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Master of Medicine

Effectiveness and Safety of Chlorhexidine Gluconate
Double Cleansing for Surgical Site Infection Prevention
in NICU surgical patients

The Graduate School
of the University of Ulsan
Department of Medicine

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Effectiveness and Safety of Chlorhexidine Gluconate
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Supervisor: Min Jeong Cho

A Master's Thesis

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Abstract

Purpose: This study aimed to assess the efficacy and safety of preoperative chlorhexidine gluconate (CHG) double cleansing in reducing surgical site infection (SSI) incidence among NICU surgical patients.

Method: A retrospective chart review was conducted, involving 56 patients who underwent 73 surgical procedures in NICU from 2013 to 2022. CHG double cleansing, comprising 0.5% CHG and 70% isopropyl alcohol, included preoperative cleansing for elective surgeries the night before and at least 1 hour before emergency surgeries in the NICU. Anterior trunk cleansing spanned from the neck to the pubis, including both axillary lines. The surgical site underwent preoperative skin preparation just before surgery using the 2% CHG. The study compared two groups: a control group (2013-2018) using 70% iodine alone and a CHG group (2019–2022) employing CHG double cleansing. The occurrence of SSIs within 30 days of the surgical procedure was assessed.

Result: The overall SSI rate was 16.4% (n=12) in the total patient cohort. SSI occurred in 22.6% of the control group, no cases of CHG group showing a statistically significant difference ($p = 0.029$). There were no statistically significant differences in other parameters. No adverse effects were reported in the CHG group.

Conclusion: CHG double cleansing, a modified approach for NICU surgical patients, effectively reduced the incidence of SSIs compared to traditional skin preparation with iodine. The study supports the safe use of CHG in neonates, including premature infants, without significant complications. Further prospective studies are warranted to validate these findings and explore optimal concentrations and application protocols.

Table of Contents

Abstract	i
Introduction.....	1-2
Methods.....	2-3
Results	4-9
Discussion	10-14
Reference	15-18
Korean abstract	19

Table and Figure

Table 1. The demographic of patients	5
Table 2. Procedure of patients.....	6
Table 3. Control group versus CHG group	7
Table 4. No SSI versus SSI group.....	8
Table 5. SSI cases.....	9
Figure 1. CHG cleansing	3

Introduction

Surgical site infection (SSI) poses a significant clinical challenge, with reported rates ranging from 1.5% to 30% adult and pediatric populations after surgery (1,2). In neonatal intensive care units (NICU), where vulnerability is heightened, SSI rates vary from 4.3% to 19%, with a staggering 40% incidence in cases of necrotizing enterocolitis (NEC) surgery (3). SSIs not only increase morbidity and mortality but also prolong hospital stays, imposing a substantial economic burden. The urgency of addressing SSIs in NICU surgical patients is underscored by their higher occurrence and more severe consequences compared to older children (4). Consequently, preventing SSIs in this vulnerable population is paramount, various management are being attempted to reduce it.

chlorhexidine gluconate (CHG) is a topical antiseptic widely used for its broad antimicrobial activity. Despite its efficacy, caution is warranted due to the potential for excessive skin irritation and increased drug absorption, current Food and Drug Administration (FDA) product labeling of 2% CHG and 70% isopropyl alcohol (IPA) prep solution ‘use with care in premature infants or infants under 2 months of age’ (5,6). Despite these guidelines, surveys indicate widespread CHG use in NICUs, escalating from 57% in 2009 to 86% in 2014 in the USA (7). Although side effects such have been reported, CHG's noteworthy efficacy in preventing and reducing central line-associated bloodstream infections (CLABSIs) in neonates has contributed to its increased usage (8,9). Nonetheless, research on CHG use in NICU has focused mainly on antisepsis of CVC, and there are no data on its use in surgical neonates (10,11).

Recommendations for SSI prevention practices include baths and/or wipes with an antiseptic agent before the operative day, largely based on studies assessing preventability in adults, have been published (12,13). The Centers for Disease Control and Prevention (CDC) recommends that patients be cleansed with antimicrobial soap the night before the surgical intervention and advises using an alcohol-based solution for cleansing the surgical site before an incision (14). Many studies for adult populations showed preoperative baths with CHG has broad antiseptic activities, reduces skin colonization, and is associated with significantly fewer SSIs (12,15). However, there is limited data in children and no data in neonates (16).

We attempted to apply CHG as a preoperative skin antiseptic. We also endeavored to apply CHG baths used in adults to in NICU surgical patients. Modification of the CHG baths employed in adults became necessary due to practical challenges inherent in NICU environments, characterized by ventilators and intravenous lines that complicate bathing procedures. Because CHG cleansing was performed once in

NICU before surgery and again in the operating room, we called this new practice “CHG double cleaning” and applied it to NICU surgical patient.

