Effect of Daily Chlorhexidine Bathing on Reducing Infections Caused by Multidrug-Resistant Organisms in Intensive Care Unit Patients: A Semi-Experimental Study with Parallel Controls

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Research

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Abstract

Background: A number of studies have shown that daily bathing by chlorhexidine (CHG) wipes in ICU can reduce healthcare-associated infections (HAIs) caused by methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant Enterococci (VRE). However, the impact of CHG bathing on carbapenem-resistant *Acinetobacter baumannii* (CRAB), carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), and carbapenem-resistant Enterobacteriaceae (CRE) is not clear and remains controversial.

Methods: A semi-experimental study which employs both pre-controls and a parallel control was conducted. In the intervention period (from July 1 to December 31, 2016), strengthened infection control measures and daily bathing with 2% CHG-impregnated wipes once daily was performed in the ICU. Fifty-seven non-ICU wards with the occurrence of multidrug-resistant organisms (MDRO) infections during the same time period were selected as parallel control group (only CHG bathing was not performed). The net effect of the 2% CHG daily bathing was evaluated by the difference in difference (DID) model.

Results: The incidence of HAIs caused by CRPA in ICU was significantly decreased between the intervention and pre-intervention period (2.5, 95% confidence interval (CI) 1.6–3.8 vs. 4.6, 95% CI 3.3–6.3 cases /1,000 patient days, P = 0.02). Similarly, the incidence of HAIs caused by CRAB in intervention group was 19.75% lower than that in pre-intervention group (6.0, 95% CI 4.4–7.6 vs. 7.5, 95% CI 5.7–9.3 cases / 1,000 patient days, P = 0.24). The DID model analysis showed that CHG bathing reduced the incidence of CRAB- and CRPA-caused infections in ICU by 1.56 and 2.15 cases/1,000 patient days, respectively, P <0.01, and bathing of every 38 patients (95% CI, 21–268) and 39 patients (95% CI, 24–110) were able to prevent one case of HAIs of CRAB and CRPA, respectively. However, CHG bathing showed no effect on MRSA, VRE and CRE (P>0.05).

Conclusion: Daily bathing with 2% CHG-impregnated wipes can reduce HAIs caused by CRAB and CRPA, while it is not effective for the prevalence of infections caused by MRSA, VRE, and CRE.

1 Background

In recent years, the prevalence of healthcare-associated infections (HAIs) caused by multidrug-resistant organisms (MDROs) has become seriously, which often causes severe consequences such as prolonged length of stay and increased mortality, and has been listed as a serious threat by the World Health Organization[1, 2]. MDROs commonly seen in healthcare settings include carbapenem-resistant *Acinetobacter baumannii* (CRAB), carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), carbapenem-resistant *Enterobacteriaceae* (CRE), methicillin-resistant *Staphylococcus aureus* (MRSA), and vancomycin-resistant enterococci (VRE). In order to prevention and control the infections caused by these MDROS, many measures, including hand hygiene, surveillance, contact precaution, isolation, and environment cleaning, have been widely adopted and been recommended by guidelines[3–5].

Daily bathing with 2% or 4% chlorhexidine gluconate (CHG) has been considered as an important measure to prevent and control MDROs infections in ICU by decontamination of skin colonization, although there is an ongoing controversy about the impact of this procedure[6–8]. *In vitro* experiments have shown that CHG has broad antibacterial activity against Gram-positive and Gram-negative bacteria, and the bacteriostatic effect on the human skin bacteria lasts for 24 hours[9]. A number of studies have shown that daily bathing by CHG wipes in ICU can reduce HAIs caused by MRSA and VRE[10–12]. However, there is less evidence for CHG bathing on CRAB, CRPA, and CRE. One before-after study has showed slight reduction of infections caused by the multidrug-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa*[13], while two other studies have exhibited unsatisfactory results[6, 14]. To assess the effectiveness of CHG bathing in ICU, especially in CRAB and CRPA endemic areas, we therefore conducted this study.

