ORIGINAL ARTICLE

EFFECTIVENESS OF DAILY CHLORHEXIDINE BATHING IN REDUCING HEALTHCARE-ASSOCIATED INFECTIONS IN THE PEDIATRIC INTENSIVE CARE UNIT OF A TERTIARY GOVERNMENT HOSPITAL

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ABSTRACT

Introduction: Healthcare-associated infections (HCAIs) are a common complication of prolonged hospital stay, leading to increased morbidity and mortality. This study aims to determine the effectiveness of daily chlorhexidine bathing in reducing HCAIs in the pediatric intensive care unit (PICU).

Methodology: This is a randomized controlled, observer-blinded study conducted over a 6-month period. Included were 2 months to 18-year-old patients admitted to the PICU, randomly assigned to daily bathing with 2% chlorhexidine or to the standard practice of bathing with plain soap and water. Primary outcome was the incidence of HCAI in each group.

Results: A total of 50 patients were enrolled in the study. Overall incidence of HCAI was lower in the chlorhexidine group compared to the control group (12% versus 36%, RR=0.33, 95% CI 0.10 – 1.09, p=0.047). Incidence density rate was lower in the chlorhexidine group (5.91 versus 21.03 infections per 1000 person-days, p=0.049). Ventilator-associated pneumonia and bloodstream infections were lower in the chlorhexidine group, but results were not statistically significant. There were no significant differences in mortality rates and length of hospital stay. One adverse event of transient rash occurred in the chlorhexidine group.

Conclusion: Daily chlorhexidine bathing may be more effective in reducing HCAIs in the PICU compared to standard care.

KEYWORDS: *Chlorhexidine, healthcare-associated infection, pediatric intensive care unit*

INTRODUCTION

Health care-associated infection (HCAI) is a common complication of prolonged hospital stay leading to increased morbidity and mortality.[1] According to the World Health Organization (WHO), the overall prevalence of HCAIs in developed countries ranged from 5.1% to 11.6%, while in developing countries, this varied between 5% to 19%.[2] In the Philippines, there has been no consolidated report of rates of healthcare-associated infections across all institutions. HCAIs also pose an economic burden leading to increased health-related costs and utilization of health care resources.[3] A local study showed that the total cost of HCAIs reached P7.1M, with P3.8M shouldered by the patients and P3.3M by the hospital. This results in a cost of P49,000.00 per patient or P2,000.00 per patient-day.[4] The study reported a 19% mortality rate attributed to HCAIs. The latest data of the Section of Infectious and Tropical Diseases of Pediatrics in the tertiary government hospital where this study was conducted showed that the over-all HCAI rate for its different pediatric units, including the pediatric intensive care unit (PICU) and the neonatal intensive care unit (NICU), was relatively unchanged from a 9% rate in 2014 to 9.64% in 2015. In the 2015 report, HCAIs in the PICU accounted for the highest rate, which was 16.11%; NICU had a rate of 10.8%, while the rate for the two pediatric wards was at 9.6%.

Several infection control measures have been developed as components of a comprehensive program to decrease HCAI rates in the same hospital. These include hand hygiene, ventilator-associated pneumonia (VAP) care bundle, cohorting, barrier and isolation precautions, and regular infection control workshops.[5,6,7] Despite the implementation of these measures, HCAI rates in the PICU remained high over the past 5 years.

Chlorhexidine, although widely used in developed countries as part of aseptic technique measures, is less widely used locally. Chlorhexidine is relatively inexpensive and may prove to be a cost-effective measure when compared with the estimated cost of a hospital-acquired bloodstream infection.[4] A meta-analysis reported that daily chlorhexidine bathing can decrease the risk of HCAIs in the adult population.[5] Although several studies have already demonstrated its effectiveness, especially among the adult population, other studies, however, have shown conflicting results.[6,7,8,9] The adult ICU study showed that daily bathing with chlorhexidine did not decrease the incidence of HCAIs including central line-associated bloodstream infection (CLABSI), catheter-associated urinary tract infection (CAUTI), ventilator-associated pneumonia (VAP), or *Clostridium difficile*. [10] There was also no change in the rates of other secondary outcomes such as hospital-acquired bloodstream infections, blood culture contamination, and clinical cultures positive for multi-drug resistant organisms. The authors acknowledged, however, that their intervention period of 10 weeks was shorter compared to other studies. Their baseline infection rate was also low, suggesting that there could be a lower limit of infection rate wherein chlorhexidine bathing no longer adds any benefit.[10]