The primary aim of this study was to assess the efficacy of implementing CHG double cleansing skin preparation in reducing SSI incidence compared to the single iodine skin preparation in a consecutive series of eligible NICU patients undergoing abdominal or thoracic surgery. And the secondary aim is to evaluate the safety of the use of CHG in neonates, including premature baby.

Methods

We retrospectively reviewed the charts of all neonates who underwent surgical repair in our NICU from October, 2013 to March 2022. Ethical approval for this study was obtained. Demographic and clinical data extracted from the medical record included: gestational age at birth, birthweight, postmenstrual age and weight at the time of procedure, gender, type of operation, length of operation, type and duration of prophylactic antibiotics, presence of concomitant infection, type and duration of treatment for concomitant infection, urgency of procedure, surgical site wound closure, wound cultures, development of SSI, and type and duration of treatment for SSI.

The study included only patients who underwent open laparotomy or thoracotomy. Exclusion criteria involved patients who had undergone surgery through laparoscopy or thoracoscopy, as well as those who had minor surgeries such as hernia repair. Additionally, patients who died within 7 days after surgery were excluded due to the difficulty in assessing the surgical site

Prior to 2019, our institution used an iodine solution for preoperative skin preparation, limited to the surgical area just before the procedure on operation room. In an effort to decrease the rate of postop SSI at the authors institution, preoperative CHG double cleansing was initiated in 2019. In the NICU, CHG cleansing was performed for elective surgeries on the evening before the scheduled procedure, and for emergency surgeries, it was carried out at least 1 hour prior to the surgery. The 0.5% CHG with 70% IPA was directly poured into a sterile dish, and a sterile cotton sponge was dipped into it. Anterior trunk cleansing was carried out from the neck to the pubis and to both axillary lines (Fig.1) Before the surgery, the surgical site was additionally applied with 2% Chlorhexidine. Our standard protocol emphasized using only the minimal volume of antiseptic, ensuring avoidance of pooling in dependent areas, and not wash off.

Our institution is a level III NICU. Two pediatric surgeons and two neonatologists care for patients. Both groups were engaged in the development of this new practice. Patients were operated on by senior surgeons from 2013 to 2016, and from 2017 onwards, junior surgeons performed the surgeries. The infection control guidelines in our hospital's NICU state that for infants born within the hospital, no specific screening is conducted, and routine blood cultures are performed. However, for patients transferred from other hospital, swab cultures from the nasal and skin and blood cultures, are conducted as part of screening for methicillin-resistant *Staphylococcus aureus* (MRSA) colonization. Preoperative antibiotic prophylaxis was administered within one hour prior to surgical incision, with antibiotic given in a dosage based on the patient's weight. Patients exhibiting symptoms or signs of infection before surgery continued to receive ongoing antibiotic therapy. Although there was no standardized protocol for the duration of intravenous antibiotic treatment, cessation occurred upon ensuring patient stability and observing the absence of infection evidence in blood tests.

SSIs were categorized in accordance with the definitions set by the CDC as outlined by the National Health and Safety Network. Patients were followed for SSI for 30 days after the surgical procedure and for all other infections until discharge. If a patient underwent more than one surgical procedure, the SSI was attributed to the most recent procedure unless the procedure was performed to treat an infection, such as a wound debridement

The authors compared two groups: control (2013-2018) with 70% iodine

alone, CHG group (2019–2022) with double CHG cleansing. Data are presented as median (range). Proportions were compared using Fisher exact test, and continuous variables were compared using Mann-Whitney test. A P-value of <0.05 was considered significant.

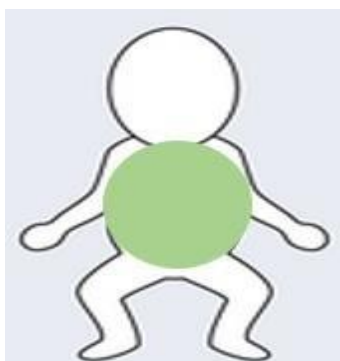


Figure 1. CHG cleansing

Results

We identified 52 patients who underwent 73 surgical procedures. Table I contains the demographic characteristics. There were 25 premature babies before 37 weeks and 27 babies over 37 weeks. The median age at the time of surgery was 40.1 days (range, 1-187). Although there are more patients who underwent surgery immediately after birth, the median was calculated as 40 days due to stomy take down patients were included. There were 27 patients born in our hospital and 25 patients transferred from other hospitals. Among all patients, 3 premature babies died on the 31st, 32nd, and 45th days after surgery due to sepsis unrelated to SSI.

The diagnoses of patients are given in Table 2. There were 22 cases of NEC, 15 cases related to stomy take down or revision, 10 cases of midgut volvulus, 7 cases of atresia, 5 cases of meconium plug, and 5 cases of TEF. Of the 52 patients, 13 had 2 surgeries and 4 had 3 surgeries.

