

Comparing Hand-hygiene Measures in a Neonatal ICU: A Randomized Cross-over Trial

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Objective: To compare plain soap, alcohol hand rub and iodophors as hand hygiene measures in a neonatal intensive care unit (NICU).

Design: Randomized, crossover, three-armed, controlled trial with blinded outcome measurement

Setting: Level III NICU

Participants: 35 NICU nurses

Intervention: Participants were assigned to plain soap hand washing, alcohol hand rub and povidone-iodine hand scrub by a random cross-over design. Interventions were preceded by 14-day neutral periods. Cultures from hands were taken before and after each hand-hygiene use, prior to 5 patient-care activities.

Main outcome measure: The primary outcome was mean post-hygiene colony forming unit count (CFU-C).

Results: There were differences between soap, alcohol and povidone groups *vis-à-vis* post-hygiene CFU-C [median: 60, 8 and 10.5, respectively ($P<0.001$)], absolute reduction in CFU-C [median: 15, 100 and 40, respectively ($P<0.001$)], percent reduction in CFU-C [median: 33.3, 92 and 87, respectively ($P<0.001$)] and proportion with "low CFU-C" [47%, 71% and 72%, respectively ($P<0.001$)]. Alcohol [Adjusted OR 3.2 (95% CI 1.9, 5.3)], povidone-iodine [AOR 3.1 (95% CI 1.8, 5.3)] and high pre-hygiene CFU-C (>300) [AOR 0.18 (95% CI 0.1, 0.3)] were independently associated with "low CFU-C".

Conclusions: After a 2-minute hand wash at entry into NICU, alcohol hand rub and povidone-iodine scrub are superior to plain soap hand wash for subsequent decontamination of hands of nurses working in NICU.

Keywords: Hand hygiene, Newborn, Nurse.

Hand hygiene is the most important practice that reduces the risk of transmission of microbes by contact, thereby reducing nosocomial infections [1]. Although hand washing with plain soap has been a time-honored practice, hand rubbing with alcohol-based solutions ensures better compliance and greater reduction of bacterial counts, as do iodophors [2-4]. The Centers for Disease Control (CDC) recommended the use of alcohol-based hand rubs, based on available evidence [5]. However, the CDC acknowledged that there are still several lacunae in the evidence, and need for better trials.

There is a paucity of well-designed randomized, cross-over trials in patient care settings, particularly so in the setting of a Neonatal Intensive Care Unit (NICU). There are no such studies directly comparing hand washing with plain soap, alcohol-based hand rub and iodophors. We, therefore, conducted a trial with the aim of comparing the efficacy of the three common methods.

METHODS

It was a randomized, cross-over clinical trial with blinded

outcome measurement. The trial compared hand washing with plain soap, alcohol hand-rub and povidone iodine hand scrub. It was performed in a level III NICU of a tertiary care institute in Northern India. Subjects were staff nurses working for 1 year or more in the NICU, and willing to comply with the instructions related to hand hygiene. Nurses with a history of iodine sensitivity were excluded. Subjects were enrolled after informed written consent. The study was approved by the Institutional Ethics Committee.

There were 14-day neutral periods for each subject prior to each intervention. During the neutral periods, enrolled nurses received detailed instructions regarding the correct use of the hand hygiene measures. Elbow operated taps were used. To allow the natural hand flora to establish, they were asked to use only non-antimicrobial soaps both in the NICU and at home and elsewhere during the neutral periods [6]. They were also provided a list of brand names of items that they had to avoid during these periods- soaps, lotions, body washes, shampoos and deodorants, with antimicrobial activity.

Randomization was done at the end of the first neutral period. Serially numbered opaque and sealed envelopes were opened as nurses were enrolled. Each envelope had a slip of paper bearing the random sequence of the 3 hand-hygiene methods. The sequence was generated online. The methods were:

- (a) *Soap*: Hands washed with a plain (i.e. non-antimicrobial) bar soap for 15 seconds and rinsed under running tap water. Hands were dried with autoclaved hand wipes after the hand wash. The bar soap was placed in a soap tray with drainage system.
- (b) *Alcohol*: Alcohol hand rub, which comprised of 45% 2-propranol, 30% 1-propranol and 0.2% ethyl-hexadecyl-dimethyl-ammonium-ethylsulphate (Sterilium, Raman and Weil Pvt Ltd., Mumbai, India). Two ml of the solution was dispensed, smeared on the hands and allowed to dry.
- (c) *Povidone*: Povidone-iodine hand scrub with 0.5% w/v available iodine (Povicidal, Cadila Pharmaceuticals Ltd., Dhokla, India). Two ml of the solution was applied, scrubbed for 15 seconds and rinsed under running tap water. Hands were dried with autoclaved hand wipes after the procedure.