There are limited studies involving the pediatric population on this topic. One multi-center study done on critically ill children in ten pediatric ICUs compared 2% chlorhexidine-impregnated wipes for daily baths versus soap and water using a cluster-randomized cross-over trial, with two 6-month study periods separated by a 2-week washout period. The study showed a 36% reduction in the rate of bacteremia in the treatment group, with a significant decrease in the incidence of bacteremia (4.93/1000 at-risk days vs 3.28/1000 at-risk days, aIRR 0.64, p=0.044) and a non-significant decrease in CLABSI (3.00/1000 at-risk days vs. 2.20/1000 at-risk days, aIRR 0.68, p=0.249).[11] Locally, there are no studies on chlorhexidine bathing as one component of the hospital infection control program in the pediatric population. This study, therefore, aims to investigate the effect of daily chlorhexidine bathing in reducing HCAIs among children admitted in the PICU, aged 2 months to 18 years.

METHODS

This study is a single-center randomized controlled, observer-blinded study conducted in the pediatric ICU of a tertiary government institution over a 6-month period. Approval from the Research Ethics Board of the University of the Philippines Manila (UPMREB) was obtained prior to study initiation. Based on the study conducted by Milstone and colleagues, with 1.50 Rate Ratio and a target reduction in nosocomial infections by 45% favoring the intervention, a total sample size of 47 was computed to give the study 80% power at an alpha of 0.05.[11]

Patients admitted to the PICU are a heterogeneous group admitted either directly from the emergency room, pediatric wards, and operating room (surgical, neurosurgical, cardiac), or are transferred from another institution. The PICU is a 12-bed capacity ICU, with a 1:3 nurse to patient ratio. Study subjects were patients aged 2 months to 18 years admitted to the PICU with none of the following: 1) burn injuries or large wounds covering >20% body surface area, 2) patients with a history of allergy to chlorhexidine, 3) patients less than 2 months old, 4) critically ill patients whom the primary physician deemed bathing as unsafe, and 5) patients admitted to the PICU for less than 48 hours. During the pre-trial period, all PICU nursing aides who were to perform the bathing procedure were educated on the proper bathing technique using an instructional video.[12]

Admissions to the PICU were checked daily. For those who fulfilled the inclusion criteria and agreed to participate in the study, informed consent was sought from the parent or primary caregiver. In addition, for those who were able to provide assent, verbal assent was obtained from those aged 7 to 11 years old and written assent from those aged 12 to less than 18 years old. The patients were then randomized to either the control group, using soap and water, or to the intervention group, using 2% chlorhexidine gluconate (CHG) (MIcroshield®, Johnson and Johnson) based on a computer-generated randomization program.

Blinding of the bathers, parents or caregivers, and patients was not possible due to difference in appearance and smell of the chlorhexidine solution. However, the outcome assessor was blinded to the patient assignment. Demographic data and admitting diagnosis were obtained from the patient's chart. Randomization was done by a third party and concealment of treatment allocation was done using consecutively numbered sealed opaque envelopes that were opened only upon enrolment of the patient.

Bathing Procedure. The bathing procedure was carried out once every 24 hours by the PICU nursing aide on duty daily until discharge, following their routine schedule for bathing patients in two batches, either in the evening or early morning. Although bathing at the same time would have been ideal, the regular schedule for bathing of the PICU nursing aide was followed in order to minimize disruption in their activities. In both groups, bathing attendants practiced proper handwashing before handling the patient.