Overall SSI rate is 16.4% (n=12) in total patients. When comparing the control group and CHG group, there were no statistically significant differences in other parameters such as age or weight. SSI occurred in 22.6% of the control group, no cases of CHG group showing a statistically significant difference ($p = 0.029$) (Table 3). There were no side effects reported after use in the CHG group.

Comparing the 12 cases with SSI and 61 cases, there were no significant differences in gestational age, birth weight, and hospital stay (Table 4). MRSA screening was performed only 29 patients, and the positive rate was not different between the two groups ($p=0.785$). However, the infection rate was significantly higher in patients coming from other hospital ($p=0.018$) and those with more weight at the time of surgery ($p=0.040$). There was no difference in the occurrence of SSI depending on the operator, and there was no difference in the number of surgeries performed on one patient. There was a statistically significant difference in whether CHG double cleansing were performed before surgery ($p=0.029$).

There are 12 cases with SSI in Table 5 This showed SSI occurred not only in dirty wounds but also in clean-contaminated wounds, and 4 premature babies were included. Surgical site culture showed positive results in 8 patients, and methicillin-resistant staphylococcus aureus (MRSA) or extended-spectrum β -lactamase (ESBL) was cultured in 4 cases. There was no mortality related to SSI, but one patient had SSI immediately after surgery, which resulted in vacuum application and five wound revisions, followed by enterocutaneous fistula. Fistula improved after conservative treatment.

Table 1. The demographic of patients

Patient characteristics	N = 52
Gestational age (wks), median (range)	32.9 (22-41)
≥ 37wks (n)	27
< 37wks (n)	25
Birth weight (g), median (range)	2131.9 (340-3830)
Age at operation (days), median (range)*	40.1 (1-187)
Weight at operation (g), median (range) *	2549.3 (440-5510)
Birth (n)	
in UUH	27
other hospital	25
Mortality (n)	3**

* No. of procedures = 73

**Three premature babies. They died 31, 32, and 45 days after surgery due to sepsis unrelated to SSI.

Table 2. Procedure of patients

Patient characteristics	n
Diagnosis (No. of procedures = 73)	
NEC, gastric/colon perforation	22
For stomy revision, take down	15
Midgut volvulus	10
Atresia (duodenum, jejunum, ileum)	7
Meconium plug	5
TEF	5
Mechanical ileus	3
CDH, paraesophageal hernia	3
Duplication cyst	1
Intussusception	1
Meckel's diverticulum	1
Procedures per patient (No. of patients = 52)	
1	35
2	13
3	4

Table 3. Control group versus CHG group

	Control Group n = 53	CHG group [‡] n = 20	P value
Gender M:F*	26:9	9:8	0.378
Gestational age (wks)*	32.8 ± 6.4	32.9 ± 6.3	0.965
Birth weight (g)*	2151.1 ± 1188.0	2080 ± 1210.6	0.850
Transferred from other hospital (n,%)	21 (39.6%)	8 (40)	0.067
MRSA (%)**	8/18 (44.4)	3/11 (27.3)	0.466
SSI (n,%)	12 (22.6)	0	0.029
Age at operation (days)	32.1 ± 39.2	61.2 ± 62.9	0.065
Weight at operation (g)	2467.6 ± 1277.9	2766 ± 1017.1	0.352
Operation time (min)	172.6 ± 73.6	207.0 ± 107.6	0.198
Preop Hospital Day (days)	30.1 ± 39.6	56.7 ± 64.1	0.096
Postop Hospital Day (days)	62.5 ± 46	63.2 ± 59.1	0.962

Values are presented as mean ± standard deviation or number (%)

[‡] No side effects were observed after use of CHG

*No. of patients = 52, **Positive cases/No. of patients examined

Table 4. No SSI versus SSI group

*No. of patients = 52

	No SSI (n=61) (%)	SSI (n=12) (%)	<i>P</i> value
Gestational age (wks)*	32.2 ± 6.3	36.9 ± 4.9	0.054
Birth weight (g)*	2019.8 ± 1185.8	2852.9 ± 934.9	0.083
Age at operation (wks)	41.9 ± 49.9	34.8 ± 39.3	0.684
Weight at operation (g)	2420.7 ± 1204.3	3203.3 ± 1074.5	0.040
MRSA (%)	8/21 (38.1)	3/8 (37.5)	0.785
CHG use	20 (32.8)	0 (0)	0.029
Transfer from other hospital	18 (38.3)	7 (87.5)	0.018
Operator			0.112
Surgeon 1	20 (74.1)	7 (25.9)	
Surgeon 2	41 (89.1)	5 (10.9)	
Procedures per patient			0.306
1	45 (86.5)	7 (13.5)	
2	13 (76.5)	4 (23.5)	
3	3 (75)	1 (25)	
Operation time (mins)	177.4 ± 85.6	205.4 ± 80.6	0.299
Preop Hospital Day (days)	38.3 ± 50.5	32.9 ± 39.1	0.712
Postop Hospital Day (days)	65.0 ± 52.0	47.4 ± 21.8	0.135