2 Data And Methods

2.1 Study Design

A before-after study with parallel controls was conducted in a teaching hospital with 4,300 beds in Mainland China. Routine prevention and control measures was conducted before July 2016 while strengthened procedures were employed since then in the whole hospital. In addition, daily bathing with 2% CHG-impregnated wipes was performed in a general ICU with 50 beds from July 1 to December 31, 2016. In order to masking the influence of seasonal fluctuations on the incidence of HAIs of MDROs, patients who admitted to ICU since July to December 2015 were selected as a control group (pre-intervention group). Meanwhile, 57 non-ICU wards in the hospital which had MDROs infections during the same period were used as parallel controls. Besides daily CHG bathing, all of the measures in these wards were the same as the ICU. The net effect of CHG was evaluated by the difference in difference model (DID). The study design is shown in Fig. 1.

2.2 Inclusion and exclusion criteria

All of the patients older than 18 years admitted to the general ICU were included. Patients were excluded if they are 1) younger than 18 years; 2) patients with trauma or skin ulceration when stay in ICU; 3) patients stay in ICU less than 48 hours.

2.3 Intervention Procedure

2.3.1 Daily bathing with 2% CHG-impregnated wipes

In June 2016, all ICU nurses received training on the standardized procedure of bathing patients using 2% CHG-impregnated wipes. From July to December 2016, trained nurses performed daily bathing using 2% CHG-impregnated wipes (Guardwell disposable care wipes, produced by Sichuan Yingnaide Medical Technology Co., Ltd.) for all newly-admitted ICU patients who met the inclusion criteria until they left the ICU. Each pack of the wipes has a total of eight pieces. The wipes were placed in an incubator at the constant temperature of 40 °C for heat treatment before use. The bathing steps were carried out in accordance with the recommended sequence of Agency for Healthcare Research Quality[15], briefly as follows: Cloth 1: Neck, shoulders and chest; Cloth 2: Both arms, hands, web spaces, and axilla; Cloth 3: Abdomen and then groin/perineum; Cloth 4: Right leg, foot, and web spaces; Cloth 5: Left leg, foot, and web spaces; Cloth 6: Back of neck, back and then buttocks. Use additional CHG bathing cloths, if necessary, to thoroughly cleanse the body. The infection control link nurse in the ICU supervised the compliance of the bathing.

2.3.2 Strengthened measures for MDROs

"MDRO prevention and control policy" had been revised and implemented in the whole hospital since July 2016. The newly added strengthened measures included four contents: 1) MDROs' information was immediately informed to the doctors of the corresponding patients when detected by the microbiology lab, and an isolation tag was automatically added on the hospital information system (HIS); 2) The summary of MDRO infections (the total patient numbers, the bed number for each patient, and the species and resistance type of each MDRO) in the unit was briefed in the daily morning shift meeting; 3) The number of doctors perform medical rounds in the room was not allowed to exceed 3 for patients with MDRO infections, and only a single designated nurse is in charge of the care for patients with MDRO infections during each shift; 4) a single room was preferred for placing patients with MDRO infections whenever possible. When single rooms are not available, the patients are settled in the corner area (rather than in the middle of multiple beds) of the room.

2.4 Definitions

The diagnostic criteria for HAIs were the Diagnostic Standards for HAIs published by the Ministry of Health in 2001[16]. The MDROs in this study include CRAB, CRPA, CRE, VRE, and MRSA.

2.5 Data Collection

Demographic and clinical data of patients were collected, including gender, age, ethnicity, invasive procedures, medical orders, underlying disease, APACHE II score, and length of stay.

2.6 Outcome Indices

The incidence density of HAIs of targeted multidrug-resistant bacteria (cases/1,000 patient days) in ICU was used as the primary evaluation index. Other indices included the number needed to treat (NNT) and its 95% confidence interval.

2.7 Statistics

For descriptive analyses, qualitative data are expressed in terms of frequency (rate), and quantitative data are expressed as the median (interquartile range). Qualitative data were analyzed by the chi-square test or Fisher's exact test. Quantitative data which were skewed based on the normality test and were analyzed using the Mann–Whitney U test. Using intention-to-treat (ITT) analysis, all patients who met the inclusion criteria in the ICU ward during the intervention period were analyzed as being given the CHG sponge bath. Poisson's test was used to compare the incidence density of multidrug-resistant bacterial infections before and after intervention in ICU.