In the chlorhexidine or intervention group, six clean reusable washcloths were provided for each patient, which were color coded per body part (neck & chest, arms, legs, perineum, back and buttocks). Washcloths were dipped in a basin labeled solely for each patient's use, containing 2% CHG. This was prepared as a 1:2 dilution (500 ml of 4% CHG diluted in 1 liter of distilled water), and stored in clean, disposable plastic bottles. A different washcloth for everybody area was used. The solution was allowed to dry, without rinsing. Bathers were instructed to avoid contact with the face, mucous membranes, and wounds, and not use additional water during baths.

In the soap and water or control group the same procedure was followed using a liquid non-antiseptic soap that was rinsed after application. Random compliance checks, three times each week was done by a research assistant who was knowledgeable on the proper bathing technique. If there was a breach in the procedure, the research assistant would inform the investigator without revealing the subject, and verbal reminders were sent to all nursing aides.

Patients were monitored daily for development of HCAIs, these were suspected when the patient developed any signs of systemic inflammatory response syndrome (SIRS) 48 hours after the patient was admitted to the PICU. All patients suspected to have HCAI underwent work-up. Specific HCAIs determined were the following: sepsis [bacteremia or laboratory-confirmed blood stream infection (BSI), clinical sepsis, or CLABSI], health-care associated pneumonia (VAP and non-VAP), CA-UTI, and surgical site infection (SSI). Diagnosis of the specific HCAI was based on CDC operational definitions. [13]

The pediatric residents on duty in the PICU were tasked to extract specimens for the laboratory tests. The occurrence of a HCAI was recorded per incident, thus, the patient was monitored from the time of admission until either 48 hours after discharge from the PICU had elapsed, or death had occurred. The investigator was not involved in the management of the patients' clinical conditions.

Patients were also monitored for adverse events (such as development of skin rashes or anaphylaxis) and need for medical management or withdrawal from the study.

Outcome and Outcome Measurements. Each patient's demographic and clinical data, including age, sex, diagnosis, length of PICU stay, outcome of hospitalization, and presence and duration of indwelling device were obtained. Clinical culture results were obtained from the microbiology laboratory and patient's medical chart.

The primary outcome measure was the frequency of HCAIs defined as the incidence proportion of each group. HCAI proportion is computed as the total number of HCAI over the total number of patients at risk. Secondary outcome measures were individual rates of HCAIs, mortality rate, deaths attributable to sepsis or HCAI, and occurrence of adverse events.

Data Analysis. Statistical analysis was performed using STATA 12.0 statistical software. Descriptive statistics were used to summarize the clinical characteristics of the patients. Frequencies and proportions were used for nominal variables, and median and range were used for ordinal variables. Mann-Whitney U test and Chi-square or Fisher's Exact test was used to determine the difference of medians and frequencies between control and chlorhexidine groups, respectively. All valid data were included in the analysis. Results were reported as risk ratio with 95% confidence interval and as infection incidence density rates per 1000 ICU days of healthcare-associated infections. Null hypothesis was rejected at 0.05α-level of significance.

RESULTS

A total of 85 patients were admitted to the pediatric ICU during the 6-month study period. Twenty-eight (28) were excluded (21 neonates, 3 critically ill not deemed safe for bathing by primary physician, 4 admitted for less than 48 hours). Of the 57 eligible subjects, 7 refused to give consent, leaving a total of 50 enrolled patients (25 in the control group and 25 in the chlorhexidine group). All patients were analyzed and there were no drop outs during the study period.

Table 1 provides the clinical profile of the subjects. The 2 groups were comparable in terms of age, sex, number of patients who were intubated, had central lines or surgery, duration of intubation or central catheter lines, and post-surgical patients.