**Positive cases/No. of patients examined, Values are presented as mean ± standard deviation or number (%)

Table 5. SSI cases

No.	Dx	Operation	Gestational age	Birth weight	MRSA screening	Preop HD(days)	Postop SSI (days)	Wound culture	Antibiotics	Use of Antibiotic	Cx
1	SB Perforation	SB R&A	39	3240	negative	0	8		amp, GM	6	
2	M. ileus	small bowel decompression	39	3240		26	7		mero	5	
3	Gastric Perforation	wedge resection, primary repair	41	3800	negative	0	20	E.coli	vanco, mero ->mero	30	
4	Ileostomy status d/t NEC	ileostomy T/D	22	600		103	5		vanco, mero	14	
5	NEC	ileal segmental resection, ileostomy	26	890	negative	41	9	K.pneumoniae	vanco, mero	8	
6	Colon Perforation	colostomy	38	3420	MRSA(+)	0	1*	S.hemolyticus	vanco, mero	31	Yes**
7	NEC	Colostomy T/D	28	780		78	5	S.hemolyticus	vanco, mero	31	
8	EA c TEF	TEF ligation & EEstomy	38	2790	negative	3	7		vanco, mero	12	
9	Ileal atresia	SB R&A	37	2840	MRSA(+)	4	15	MRSA	cefa,metro-> vanco, mero	29	
10	Colonic atresia	ileocolic anastomosis	30	1310		93	1	MRSA, ESBL E.coli	cefa,metro-> vanco, mero	25	
11	Ileal atresia	Ileocecal R&A	39	2990	MRSA(+)	2	3	MRSA	cefa,metro-> vanco, mero	23	
12	Jejunostomy status d/t midgut volvulus	jejunostomy T/D	38	3340	negative	80	3	MRSA, ESBL E.coli	cefa,metro-> vanco, mero	15	

*open wound, vaccumm apply, **enterocutaneous fistula Dx;diagnosis, Cx;complication, SB;small bowel, T/D;take down, MRSA;Methicillin-resistant Staphylococcus

aureus, ESBL;Extended-spectrum β -lactamase, amp;ampicillin, GM;gentamycin, vanco;vancomycin, mero;meropenem, cefa;ceftotaxime, metro;metronidazole

Discussion

Our study demonstrated the efficacy of CHG double cleansing in reducing SSIs among NICU surgical patients and confirmed the safe use of CHG in neonates, including premature infants, without significant complications.

CHG a chlorinated cationic bisguanide, initially discovered in the United Kingdom, stands as the most widely employed antiseptic agent (17). Exhibiting bacteriocidal properties, CHG augments cell membrane permeability, resulting in a swifter onset of action and is effective against both Gram-positive and Gram-negative bacteria (18). Particularly noteworthy is its effectiveness against resistant organisms including MRSA, Vancomycin resistant enterococcus (VRE), Streptococci, which are a significant cause of infection among NICU patients (15,19). CHG also more strongly binds to protein in the outermost layer of the skin, withstanding removal by alcohol and promptly diminishing skin organisms after a single application (20).

Surgical sites face an increased risk of SSIs when tissue harbors over 10^5 microorganisms per gram of tissue. Preoperative CHG usage aims to reduce microbial burden on the skin, thereby minimizing intraoperative contamination at the surgical site (21). Literature review indicates that CHG is more effective than iodine at reducing skin colonization, bacteremia, CLASBI, and culture contamination (22,23).

Despite the usefulness of CHG, safety issues of CHG preparations still remain a concern in infants, including preterm infants. UK national evidence-based guidelines recommend use of 2%CHG-70%IPA for skin antisepsis in “adults and older children” due to the lack of evidence and specific safety concerns in infant population (24). The CDC offers research-based skin preparation recommendations for adults but lacks guidance for infants (14).

The immature skin of preterm infants, characterized by poor dermal-epidermal cohesion and a thin, poorly developed stratum corneum, renders them susceptible to chemical burns, dehydration, infection, and systemic absorption of topical solutions like CHG and iodine (25). Because of these characteristics, concerns regarding skin breakdown and percutaneous absorption were the most common reservations clinician cited for their hesitation to use CHG (20).

Skin irritation, in the form of erythema and contact dermatitis, stands out as the most commonly reported adverse event after CHG use (17). While these episodes of dermatitis may have been secondary to CHG, it is noteworthy that local skin reactions post-CHG use, particularly when associated with

occlusive dressings, have been documented in multiple studies (22,26). Interestingly, contact dermatitis has not been reported in infants undergoing full-body CHG skin cleansing when occlusive dressings were deemed unnecessary, even for very low birth weight infants and neonates as young as 28 weeks gestational age (20,27). Consistent with these findings, our study observed no instances of skin irritation, we concur with the perspective that skin irritation may indeed be associated with the use of occlusive dressings. However, we still emphasize the need for caution during CHG use and advocate for meticulous post-application skin observation. We acknowledge the importance of ongoing vigilance, as there have been reported cases of skin burns following CHG use. These instances, although rare, have been noted primarily in low-birth-weight neonates (<1,500 g) (22,28). Caution is paramount as chemical burn can lead to hypothermia, excessive water loss, sepsis and renal failure (29).