The difference in difference model (DID) of the fixed effect estimation method was used to quantitatively analyze the effect of daily CHG sponge bath on reducing multidrug-resistant bacterial infection. The basic setting of the DID model is

$$y_{it} = \beta_0 + \beta_1 group_i \cdot time_t + \beta_2 group_i + \gamma time_t + \varphi \mathrm{Xit} + \varepsilon_{it} \ (i = 1, \dots, 46; t = 1,2)$$

where $group_i$ is the dummy variable for group (if $group_i = 1$, then it belongs to the experimental group; if $group_i = 0$, it belongs to the control group), which characterizes the difference of the experimental group and the control group themselves (that is, even without sponge bath, this difference still exists.); $time_t$ is the dummy variable for time (if t = 2 and $time_t = 1$, it is in the intervention period; if t = 1 and $time_t = 0$, it is in the pre-intervention period), and even without sponge bath, this time tendency still exists; $group_i \bullet time_t$ is an interaction term, and its coefficient β_1 is a DID estimation value that measures the effect of CHG. To assess whether the results are robust, other explanatory variables, X_{it}, were introduced for sensitivity analysis, including mortality, average bed turnover frequency, bed occupancy rate, average bed occupied days, hand hygiene accuracy rate, and hand hygiene compliance.

Microsoft-Excel 2016 was used to build a database for data processing and management. Statistical analysis and the DID method were processed using Stata 9.2 (Stata / SE 9. 2 Stata Corporation, College Station, TX, USA) software.

2.8 Ethics Approval

The study was approved by the Ethics Committee of Sichuan University. Bathing had been regarded as part of the normal care for ICU patients and inform consents were waived.

3 Results

3.1 Characteristics of ICU Patients of the Pre-Intervention and Intervention Period

From July 1 to December 31, 2016, a total of 1,009 patients were admitted to the general ICU. The compliance with the daily CHG bathing was 81.96% (827/1,009). Both of the demographic characteristics and underlying diseases of ICU patients during the intervention and pre-intervention period are comparable (Table 1). The occupancy rate of beds and the compliance of basic infection control measures including hand hygiene and environment cleaning are also comparable (Table 2).

Table 1
Characteristics of patients with or without chlorhexidine bathing

Characteristic	Without Chlorhexidine (n = 833)	With Chlorhexidine (n = 1009)	*P* Value
Age, median (interquartile range)	58 (45–69)	58 (45–68)	0.64
Male sex	550 (66.0)	638 (63.2)	0.21
Han nationality	799 (96.3)	958 (94.9)	0.81
Indwelling CVC	368 (44.2)	487 (48.3)	0.08
Mechanical ventilation	735 (88.2)	862 (85.4)	0.08
Indwelling urinary catheter	799 (95.9)	960 (95.1)	0.43
Hypertension	200 (24)	240 (23.8)	0.91
Diabetes	113 (13.6)	139 (13.8)	0.90
Pancreatitis	78 (9.4)	95 (9.4)	0.97
Respiratory failure	194 (23.3)	211 (20.9)	0.22
Renal insufficiency	104 (12.5)	118 (11.7)	0.60
AIDS	1 (0.1)	0 (0)	0.27
Malignant tumor	312 (37.5)	350 (34.7)	0.22
Hematonosis	18 (2.2)	11 (1.1)	0.07
COPD	37 (4.4)	41 (4.1)	0.69
Tuberculosis	10 (1.2)	28 (2.8)	0.02
APACHE II score, median (interquartile range)	15 (9–22)	14 (8–21)	0.13
Length of stay, median (interquartile range)	21 (13–32)	20 (13–33)	0.67

Abbreviations: CVC, Central venous catheter; APACHE II, Acute Physiology and Chronic Health Evaluation II; AIDS, Acquired immune deficiency syndrome; COPD, Chronic obstructive pulmonary disease.