Table 1. Demographic profile of the study population

	Chlorhexidine (n=25)	Soap&Water (n=25)	P-Value
	Frequency (%); Median (Range)		
Age in months	48 (3 to 204)	24 (3 to 216)	0.954*
Sex			1.000ǂ
Male	17 (68)	17 (68)	
Female	8 (32)	8 (32)	
Number of intubated patients	16 (64)	15 (60)	0.771ǂ
Number of patients with central line	11 (44)	10 (40)	0.774ǂ
Number of post-surgical patients	13 (52)	13 (52)	1.000ǂ
Length of intubation (days)	18 (5 to 48)	12 (4 to 110)	0.513*
Length of central catheter line (days)	13 (5 to 26)	5.5 (4 to 22)	0.189*

*Statistical tests used: * - Mann-Whitney U test; ǂ - Chi Square Test; ł – Fisher's Exact test*

Table 2 compares the incidence of healthcare-associated infections between the chlorhexidine and the control groups. The overall incidence of HCAI is lower in the chlorhexidine group (12%) compared to the control group (36%). The risk ratio indicates a possible beneficial effect of bathing with chlorhexidine compared to soap and water although the upper limit of the 95% confidence interval crossed the level of no significant difference and the p value showed only borderline significance, probably due to the small number of patients who developed HCAI (RR = 0.33, 95% CI 0.10 – 1.09, p=0.047). There was a trend for reduced incidence of ventilator-associated pneumonia (RR 0.500, 95% CI 0.05-5.17) and sepsis (RR 0.200, 95% CI 0.03-1.59) in the treatment group as compared to the control group, however, these were not statistically significant. In addition, there were only 2 culture-positive infections in the treatment group: 1 VAP (*Stenotrophomonas maltophilia*) and 1 CA-UTI (*Klebsiella oxytoca*), while the control group had 6 culture-positive infections 1 *Pseudomonas aeruginosa* (VAP), 1 *Klebsiella pneumonia* (BSI), 1 *Burkholderia cepacia* (CLABSI), 1 Candida (CLABSI), 1 *Staphylococcus epidermidis* (BSI), 1 mixed infection with *Klebsiella pneumoniae*, *Serratia marcescens*, and *Pseudomonas aeruginosa* (VAP). There were no surgical site infections in the chlorhexidine group, on the other hand no urinary tract infection was noted for the control group.

Table 2. Comparison of incidence of HCAI between the treatment and control groups

	Chlorhexidine (n=25)	Soap&Water (n=25)	Relative Risk (95% CI)	P-value
	Frequency (%)			
Ventilator associated Pneumonia	1 (4)	2 (8)	0.500 (0.05 – 5.17)	0.552
Blood stream infection/clinical sepsis	1 (4)	5 (20)	0.200 (0.03 – 1.59)	0.082
Surgical site infection	0	2 (8)	-	-
UTI	1 (4)	0	-	-
Total	3 (12)	9 (36)	0.33 (0.10 – 1.09)	0.047

Statistical tests used: Fisher's Exact Test

Table 3 compares the incidence of healthcare-associated infections between the chlorhexidine and control groups among patients with an indwelling device (endotracheal tube and central venous catheter) and post-surgical patients. Among patients who were intubated, there was a lower incidence of bacteremia or pneumonia in the chlorhexidine group (18.75%) compared to the control group (53.3%) (RR 0.352, CI 0.083 - 1.167, p value 0.044). Although this indicates that bathing with chlorhexidine may be more beneficial than the control, the upper limit of the 95% CI crosses the level of no significant difference, probably because of the small number of the measured outcomes. Among patients with a central venous catheter, there was also a lower incidence of bacteremia in the chlorhexidine group compared to the control group (18.2% versus 30%), but the difference was not statistically significant (RR 0.788 (0.097 – 5.195), p value 0.769). Among post-surgical patients, the number of patients who developed HCAIs was also lower in the treatment group (7.7% versus 38.5%), but the difference was not significant as well (RR 0.20, CI 0.009 – 1.47).