The clinical significance of detecting CHG in the blood is unknown as there are no established values defining a safe concentration of CHG in the blood. In this study, the measurement of CHG concentrations in the patients' blood was not performed, precluding the confirmation of systemic absorption of CHG. Mullany's review study revealed that after topical applications of CHG, some percutaneous absorption occurs, particularly in preterm newborns, but only at trace levels (30). Although CHG was detected in their bloods, none of them have reported any side effects, including neurotoxicity or skin toxicity. However, the available data on safety are incomplete. The clinical significance of elevated CHG concentrations remains to be determined in further clinical investigations.

Despite these issues, practice surveys have confirmed its use in patients with a broad range of chronological ages, gestational ages, and birth weights (10,11, 19). Surveys showed that CHG used in NICU, increasing from 57% in 2009 to 86% in 2014 in the USA (7,28). In 2012, FDA relaxed its labelling wording on CHG from 'do not use in premature or low birth weight infants or children less than 2 months of age' to 'use with care in premature infants or infants under 2 months of age'(5).

Nevertheless, CHG usage in NICU has primarily centered around the antisepsis of CVC or cord cleansing, with a noticeable dearth of data regarding its application in NICU surgical patients. Despite the absence of comparative effectiveness evidence in SSI prevention and the documented risk of systemic toxicity through cutaneous iodine absorption leading to subclinical hypothyroidism, Povidone-Iodine (PI) is commonly employed as a skin preparation agent for neonatal surgery in most children's hospitals. A recent systematic review encompassing 34 articles on preoperative preparation solutions for infants aged between 24 weeks postmenstrual age and 3 months old revealed moderate-quality evidence supporting the use of CHG over iodine for skin antisepsis before surgery (22). The authors

also have traditionally employed PI; however, recent studies demonstrating the safe use of CHG in NICU prompted a shift to CHG as the preoperative skin antiseptics for neonates, including premature infants from 2019.

In the past, the routine practice of employing antiseptic agents for full-body cleansing of newborn infants was widespread, although this approach has seen a decline in recent decades due to the advocacy of dry skin care. Research on whole-body CHG cleansing on neonatal infections is only a few studies available. In Norway and Nepal, have delved into the realm of whole-body CHG cleansing, demonstrating a reduction in superficial infections and mortality among neonates (19). However, here is a notable absence of studies specifically investigating the use of CHG in NICU surgical patients. Berrondo reported is the only study to evaluate the use of pre-operative CHG baths in an exclusively pediatric population (16). In that study, the authors found that the use of pre-operative antiseptics with CHG baths and wipes in pediatric patients undergoing outpatient hernia/hydrocele repair and/or orchiopexy did not affect the rate of postop SSI and no adverse events. However, as SSI in pediatric inguinal hernia repair, hydrocele repair, and orchiopexy is low, range from 0.8% to 1.6%, and that study primarily focus on older children, the authors believe that this differs from our study, which specifically targeted NICU patients with clean-contaminated/dirty wounds.

In the adult population, many studies have demonstrated the efficacy of preoperative antiseptics using CHG baths and/or wipes. A 2015 study assessed the benefit of a pre-admission shower with 4% CHG from a pharmacokinetic perspective, defining the appropriate dose, timing and duration (14). Our CHG double cleansing method adapted from whole-body baths in adults, aim to minimize side effects and to maximize the baths effect by covering the broadest possible surgical area, including the abdomen and chest.

Regarding the appropriate dose and the presence of alcohol in CHG use, opinions in adults are still divided, and there is even less consensus on suitable guidelines for neonatal use. There have been several studies the concentration of CHG in neonates with conflicting results. Adams demonstrated that 2% CHG is more effective than 0.5% CHG in reducing colony-forming units (32). A systemic review study indicated that 0.25% was the more effective than 0.4% and 0.44% in reducing neonatal skin bacterial colonization (7). In Mullany's study, the decline in skin bacterial colonization was greatest in the 1.00% group, followed by 0.50% and the 0.25% group (30). Therefore, the optimal concentration of CHG remains to be determined in future studies.

The CHG-alcohol product used for most of preoperative preparations, which contains 70% isopropyl

alcohol and 2% CHG. In addition to faster drying times, it is believed that the combination of alcohol and another antiseptic delivers synergistic mechanisms to reduce microbial count. In vitro studies have shown that alcohol based CHG achieved better bactericidal activity than aqueous CHG of the same concentration (32). In UK NICU survey showed that approximately half use a 2% concentration of CHG and 60% an IPA-containing CHG formulation are presently being used (33).