Table 2
Characteristics of units comparing the baseline and intervention periods

Unit characteristics	Baseline period	Intervention period	*P* Value
Average number of open beds	50	50	/
Mean length of stay (d)	26.2	26.7	/
Occupancy rate of beds (%)	94.6 (8700/9200)	94.3 (8672/9200)	0.37
Hand hygiene compliance (%)	89.3 (67/75)	94.6 (122/129)	0.17
Environment cleaning compliance (%)	94.0 (63/67)	96.7 (269/280)	0.46

3.2 The Combined Effect of Strengthened Prevention and Control Measures and CHG Bathing

The incidence density of HAIs caused by CRPA during the intervention period was significantly decreased compared with that during the pre-intervention period (2.5 [95% CI 1.6–3.8] cases/1,000 patient days vs. 4.6 [95% CI 3.3–6.3] cases/ 1,000 patient days, P = 0.02). HAIs caused by CRAB decreased by 19.75%, although the difference was not statistically significant (6.0 [95% CI 4.4–7.6] cases / 1,000 patient days vs. 7.5 [95% CI 5.7–9.3] cases / 1,000 patient days, P = 0.24). On the basis of strengthened prevention and control measures, application of 2% CHG bathing every 38 (95% CI, 21–268) patients would prevent 1 case of HAIs caused by CRAB, and application of CHG to bath every 39 (95% CI, 24–110) patients would prevent one case of HAIs caused by CRPA. However, the HAIs rate caused by MRSA, VRE, and CRE were not decreased significantly in the intervention (Table 3). The incidence density of HAIs caused by MRSA, VRE and CRE during the pre-intervention period was 0.2 [95% CI 0–0.8], 0.1 [95% CI 0–0.6] and 0.5 [95% CI 0.1–1.2] cases/1,000 patient days separately. And The incidence density of HAIs caused by MRSA, VRE and CRE during the intervention period was 0.2 [95% CI 0–0.8], 0.1 [95% CI 0–0.6] and 0.6 [95% CI 0.2–1.3] cases/1,000 patient days separately.

Table 3
HAIs caused by MDROs comparing the baseline and intervention periods in the ICU

MDROs	Baseline period		Intervention period		*P* value
	Cases	Incidence density (95% CI)	Cases	Incidence density (95% CI)	
CRAB	65	7.5 (5.7–9.3)	52	6.0 (4.4–7.6)	0.24
CRPA	40	4.6 (3.3–6.3)	22	2.5 (1.6–3.8)	0.02
MRSA	2	0.2 (0–0.8)	2	0.2 (0–0.8)	1.00
VRE	1	0.1 (0–0.6)	1	0.1 (0–0.6)	1.00
CRE	4	0.5 (0.1–1.2)	5	0.6 (0.2–1.3)	1.00
Total	112	12.9 (10.5–15.3)	82	9.5 (7.4–11.5)	0.03

The unit of incidence density is cases per 1,000 inpatient days.

Abbreviations: HAIs, Healthcare associated infections; MDROs, Multi-drug resistant organisms; CRAB, Carbapenem-resistant *Acinetobacter baumannii*; BSI, Bloodstream infection; CRPA, Carbapenem-resistant *Pseudomonas aeruginosa*; MRSA, Methicillin resistant *Staphylococcus aureus*; VRE, Vancomycin-resistant Enterococci; CRE, Carbapenem-resistant Enterobacteriaceae.

3.3 The Net Effect of 2% CHG Bathing

There was no statistically significant difference in compliance to the strengthened prevention and control measure between ICU and the general wards (644 observations, 94.57% vs. 664 observations, 92.32%, $P = 0.101$). After introduction of the parallel control, the DID model showed that CHG bathing significantly reduced the incidence density of HAIs caused by CRAB and CRPA by 1.56 and 2.15 cases/1,000 patient days, respectively ($P < 0.01$), and appeared to reduce the incidence density of HAIs caused by MRSA by 0.05 cases/1,000 patient days but without statistical significance ($P = 0.92$), while showing no effect on VRE and CRE (Table 4).

