P*
CLABSI	35	15	20	
Gram positive[†]	29 (82.9)	12 (80.0)	17 (85.0)	1.000
Staphylococcus aureus	8 (22.9)	4 (26.7)	4 (20.0)	0.700
Coagulase-negative *staphylococcus*	23 (65.7)	9 (60.0)	14 (70.0)	0.721
Other Gram-positive coccus	1 (2.9)	0 (0.0)	1 (5.0)	1.000
Gram negative[†]	9 (25.7)	4 (26.7)	5 (25.0)	1.000
Pseudomonas spp.	2 (5.7)	1 (6.7)	1 (5.0)	1.000
Enterobacter spp.	2 (5.7)	2 (13.3)	0 (0.0)	0.176
Escherichia coli	2 (5.7)	1 (6.7)	1 (5.0)	1.000
Acinetobacter baumannii	1 (2.9)	1 (6.7)	0 (0.0)	1.000
Klebsiella pneumoniae	1 (2.9)	0 (0.0)	1 (5.0)	1.000
Serratia marcescens	2 (5.7)	0 (0.0)	2 (10.0)	0.496
Fungi	2 (5.7)	0 (0.0)	2 (10.0)	0.496
Candida spp.	2 (5.7)	0 (0.0)	2 (10.0)	0.496
Catheter colonization	29	9	20	
Gram positive[†]	26 (89.7)	7 (77.8)	19 (95.0)	0.220
Staphylococcus aureus	4 (13.8)	1 (11.1)	3 (15.0)	1.000
Coagulase-negative *staphylococcus*	19 (65.5)	5 (55.6)	14 (70.0)	0.675
Other Gram-positive coccus	6 (20.7)	2 (22.2)	4 (20.0)	1.000
Gram negative	4 (13.8)	2 (22.2)	2 (10.0)	0.568
Pseudomonas spp.	1 (3.4)	1 (11.1)	0 (0.0)	1.000
Enterobacter spp.	3 (10.3)	1 (11.1)	2 (10.0)	1.000

CHG, chlorhexidine gluconate; CLABSI, central-line-associated bloodstream infection.
[†]More than one microorganism recovered in some cases.

Table 5 Local adverse events

Variable	All catheters (*n* = 307)	CHG-impregnated dressing (*n* = 151)	Standard dressing (*n* = 156)	*P*
Total local adverse event, *n* (%)	18 (5.8)	11 (7.2)	7 (4.4)	0.346
Mild, *n* (%)	14 (4.5)	8 (5.2)	6 (3.8)	0.593
Moderate, *n* (%)	4 (1.3)	3 (1.9)	1 (0.6)	0.317

CHG, chlorhexidine gluconate.

significantly reduced with CHG-impregnated dressing, similar to the studies by Gerland *et al*. (in the neonatal ICU) and Levy *et al*. (in the cardiac PICU).[24,25] However, it is evident that the reduction in colonization frequency did not translate into positive effects in terms of CLABSI and CRBSI frequency. The studies by Duzkaya *et al*. and Jitrungruengnij *et al*. did not find any significant decrease in neither CLABSI/CRBSI frequency nor catheter colonization in their respective study groups.[27,35]

Our results show that the majority of cases with CLABSI and colonization were due to Gram-positive bacteria in both the CHG-impregnated and standard dressing groups, with coagulase-negative staphylococci identified as the leading cause. Similarly, Gram-positive cocci are often reported as the most common agents in large cohort studies evaluating CLABSI and catheter colonization.[36,37] In the meta-analysis by Safdar *et al*., which assessed the efficacy of CHG-impregnated dressing, *Staphylococcus epidermidis* was found to be the most common organism isolated, followed by *Staphylococcus aureus* and other Gram-positive cocci.[23] However, the RCTs by Timsit *et al*. and Levy *et al*. have shown that Gram-negative microorganisms were common in CLABSI etiology, and coagulase-negative staphylococci were common in catheter colonization. These studies also reported that the CHG-impregnated dressing did not demonstrate any significant difference from standard dressing in terms of microorganisms causing CLABSI or catheter colonization.[18,24] In contrast with our findings, these two studies mostly identified Gram-negative bacteria in CLABSI etiology; however, similar to our results, the use of CHG-impregnated dressing was not found to be associated with any alterations in the distribution of microorganisms causing CLABSI or colonization.

None of the studies in the literature, either in adults or children, have reported systemic AEs with CHG use, similar to our findings.[17–20,23–25,27,35] Contact dermatitis in relation to CHG-impregnated dressing was the most common local AE reported in prior studies. None of the patients in the present study were found to have severe contact dermatitis. Even though mild to moderate local AE frequency was higher in the

CHG-impregnated group, there was no statistical difference between the groups (events/catheters: 7.2% vs 4.4%). Timsit *et al*. found that the incidence of severe contact dermatitis requiring catheter removal was higher in the CIDG compared to the SDG.[19] Garland *et al*. reported the overall frequency of contact dermatitis to be 5.7% in their neonatal group but found that preterm infants weighing <1,000 g had a frequency of 15%.[25] In another study, which included PICU patients, local AE frequency was reported to be 6.8% and CHG-impregnated dressing was not found to increase AE frequency.[35] It therefore appears that, apart from very low-weight preterm infants, CHG-impregnated dressing can be used safely in the neonatal and pediatric age groups.

Our study has several limitations. First, double-blinding was not feasible because CHG-impregnated dressing was easily distinguishable from standard dressing due to the presence of gel. However, catheter cultures were conducted in a blinded fashion, and independent assessors conducted a blind review of all suspected catheter infections. As a side note, researchers planning similar studies could try to find methods that can ensure blinded application/follow up of different dressing types, for instance, by using dressings that are indistinguishable from each other. Another important strength is associated with the exclusion of patients who were discharged from the PICU to another ward; thus, all catheters included in the study had undergone culture analysis. Despite reaching the highest number of patients and catheter days among PICU studies, this was a single-center study, and adult studies on this topic have frequently included greater patient numbers. Another limitation of the study pertains to the use of CHG-alcohol solutions during skin antisepsis for catheter insertion –which was a routine procedure in our center; this approach may have reduced the frequency of infection and colonization in the SDG; thereby possibly reducing the likelihood of finding statistically significant difference between the two groups.

In conclusion, the use of CHG-impregnated dressing, when compared with standard dressing, does not significantly decrease CLABSI rate in critically ill pediatric patients, but it is effective in reducing catheter colonization. In both groups, the most frequent microorganism was identified as coagulase-negative staphylococci, and there were no differences in terms of the distribution of microorganisms.

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Disclosure

The authors declare no conflict of interest.

Author contributions

M.D. was responsible for study design, statistical analysis, drafted the manuscript, and is responsible for the overall content. Z.K.: was involved in study design, quality assessment, contributing to the writing of the manuscript and revising the manuscript for important intellectual content. P.Y. was involved in study design, quality assessment. S.Y.: was involved in data extraction and quality assessment. N.M.Y. was involved in data extraction and quality assessment. O.M.T. was involved in microbiological results assessments, data extraction, and quality assessment. N.F. was involved in data extraction and quality assessment. O.B. was involved in data extraction and quality assessment. Y.C.M. was involved in study design, data extraction, and quality assessment. All authors have agreed on the final version of this manuscript.

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