The optimal number of applications of CHG to ensure a maximum skin surface concentration is not determined. Most protocols recommend two to three separate applications of CHG prior to surgery because it is accepted that skin surface antimicrobial activity is enhanced following multiple applications (31). However, there is no clinical or pharmacologic data suggesting that three, rather than two.

In this study, a 0.5% CHG formulation containing 70% isopropyl alcohol (IPA) and 2% CHG were utilized. Further detailed investigations on the concentration, presence of alcohol, frequency, and applied time of CHG use are still warranted. However, regardless of the concentration or application method chosen, extreme caution is always necessary concerning skin toxicity in neonates. Close observation of the skin before and after use is required, with efforts to minimize the amount of solution applied and careful attention to prevent the solution from spreading beyond the targeted area. Special care should be taken to avoid solution pooling in areas under or dependent on the infant. As demonstrated in several studies, heightened caution is particularly crucial in extremely preterm infants.

Although this study confirmed that the use of CHG double cleansing was effective and safe for SSI rate in our patients, based on an absence of any toxicity, it does have limitations some of which are inherent to study design. This study was retrospective nature and comparison with historic controls, which allow the possibility of other confounding factors. The comparison solely with the iodine-alone group, specifically with the CHG double cleansing protocol, limits our ability to discern whether the preoperative skin preparation efficacy of CHG is superior to that of iodine or if it is a result of the additional cleansing associated with the modified baths concept. Moreover, the inclusion of diverse procedure type, different gestational age, weight, specific patient situations such as septic condition, and different time that applying CHG according to elective or emergency surgery, introduces confounding factors that may impact SSI rates. A further matched cohort study is needed to identify factor which influence rates of SSI. In this study, SSI were identified through review of documentation in the medical chart rather than in real time, potentially leading to incomplete or missing data. This study is a single institutional experience and a relatively small sample size emphasizes the need for

larger multicenter trials to comprehensively assess the efficacy and safety of CHG. Additionally, these trials should explore variations in CHG formulations, concentrations, and combinations for use in NICU patients. Future research should also focus on long-term safety considerations.

Nevertheless, this study represents, to the best of our knowledge, the first application and description of preoperative preparation with CHG double cleansing to reduce SSI in NICU surgical patients. We anticipate that this study serves as an initial step towards establishing standard antibiotic practices in surgical neonates.

References

1. Clements KE, Fisher M, Quaye K, O'Donnell R, Whyte C, Horgan MJ. Surgical site infections in the NICU. *J Pediatr Surg*. 2016 Sep;51(9):1405-8. doi: 10.1016/j.jpedsurg.2016.04.002. Epub 2016 Apr 11.
2. Magill S, Hellinger W, Cohen J, Kay R, Bailey C, Boland B, et al. Prevalence of healthcare-associated infections in acute care hospitals in Jacksonville, Florida. *Infect Control Hosp Epidemiol* 2012;33:283–91. doi: 10.1086/664048. Epub 2012 Jan 12
3. Segal I, Kang C, Albersheim SG, Skarsgard ED, Lavoie PM. Surgical site infections in infants admitted to the neonatal intensive care unit. *J Pediatr Surg* 2014;49:381–4. doi: 10.1016/j.jpedsurg.2013.08.001
4. Zachariah P, Saiman L. Expanding antimicrobial stewardship strategies for the NICU: Management of surgical site infections, perioperative prophylaxis, and culture negative sepsis. *Semin Perinatol* 2020;44:151327. doi:10.1016/j.semperi.2020.151327.
5. Drugs@FDA: FDA approved drug products. New drug application (NDA): 021669. US food and drug administration website, 2018. Available: <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=021669>
6. The Food and Drug Administration. Front panel labeling format for chloraprep one step, https://www.accessdata.fda.gov/drugsatfda_docs/label/2003/20832scp004_chloraprep_lbl.pdf; 2013 [accessed 10 October 2021]
7. Zhou J, Mei L, Chen S. Effect of chlorhexidine cleansing on healthcare-associated infections in neonates: a systematic review and meta-analysis. *Arch Dis Child Fetal Neonatal Ed*. 2022 Jul;107(4):398-407. doi: 10.1136/archdischild-2021-322429. Epub 2021 Dec 23
8. Cleves D, Pino J, Patiño JA, Rosso F, Vélez JD, Pérez P. Effect of chlorhexidine baths on central-line-associated bloodstream infections in a neonatal intensive care unit in a developing country. *J Hosp Infect*. 2018Nov;100(3):e196-e199. doi: 10.1016/j.jhin.2018.03.022. Epub 2018 Mar 26.
9. Quach C, Milstone AM, Perpête C, Bonenfant M, Moore DL, Perreault T. Chlorhexidine bathing in a tertiary care neonatal intensive care unit: impact on central line-associated bloodstream infections. *Infect Control Hosp Epidemiol* 2014 Feb;35(2):158-63. doi: 10.1086/674862. Epub 2013 Dec 24.