Table 4
DID model estimation results of HAIs caused by MDROs

MDRO	Diff-in-Diff	S. Err.	*|t|*	*P* value
CRAB	−1.555	0.107	14.5	< 0.01
CRPA	−2.152	0.033	65.4	< 0.01
MRSA	−0.053	0.536	0.1	0.92
VRE	0.029	0.017	1.7	0.10
CRE	0.053	0.045	1.2	0.25
Total	−3.617	0.501	7.23	< 0.01

After the inclusion of the covariates that may affect the results, the sensitivity analysis of the model (Table 5) shows that the results of the statistical differences do not change. This indicates that the results are robust.

Table 5
Sensitivity analysis of DID model

MDRO	Diff-in-Diff	S. Err.	*|t|*	*P* value
CRAB	−1.538	0.188	8.2	< 0.01
CRPA	−2.235	0.090	24.9	< 0.01
MRSA	−0.263	1.477	0.2	0.86
VRE	0.030	0.033	0.9	0.37
CRE	0.218	0.190	1.2	0.26
Total	−3.030	1.042	2.9	< 0.01
Note: Included covariates are mortality, average bed turnover frequency, bed occupancy rate, average bed occupied days, hand hygiene accuracy rate, and hand hygiene compliance.				

3.4 Adverse Reactions

All patients who received daily 2% CHG bathing did not develop any adverse reactions such as skin redness and allergies.

4 Discussion

HAIs caused by MDRO have always been the focus of infection prevention and control. Before July 2016, a series of prevention and control measures were practiced in our hospital according to the Guidelines[5], including hand hygiene, environment cleaning and disinfection, monitoring and feedback, education for healthcare workers, and patient isolation. However, these measures had little effect as the occurrence of MDRO infections was still high and showed no a decreasing trend. Since July 1, 2016, we implemented strengthened measures on the basis of previous measures according to the actual conditions of the hospital and introduced the CHG bathing in ICU. Our study showed that the application of bathing with 2% CHG wipes reduced CRAB and CRPA infection in the ICU by 1.56 and 2.15 cases/1,000 patient days, respectively, similar to the studies before[13, 17]. However, Ruiz[13] only performed bath for patients who used mechanical ventilation and those who colonized with MDRO, and Chung[17] only evaluated the effect on CRAB. Because this study was performed in the real world, the ICU had taken strengthened prevention and control measures while we were performing the daily bathing using 2% CHG wipes, and thereby the comparison with ICU itself before and after intervention can only reflect the combined effect of these two measures. Therefore, we selected 57 non-ICU wards that implemented the same strengthened measures and had a compliance rate similar to that of the ICU as parallel control, and used the DID model to estimate the net effect of CHG. The DID model is an econometric method which widely used in the fields of economics and sociology and has been used in the field of infection prevention and control before[18]. This study applied this model to the semi-experimental research of prevention and control of MDROs, which effectively evaluated the control effect of 2% CHG daily bath on MDROs.

Furthermore, one study[10] have shown that using CHG bathing to decolonize every 54 patients can prevent one case of bloodstream infection caused by MRSA. However, few studies have demonstrated the efficacy of daily 2% CHG bathing on CRAB and CRPA infection. This study shows that on the basis of strengthened prevention and control measures, 2% CHG bathing for every 38 patients can prevent one case of HAIs caused by CRAB, and 2% CHG bathing for every 39 patients can prevent one case of HAIs caused by CRPA, demonstrating good cost-effectiveness. Unlike the results of other studies[10–12], our study did not find that CHG bathing could reduce HAIs caused by MRSA, VRE and CRE. This may be due to the fewer cases of HAIs caused by MRSA, VRE and CRE in the ICU during the study period, suggesting that in the low-prevalence areas, general decolonization using 2% CHG wipe has limited value.

In addition, in this study we did not employ the routine time-series design but decided to choose the same time period of the previous year as a pre-intervention control. This is mainly due to the fact that some studies have shown that seasonal factors may affect the incidence of HAIs caused by MDROs[19–22], especially in the summer when the infections caused by Gram-negative bacilli may increase significantly. Therefore, our choice of the same time period of the previous year would well mask this confounding factor.