Table 3. Comparison of incidence of HCAI between treatment and control groups–with an indwelling device and post-surgical patients

Patients with Risk Factor for HCAI	Chlorhexidine	Control	Relative Risk (95% CI)	P-value
	Frequency (%)			
Intubated patients	3/16 (18.75)	8/15 (53.3)	0.352 (0.083 - 1.167)	0.044
Patients w/ central lines	2/11 (18.2)	3/ 10 (30)	0.788 (0.097 – 5.195)	0.769
Post-surgical patients	1/13 (7.7)	5/13 (38.5)	0.200 (0.009 – 1.474)	0.063

Statistical test used: Fisher's Exact Test

Table 4 compares the incidence density rates of healthcare-associated infections between the chlorhexidine and control groups. Overall, the chlorhexidine group was less likely to incur healthcare-associated infections (5.91 versus 21.03 infections per 1000 person-days, p=0.049). However, the rate ratio 95% CI ranged from 0.05 to 1.13. We have insufficient evidence to demonstrate a difference in the incidence density rate of VAP (RR 0.42, 95% CI 0.007 – 8.09), sepsis (RR 0.17, 95% CI 0.004 – 1.51), and overall HCAIs (RR 0.28, 95% CI 0.05 – 1.13).

Table 4. Comparison of incidence density rate per 1000 ICU days of HCAI between treatment and control groups

	Chlorhexidine (508 ICU days)	Control (428 ICU days)	Rate ratio (95% CI)	P-Value
	Incidence density rate per 1000 person days			
Ventilator-associated pneumonia	1.97	4.67	0.42 (0.007 to 8.09)	0.532
Blood stream infection/clinical sepsis	1.97	11.68	0.17 (0.004 to 1.51)	0.083
SSI	0	4.67	-	-
UTI	1.97	0	-	-
Total	5.91	21.03	0.28 (0.05 to 1.13)	0.049

Statistical test used: Fisher's Exact Test

Table 5 provides the clinical outcomes of the pediatric ICU patients included in this study. In terms of length of hospital stay, there was a higher median number of hospital days in the chlorhexidine group versus the control group (17 days versus 12 days, p=0.097), however the difference was not statistically significant. For both groups, there were four patients in each group who expired, with a crude mortality rate of 16% (p=1.00).

There were no serious adverse reactions noted during the study. One patient in the treatment group was reported to have a localized rash on the trunk after the 3rd day of chlorhexidine bathing that spontaneously resolved. This patient was also undergoing chemotherapy during the time of the study.

Table 5. Clinical outcomes of treatment and control groups

	Chlorhexidine (n=25)	Control (n=25)	P-value
Length of hospital stay, median (range in days)	17 (5 to 48)	12 (4 to 110)	0.097*
In-hospital overall mortality incidence	4 (16%)	4 (16%)	1.000ⱡ
Sepsis-related death	0	2 (50)	
Pneumonia-related death	1 (25)	1 (25)	
Adverse event			
Rash	1 (4)	0	1.000ⱡ

*Statistical tests used: * - Mann-Whitney U test; ⱡ Fisher's Exact test*

DISCUSSION

This study conducted in a tertiary government hospital PICU showed that daily bathing with 2% chlorhexidine was able to reduce the occurrence of HCAIs by 67%. The overall HCAI incidence density rate per 1000 PICU days was also four times higher in the control group (5.91 in treatment group versus 21.03 infections in control group per 1000 person-days). The results were not statistically significant, however, which may be attributed to the small number of patients who developed HCAI.

Previous large-population studies and two meta-analyses on chlorhexidine bathing in adult ICU units have shown benefits in the reduction of HCAIs in this population. Furthermore, a recent meta-analysis concluded that daily chlorhexidine bathing appears to be of most clinical benefit in reducing CLABSI and methicillin-resistant *Staphylococcus aureus* (MRSA) infections when infection rates are high in that certain population.[18] The findings in our study support and are consistent with these studies in the adult population. The only large-scale study done among children by Milstone and colleagues showed a significant reduction in HCAIs by 36%. Our study is the first known local study conducted in critically ill children admitted in the intensive care unit, comparing bathing with chlorhexidine with the standard bathing with soap and water. This study differed from that of the former in that their study was a multi-center, cross-over trial using cluster randomization, while our study used a single center, randomized controlled design.