10. Garland JS, Alex CP, Mueller CD, D Otten, C Shivpuri, M C Harris, et al. A randomized trial comparing povidone-iodine to a chlorhexidine gluconate-impregnated dressing for prevention of central venous catheter infections in neonates. *Pediatrics*. 2001 Jun;107(6):1431-6. doi: 10.1542/peds.107.6.1431.
11. Levy I, Katz J, Solter E, amra Z, Vidne B, Birk E, et al. Chlorhexidine-impregnated dressing for prevention of colonization of central venous catheters in infants and children: a randomized controlled study. *Pediatr Infect Dis J*. 2005 Aug;24(8):676-9. doi: 10.1097/01.inf.0000172934.98865.14.
12. Anderson DJ, Podgorney K, Berrios-Torres SI, Bratzler DW, Dellinger EP, Greene L, et al. Strategies to prevent surgical site infections in acute care hospitals. *Infect Control Hosp Epidemiol*. 2014 Jun;35(6):605-27. doi: 10.1086/676022.
13. Persichino J, Lee H, Sutjita M, Talavera K, San-Agustin G, Gnass S. Reducing the Rate of Surgical Site Infections After Breast Surgery With the Use of Larger Volumes of 4% Chlorhexidine Gluconate Solution as Preoperative Antiseptic Showering. *Infect Control Hosp Epidemiol*. 2017 Mar;38(3):373-375. doi: 10.1017/ice.2016.293. Epub 2017 Jan 5.
14. Berrios-Torres SI, Umscheid CA, Bratzler DW, Leas B, Stone EC, Kelz RR, et al. Centers for Disease Control and Prevention Guideline for the Prevention of Surgical Site Infection, 2017. *JAMA Surg*. 2017 Aug 1;152(8):784-791. doi: 10.1001/jamasurg.2017.0904.
15. Climo MW, Sepkowitz KA, Zuccotti G, Fraser VJ, Warren DK, Perl TM, et al. The effect of daily bathing with chlorhexidine on the acquisition of methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, and healthcare-associated bloodstream infections: results of a quasi-experimental multicenter trial. *Crit Care Med*. 2009 Jun;37(6):1858-65. doi: 10.1097/CCM.0b013e31819ffe6d.
16. Berrondo C, Ahn JJ, Shnorhavorian M. Pre-operative skin antisepsis with chlorhexidine gluconate baths and wipes does not prevent postoperative surgical site infection in outpatient pediatric urologic inguinal and scrotal surgery. *J Pediatr Urol*. 2019 Dec;15(6):652.e1-652.e7. doi: 10.1016/j.jpuro.2019.08.013. Epub 2019 Aug 24.
17. Sathiyamurthy S, Banerjee J, Godambe SV. Antiseptic use in the neonatal intensive care unit - a dilemma in clinical practice: An evidence based review. *World J Clin Pediatr*. 2016 May 8;5(2):159-71. doi: 10.5409/wjcp.v5.i2.159.

18. Helgeland K, Heyden G, Rolla G. Effect of chlorhexidine on animal cells in vitro. *Scand J Dent Res* 1971; 79(3): 209–215.
19. Hocevar SN, Lessa FC, Gallagher L, Conover C, Gorwitz R, Iwamoto M. Infection prevention practices in neonatal intensive care units reporting to the national healthcare safety network. *Infect Control Hosp Epidemiol*. 2014 Sep;35(9):1126-32. doi: 10.1086/677636. Epub 2014 Jul 25.
20. Chapman AK, Aucott SW, Milstone AM. Safety of chlorhexidine gluconate used for skin antisepsis in the preterm infant. *J Perinatol*. 2012 Jan;32(1):4-9. doi: 10.1038/jp.2011.148. Epub 2011 Oct 27.
21. Echols K, Graves M, LeBlanc KG, Marzolf S, Yount A. Role of antiseptics in the prevention of surgical site infections. *Dermatol Surg*. 2015 Jun;41(6):667-76. doi: 10.1097/DSS.0000000000000375.
22. Ng AL, Jackson, C, Kazmierski M. Evaluation of antiseptic use in pediatric surgical units in the United Kingdom-Where is the evidence base? *European Journal of Pediatric Surgery*, 2016 Aug;26(4):309-15. doi: 10.1055/s-0035-1559883.
23. Sankar MJ, Paul VK, Kapil A, Kalaivani M, Agarwal R, Darmstadt GL, et al. Does skin cleansing with chlorhexidine affect skin condition, temperature and colonization in hospitalized preterm low birth weight infants? A randomized clinical trial. *Journal of Perinatology*. 2009 Dec;29(12):795-801. doi: 10.1038/jp.2009.110. Epub 2009 Aug 27.
24. Loveday HP, Wilson JA, Pratt RJ, Golsorkhi M, Tingle A, Bak A, et al. epic3: national evidence based guidelines for preventing healthcare-associated infections in NHS hospitals in England. *J Hosp Infect* 2014;86:S1–70.
25. Oranges T, Dini V, Romanelli M. Skin Physiology of the Neonate and Infant: Clinical Implications. *Adv Wound Care (New Rochelle)*. 2015 Oct 1;4(10):587-595. doi: 10.1089/wound.2015.0642.
26. Visscher M, deCastro MV, Combs L, Perkins L, Winer J, Schwegman N, et al. Effect of chlorhexidine gluconate on the skin integrity at PICC line sites. *J Perinatol*. 2009 Dec;29(12):802-7. doi: 10.1038/jp.2009.116. Epub 2009 Aug 20.
27. Cowen J, Ellis SH, McAinsh J. Absorption of chlorhexidine from the intact skin of newborn infants. *Arch Dis Child* 1979; 54(5): 379–383.