On the day of intervention, the nurse was allowed to care for only one baby in the NICU. That baby's blood culture reports of the last 14 days were recorded and skin swab cultures were taken from the baby's dorsum of hand, umbilical stump and groin. Irrespective of the allocated hand hygiene measure, two minutes of hand washing with plain soap and water was done when the enrolled nurse entered the NICU at the beginning of her shift. Following the mandatory 2-minute hand wash, the nurse used only the allocated method of hand hygiene during the rest of that shift; and was observed till she performed five healthcare activities that required prior hand hygiene. These included tube feeding, suctioning, recording vital parameters, measuring abdominal girth, changing sheets, attaching probes, handling vascular access, changing position, clothing baby, removing nappy and handling incubators or ventilators. One minute before and one minute after each hand hygiene procedure, the finger tips and palm of the dominant hand were pressed against a sterile media plate [Standard Methods Agar with Tween 80 and Lecithin (Catalogue No. M302, HiMedia Labs, Mumbai, India)]. The plates were incubated under aerobic conditions for 48 hrs and colonies counted. Bacterial contamination of the hand was assessed in terms of colony forming unit count (CFU-C). CFU-C was limited to 300 units, beyond which confluent growth occurred. The microbiologist was blinded to the hand hygiene method used and the

identity of the subject. Enrolled nurses were asked to avoid tasks involving direct contact with infected fluids, fecal matter or other grossly soiled materials, because these tasks would have resulted in much higher degree of hand contamination and necessitated hand washing for 2 minutes. These tasks were performed by other nurses not involved in the study. Nurses were asked to report adverse effects, if any, after use of the prescribed hand hygiene measures; and to rate the most convenient measure.

The primary outcome was mean post-hygiene CFU-C. Secondary outcomes included absolute and percentage reduction of CFU-C, and post-hygiene "low CFU-C" (arbitrarily taken as less than 50). In a cross-over study, 35 subjects could identify an inter-group difference in the mean post-hygiene CFU-C, which was 70% of the within-subject standard deviation, with 80% power and a 5% level of two-sided -error.

Statistical analysis: Tests of normality confirmed the skewed distribution of numerical data. Three-way comparison of numerical variables was done by the Kruskal-Wallis test and two-way by the Mann Whitney U test. The absolute decrease in CFU-C was defined as difference between pre and post-hygiene CFU-C, while the percent decrease was $[\text{pre-hygiene CFU-C} - \text{post-hygiene CFU-C}] \times 100 / \text{pre-hygiene CFU-C}$. Multivariate logistic regression was performed with post-hygiene "low CFU-C" as the dependent variable and hand hygiene measures, high pre-hygiene CFU-C (≥ 300), neonatal surface colonization, and neonatal sepsis status as predictor variables.

RESULTS

A total of 36 female staff nurses were evaluated, of which 35 were included, as one had iodine sensitivity (**Fig. 1**). The age of the nurses ranged from 25 to 48 years. They were working in the NICU for a mean duration of 7.1 years, ranging from 1 to 19 years.

The total number of patient care activities monitored was 175 in each group. The pre-hygiene and post-hygiene measure sample was 166 and 167, 164 and 167, and 162 and 162, respectively for Plain soap, alcohol hand rub and povidone iodine group, respectively. Thirty-three pre-hygiene and 29 post-hygiene plates were not readable after incubation due to extraneous contamination of the plate; and were excluded from analysis. The number of procedures for which both pre- and post-hygiene CFU-C were available was 159, 161 and 153 in the Soap, Alcohol and Povidone groups, respectively.