This study also has some limitations. First, it is a single-center study which was carried out in an area where CRAB and CRPA are notably prevalent, which limits the extrapolation of the results; however, it has significance for areas with high CRAB and CRPA prevalence. Second, we did not conduct an active surveillance screening of CRAB and CRPA and could not evaluate the effect of CHG bathing on colonized bacteria. Studies have confirmed that CHG bathing can reduce the colonization rate of MDRO on the body surface, and this study shows that CHG bathing can reduce HAIs caused by CRAB and CRPA, which may also be due to the reduction of body surface colonized bacteria by the entire body bath, thereby reducing the risk of HAIs caused by these bacteria. Finally, as the ICU ward adopted two measures simultaneously during the intervention, the comparison before and after the intervention could not reflect the role of CHG alone. Therefore, we resorted to the DID model to introduce the common wards as a control to assess the net effect of CHG.

5 Conclusion

In conclusion, this study demonstrates that daily bathing for ICU patients with 2% CHG wipes can reduce HAIs caused by CRAB and CRPA in endemic areas. However, in the future, multicenter clustered randomized controlled studies are required to evaluate the prevention and control the effect of a daily CHG sponge bath against multidrug-resistant Gram-negative bacteria.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Sichuan University. Bathing had been regarded as part of the normal care for ICU patients and inform consents were waived.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Wenzhi Huang, Zhiyong Zong and Wei Zhang contributed to study conception and design. Wenzhi Huang, Fu Qiao and Lin Cai contributed to acquisition of data. Wenzhi Huang analyzed and interpreted data. Wenzhi Huang, Zhiyong Zong and Wei Zhang drafted the manuscript. All authors revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Figures

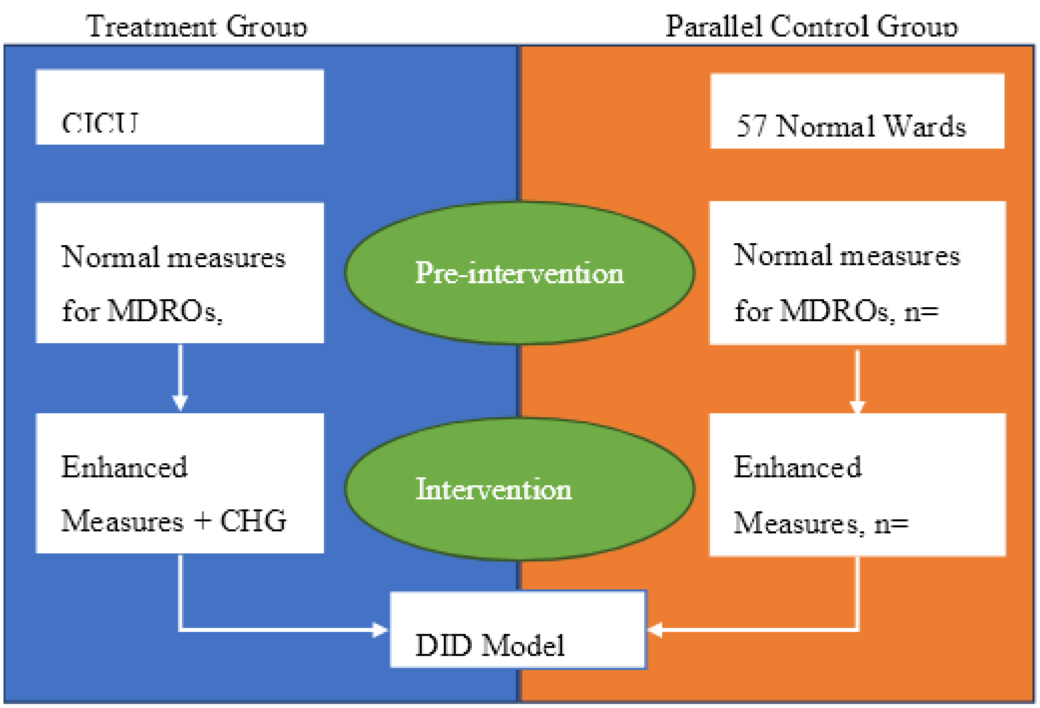

Figure 1. Study design

Figure 1

Study design