28. Tamma PD, Aucott SW, Milstone AM. Chlorhexidine use in the neonatal intensive care unit: results from a national survey. *Infect Control Hosp Epidemiol.* 2010 Aug;31(8):846-9. doi: 10.1086/655017.
29. Reynolds PR, Banerjee S, Meek JH. Alcohol burns in extremely low birthweight infants: still occurring. *Arch Dis Child Fetal Neonatal Ed.* 2005 Jan;90(1):F10. doi: 10.1136/adc.2004.054338.
30. Mullany LC, Darmstadt GL, Tielsch JM. Safety and Impact of Chlorhexidine Antisepsis Interventions for Improving Neonatal Health in Developing Countries. *Pediatr Infect Dis J.* 2006 Aug;25(8):665-75. doi: 10.1097/01.inf.0000223489.02791.70.
31. Edmiston CE Jr, Leaper D. Should preoperative showering or cleansing with chlorhexidine gluconate (CHG) be part of the surgical care bundle to prevent surgical site infection? *J Infect Prev.* 2017 Nov;18(6):311-314. doi: 10.1177/1757177417714873. Epub 2017 Jul 26.
32. Adams D, Quayum M, Worthington T, Lambert P, Elliott T. Evaluation of a 2% chlorhexidine gluconate in 70% isopropyl alcohol skin disinfectant. *J Hosp Infect.* 2005 Dec;61(4):287-90. doi: 10.1016/j.jhin.2005.05.015. Epub 2005 Oct 10.
33. Clarke P, Craig JV, Wain J, Tremlett C, Linsell L, Bowler U, et al. Safety and efficacy of 2% chlorhexidine gluconate aqueous versus 2% chlorhexidine gluconate in 70% isopropyl alcohol for skin disinfection prior to percutaneous central venous catheter insertion in preterm neonates: the ARCTIC randomised-controlled feasibility trial protocol. *BMJ Open.* 2019 Feb 19;9(2):e028022. doi: 10.1136/bmjopen-2018-028022.

국문요약

연구 목적: 이 연구는 신생아중환자실 환자의 수술 부위 감염(SSI) 발생률을 줄이는 데 있어 수술 전 클로르헥시딘 글루코네이트(CHG) 이중 세척의 효능과 안전성을 평가하는 데 목적이 있습니다.

연구 방법: 2013년부터 2022년까지 신생아중환자실에서 73건의 수술을 받은 56명의 환자를 대상으로 후향적 연구를 실시했습니다. CHG 이중 세척은 0.5% CHG와 70% 이소프로필 알코올을 포함하였습니다. 정규 수술의 경우 수술 전날 밤에, 응급 수술의 경우 1시간 전에 신생아중환자실에서 시행되었고, 양쪽 겨드랑이 라인을 포함하여 목에서 치골까지 몸통 앞쪽을 세척했습니다. 수술 부위는 수술 직전에 2% CHG를 사용하여 세척을 한번 더 실시했습니다. 70% 요오드만 사용한 대조군(2013~2018년)과 CHG 이중 세척을 사용한 CHG 그룹(2019~2022년)을 비교하였고, 수술 후 30일 이내에 SSI의 발생을 평가했습니다.

결과: 전체 환자군에서 SSI 발생률은 16.4%(n=12)였습니다. 대조군의 22.6%에서 SSI가 발생했으며, CHG 그룹에서는 SSI 발생 사례가 없었습니다($p = 0.029$). 다른 변수에서는 통계적으로 유의미한 차이가 없었으며, CHG 그룹에서 부작용은 보고되지 않았습니다.

결론: 신생아중환자실 환자의 수술에서 CHG 이중 세척은 요오드를 사용한 기존 피부 세척에 비해 SSI 발생을 효과적으로 감소시켰습니다. 이 연구는 미숙아를 포함한 신생아에게 심각한 합병증 없이 CHG를 안전하게 사용할 수 있음을 뒷받침합니다. 이번 연구 결과를 바탕으로 추가적인 전향적인 연구가 이루어진다면 SSI 발생률을 낮출 수 있는 최적의 치료방법을 설립할 수 있을 것으로 생각합니다.