Baseline characteristics (not directly related to

TABLE I COMPARISON OF BASELINE CHARACTERISTICS IN 3 HAND HYGIENE GROUPS

	Soap (n=35)	Alcohol (n=35)	Povidone (n=35)
Pre-hygiene CFU-C*			
Mean±SD	158.7± 129	161.8± 122	145.4± 128
Median (IQR)	105 (31-300)	150 (31-300)	89 (25-300)
Neonatal sepsis in last 14 days(%)	12 (34.2)	11 (31.4)	11 (31.4)
Neonatal skin colonization: any site(%)	23 (65.7)	16 (45.7)	20 (57.1)
Neonatal groin colonization(%)	17 (48.6)	22 (62.8)	16 (45.7)
Neonatal umbilicus colonization(%)	19 (54.3)	22 (62.8)	24 (68.6)
Neonatal hand colonization(%)	26 (74.3)	26 (74.3)	23 (65.7)

*Calculated with number of pre-hygiene plates as denominator: 166, 164 and 162 for soap, alcohol and povidone groups respectively

participants) were comparable in all 3 groups (**Table I**). Among the colonizers, gram-positive organisms predominated, constituting 70.1%. A total of 175 activities were monitored in each study group. Patient-care activities were similar across groups ($P=0.339$). Data regarding post-hygiene CFU-C are compared in **Table II**. Pair-wise comparisons showed that Soap was significantly inferior to both Alcohol and Povidone. A total of 41.9%, 36.5% and 38.3% pre-hygiene plates were labeled as having CFU-C of 300 in Soap, Alcohol and Povidone groups respectively, because colonies could not be discretely counted beyond 300; and this proportion was not significantly different across groups ($P=0.5$). For procedures where the pre-hygiene CFU-C was above 300, there may have been an underestimation of the extent of decline in the CFU-C. A repeated measure ANOVA was also performed to compare the

CFU-C before and after hand-hygiene measures. A significant main effect due to type of hand-hygiene measure was observed. The estimated marginal means of the 3 groups was significantly different, being 138.1, 106.6 and 103.1 in Soap, Alcohol and Povidone groups respectively ($P=0.002$). There was a significant decline in CFU-C, the estimated marginal means being 156.8 before and 75.1 after any hand-hygiene, respectively ($P<0.001$). The 'CFU-C x hand-hygiene method' interaction was significant ($P<0.001$).

The proportions of plates with post-hygiene "low CFU-C" was similar following use of Alcohol and Povidone, but significantly lower following use of Soap (47.3%). Despite use of a hand-hygiene measure, for some procedures there was either no decrease in the CFU-C or failure to decrease below 300. The proportion of such plates was significantly higher in the Soap versus the other groups; and was also significantly higher when the Povidone group was compared with Alcohol ($P=0.02$).

On multivariate logistic regression for post-hygiene "low colony CFU-C" as the dependent variable, the use of Alcohol, Povidone and high pre-hygiene CFU-C (≥ 300) were independently associated with post-hygiene "low CFU-C" (**Table III**).

TABLE II COMPARISON OF HAND COLONY COUNT DATA AFTER USE OF HAND HYGIENE Measure

Hand colony count	Hand hygiene measure		
	A Soap N=167	B Alcohol N=167	C Povidone N= 162
Post-hygiene	60 [#] (10,300)	8(0,60)	10.5(0,100.5)
Absolute decrease*	15(0,103)	100(15,235)	40(1.5,159)
Percent decrease*	33.3(0,82)	92(67,100)	87(40,100)
CFU-C < 50 (%) [#]	79(47.3)	119 (71.3)	116(71.6)
No decrease or confluent (%) [*]	69 (43.4)	15 (9.3)	28 (18.3)

[#] Median (1st, 3rd quartile); ^{*}Included only hand hygiene procedures for which both pre- and post hand hygiene colony counts were available: 159, 161 and 153 in groups A, B and C respectively; 3-way and A vs B P value was <0.001 for all measures and for A vs C comparison for all measures except percent decrease ($P=0.04$); All B vs C comparisons showed $P<0.05$ except last; [#]post-hygiene.

TABLE III MULTI-VARIATE LOGISTIC REGRESSION FOR PREDICTING "LOW POST-HYGIENE CFU-C"

Predictor	Adjusted OR	95% CI	P value
Alcohol hand rub	3.2	1.9–5.4	<0.001
Povidone-iodine	3.1	1.8–5.3	<0.001
High pre-hygiene CFU-C	0.18	0.1–0.3	<0.001
Surface colonization	1.1	0.7–1.7	0.78
Neonatal sepsis	0.7	0.4–0.1	0.11

All the staff nurses reported that the use of Alcohol hand rub was the most convenient measure. There were no reports of any adverse effects (including contact dermatitis, rash or dryness) due to any of the interventions during the study.

DISCUSSION

This study showed that in the setting of an NICU, hand washing with plain soap is inferior to alcohol hand rub and povidone iodine hand scrub; and between the two, alcohol hand rub is slightly superior to povidone-iodine.