The recorded reduction in incidence rates of VAP and CLABSI in the chlorhexidine group was consistent with previous studies on daily chlorhexidine bathing in children and adults. Although this reduction was not statistically significant in our study, again owing to the small number of HCAIs, analyses showed consistently a lower incidence and incidence density rate in the chlorhexidine group. This study also demonstrated that for patients with an endotracheal tube or a central line, or who had undergone an operative procedure, the risk for acquisition of a HCAI related to the risk factor may be lower in those who use chlorhexidine. For intubated patients, the risk for HCAIs was reduced by 65% in those who received daily chlorhexidine bathing. This is especially applicable in our PICU since over 60% of the patients are intubated. For patients with a central access, there was a 21% reduction in HCAI in the treatment group. Although this was not statistically significant, this was consistent with the previous study on critically ill children that also reported a significantly lower incidence of bacteremia in pediatric patients with a central line who received daily chlorhexidine bathing.[11] For post-surgical patients, the study showed a lower incidence proportion of patients who developed HCAI among patients who received chlorhexidine, with an 80% risk reduction, however, this was also not statistically significant. A larger number of post-surgical patients are needed to verify this result. A previous study on adult surgical ICU patients also failed to find a significant reduction of HCAIs in patients given daily chlorhexidine baths.

Although this was not the objective of this study, it was also noted that the overall HCAI rate during the 6-month study period was lower compared to the same period of the previous year, dropping from 18% to 10%, equivalent to a 44% reduction. Although hand hygiene and daily bathing of patients were reinforced, there was no new infection control measure implemented during this time, aside from the daily chlorhexidine bathing.

No significant difference in mortality rates were found in both groups, as with the study by Noto.[10] There was also no significant difference in the length of hospital stay in both groups. It has been suggested that although chlorhexidine may be effective in reducing HCAIs, there is no evidence for improved survival, other than the prevention of a HCAI~~.~~

Chlorhexidine bathing with 2% solution has been shown to be safe to use for children 2 months and above, and this study supports this finding.[15,16,17] There was only one adverse event in the chlorhexidine group, consisting of a transient localized rash on the trunk. This is consistent with findings from other studies of the most common adverse effect of the solution, which is transient contact dermatitis. However, since this patient had received chemotherapy a week prior to enrolment, it is uncertain if the rash was due to chlorhexidine or was drug-induced. Chlorhexidine was continued in this patient, without recurrence of the rash.

One great concern of HCAIs is the burden of cost to the patient. Although the scope of this study did not include determining cost-effectiveness, the relatively low cost of chlorhexidine bathing (P67.00 per patient-day or P1,361.60 per patient) warrants an assessment of the cost-effectiveness of this intervention in preventing HCAI and other adverse outcomes.

The strength of this study may be attributed to it being a randomized-controlled trial, with both groups receiving their treatment assignment in a parallel manner. A few limitations, however, should be considered. First was the inability to blind the bathers due to the appearance of the chlorhexidine solution. However, the outcome assessor was blinded to the treatment. Second, this trial was designed as an effectiveness trial, not an efficacy trial, wherein the interventions were performed as a component of routine patient care and there was no dedicated study bather. Lastly, this is a single government center study, hence, the findings may not be generalizable to other medical centers.

CONCLUSIONS AND RECOMMENDATIONS

The above findings suggest that daily chlorhexidine bathing in the PICU may be effective in reducing the incidence of HCAIs. A bigger sample population is further recommended to verify these results and strengthen the power of the study. It is recommended that this study be duplicated in other areas, such as in the pediatric wards, neonatal ICU or hematology-oncology ward, to assess its effectiveness in different settings and in different patient populations. It is a simple, easily implementable, and a relatively cheap infection control measure, and is safe to use in children.

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