Although the superiority of alcohol-based hand rubs has been documented previously [8], there were methodological limitations in many previous studies. There are 21 studies tabulated in CDC-MMWR-2002, regarding comparison of hand hygiene measures in terms of mean reduction of hand colony counts, out of which 13 were performed on artificially contaminated hands of volunteers and only 8 were on existing hand flora. Of the 8 studies on existing hand flora, only 4 studies were conducted in patient care settings- one in a Neonatal Unit; one in adult ICU, and two in adult wards [8,10].

An important strength of the current study was that the hand hygiene measures were evaluated during actual use in a NICU setting by an RCT with cross-over design. This eliminated selection bias and increased the power of the study. While the intervention could not be blinded for practical reasons, the outcome measurement was blinded. A minimum period of 1 year of working in the NICU environment provided an opportunity for the hand flora of all nurses to stabilize, and also to ensure that the enrolled nurses were equally familiar with NICU routines.

Webster, *et al.* [11] reported on a crossover trial in a neonatal care setting. However, the sample size was small ($n=8$) and the hygiene agents used were different: Chlorhexidine gluconate 4%, glycol-poly-siloxane gel and a bland liquid soap. Larson, *et al.* [12] conducted a clinical trial with a crossover design to compare the effect of an antiseptic hand wash and an alcohol hand sanitizer to determine the effect on nosocomial infection rates, skin condition and microbial counts on the hands of nurses working in NICUs. Unlike our study, individual users did not cross over; instead the products were used for 11 months in the NICU in random order. No significant differences were found in infection rates and in microbial colonization rates. The authors concluded that assessing the impact of a single intervention on infection rates was fraught with problems.

The study in an adult ICU was an RCT with

crossover design that compared plain liquid soap and alcohol. The mean reduction in the number of colony-forming units with hand washing was 49.6% for soap and water and 88.2% for alcohol ($P<0.001$) [10]. One of the studies conducted in a surgical ward assessed the relative effectiveness of a number of preparations, including alcohol and hand washing with a bar soap; and found lower density of *Staphylococcus aureus* after alcohol use [13]. Another study in a ward evaluated the immediate and residual efficacy of five surgical hand scrub products and concluded that Chlorhexidine was the most suitable one [14].

The main advantages of volunteer studies are that they are easier to organize, activities can be timed to calculate residual activity and the glove juice technique (rather than agar) can be used. However, their biggest drawback is that they do not resemble real-life clinical situations.

Unlike many other studies, a 14-day “neutral” period was used between measures in this study, based on a previous observation [9]. During this period subjects avoided use of any anti-microbial hand hygiene product; thus allowing the natural resident flora of the subjects’ hands to stabilize, and serving as a washout period for residual effects.

Since one cannot expect CFU-C to decline to zero after the use of a hand hygiene measure, one has to accept CFU-C below a certain cut-off value as being acceptably low. An exhaustive literature search did not yield any data about what constitutes an acceptably low hand CFU-C. Hence less than 50 CFU-C was taken arbitrarily as “low CFU-C”. This is a clinically important outcome because what ultimately matters to the patient is not the degree of reduction from baseline, but whether the actual CFU-C after using a hand hygiene measure is low or not. This also overcomes the limitation of dealing with confluent growth on the culture plate.

An alarming observation was the increase in CFU-C (or post-hygiene CFU-C remaining above 300) in a few cases. This observation was most frequently made after using Soap, followed by Povidone followed by Alcohol. In this study, the hand hygiene products were not cultured to check whether they were harboring bacteria. In the case of Soap, the presence of bacteria in the product may be explained; since it was a non-antimicrobial bar soap with which multiple users had a direct contact.

The study was not without its limitations. The types of organisms on the hands, the proportion of pathogenic organisms and their quantification were outside the scope

of this study. The outcomes that were meaningful to the patients *i.e.* reduction in sepsis, were not addressed in this study. Bacterial contamination was assessed by taking agar handprints. Glove juice technique was not used, which might be more effective in recovering the whole bacterial burden of the hands [15]. The design of this study, which was planned not to interfere with regular activities, did not allow using glove juice technique.

There were no adverse effects reported by nurses in our study. A study comparing 6 alcohol-based hand gels showed that none of them altered trans-epidermal water loss or caused irritation. Gels with higher glycerine content and 70% ethanol were preferred [16].

Contributors: VSS recruited subjects, conducted the study and entered data; SD designed the study, analyzed the data and wrote the manuscript; NT performed all the laboratory work; AN supervised the conduct of the study and the writing of the manuscript

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