Chlorhexidine Cleansing of the Umbilical Cord and Separation Time: A Cluster-Randomized Trial

WHAT’S KNOWN ON THIS SUBJECT: Chlorhexidine cleansing of the cord can reduce mortality in high-risk settings. Time to separation may increase with topical applications of chlorhexidine; 1 previous community trial quantified this increase and did not measure whether caretakers perceived the delay.

WHAT THIS STUDY ADDS: Single and multiple cleansing of the umbilical cord increases time to separation by ~50%, or an average of 2 to 2.5 days. Caretakers were able to detect this difference and expressed dissatisfaction, while still accepting the intervention.

abstract

OBJECTIVE: Cord cleansing with chlorhexidine reduces neonatal mortality. We aimed to quantify the impact of this intervention on cord separation time and the implications of such an increase on maternal and other caretaker’s acceptance of chlorhexidine in future scaled up programs.

METHODS: Between June 2007 and September 2009, 29 760 newborns were randomly assigned within communities in Bangladesh to receive 1 of 3 cord regimens: dry and clean cord care (comparison), single-cleansing, or multiple-cleansing with 4.0% chlorhexidine. Workers recorded separation status during home visits. Mothers of 380 infants in randomly selected clusters reported age at separation and satisfaction with cord regimen.

RESULTS: Compared with dry and clean care (mean 4.78 days), separation time was longer in the single (mean 6.90 days, difference = 2.10; 95% confidence interval: 1.85–2.35) and multiple (mean 7.49 days, difference = 2.69; 95% confidence interval: 2.44–2.95) cleansing groups. Increased separation time was not associated with omphalitis. Mothers in these groups more frequently reported “longer than usual” separation times and dissatisfaction with the separation time (11.1% and 17.6%, respectively) versus the comparison group (2.5%). Overall satisfaction with the received cord care regimen was high (96.2%).

CONCLUSIONS: Topical chlorhexidine increased cord separation time by ~50%. Caretakers are likely to detect this increase and might express dissatisfaction but still accept the intervention overall. When scaling up chlorhexidine cord cleansing, inclusion of appropriate messaging on expectation and nonrisks of increased cord separation time, in addition to the benefits of reduced infection and improved survival, might improve compliance. Pediatrics 2013;131:708–715

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KEY WORDS: chlorhexidine, umbilical cord, neonatal, cord separation time, Bangladesh

ABBREVIATIONS:
CI—confidence interval
CHW—community health worker
RR—relative risk
VHW—volunteer health worker

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Umbilical cord cleansing with 4.0% chlorhexidine can substantially reduce neonatal mortality among newborn infants in low-resource settings with high risk of infection. Randomized trials in Nepal, Bangladesh, and Pakistan have demonstrated mortality reductions ranging from 6% to 38% among live-born infants receiving single or multiple cleansing within the first days of life; 2 additional randomized trials are ongoing (Zambia, Tanzania). Although the World Health Organization (WHO) 1998 guidelines on optimal cord care recommend the use of topical antiseptics including chlorhexidine in facility or home births where infection risk is high, programs have emphasized the primary recommendation of clean and dry care. Updates in global recommendations or country-level policy based on the emerging evidence for public health impact (ie, mortality, infection, etc) will also require appropriate messaging related to other aspects of the practice that might influence acceptability, uptake, and compliance with chlorhexidine cleansing. One critical aspect is the time to separation of the cord, an endpoint frequently emphasized in high-resource settings, where the underlying risk of omphalitis and mortality are so low that estimation of impact on these critical health endpoints has been precluded. Actions reducing exposure of the cord stump to flora (eg, topical antiseptics, caesarian delivery, hygienic practice) will increase separation time. In settings where achieving hygienic conditions at birth is difficult and/or where traditional applications to the cord are frequently reported, exposure to pathogens is likely high, and separation times are generally shorter than in high-income settings. Cord separation time tends to be longer with the use of topical antiseptics, but such comparisons are mainly available in settings where infection risk is low. In high-risk, low-resource communities where infants are most likely to benefit from chlorhexidine cord cleansing, shifts in the distribution of cord separation time due to chlorhexidine remain uncharacterized. Community-based data from Nepal demonstrated that mean separation time among infants receiving chlorhexidine (5.32 days) exceeded that observed among infants not receiving chlorhexidine (4.24 days). The difference was highly significant from a statistical perspective, but the absolute increase (~26 hours) was substantially less than reported between antiseptic and non-antiseptic groups studied in hospital-based studies and other lower-risk settings and less than recently observed among infants in Zambia. It is unclear if this small difference was perceived by mothers and, if so, whether perception of increased separation time might negatively affect the likelihood of widespread acceptance of the intervention in subsequent scale-up activities.

Utilizing data from our recently completed randomized trial of chlorhexidine cleansing among newborns in Bangladesh, we aimed to extend the evidence base related to separation time. First, we present a larger sample size (>29,000 infants) from a region that is similar in cultural and socioeconomic aspects to the Nepal setting. Second, we compare both single (ie, first day) and multiple (first 7 days) applications of chlorhexidine with a nonchlorhexidine regimen. Third, we include a nested substudy of participating mother-infant dyads to compare maternal estimates of time to separation with the actual observed separation time and to understand satisfaction with the regimen received by their infant.

METHODS

Study Population and Design

Data on time to cord infection were collected within the context of a community-based cluster-randomized trial of the impact of 4.0% chlorhexidine-based cleansing regimens on neonatal mortality and morbidity in Bangladesh. Previous publications provide details on the design of the trial and estimates of the impact of the cord cleansing regimens on mortality, cord infection, and bacterial colonization of the cord. Three subdistricts within the Projanimo project area in rural Sylhet District (population ~540,000) were divided into 133 village-based clusters; these units were randomly allocated using a computer-generated sequence to 1 of 3 cord-care regimens: (1) a set of standard messages promoting dry and clean cord care as per World Health Organization guidelines, which served as the comparison group, or, in addition to these messages, either (2) single (first day only) or (3) multiple (first 7 days of life) cleansing of the cord with 4.0% chlorhexidine solution. Project community health workers (CHWs), each responsible for a cluster of ~4000 population, identified newly pregnant women in the community, explained the study, and obtained consent for participation through an oral consent process. Women in all 3 groups were provided with a basic set of pre-delivery interventions including promotion of antenatal care, counseling on birth and newborn care preparedness, and clean birthing kits. They were encouraged to promptly notify a locally resident volunteer village health worker (VHW) at the time of labor (there ~4–5 VHWs per cluster).

Intervention Delivery and Data Collection

Between June 1, 2007, and September 30, 2009, all live-born infants visited by the cluster-specific CHW within the first week of life were eligible for enrollment. The VHW visited all infants daily throughout the first week to provide the allocated cord care regimen. On the
first visit in the single cleansing group and on all visits in the multiple-cleansing group, the VHWs applied 4.0% aqueous chlorhexidine solution to the cord stump using cotton swabs after a standardized procedure.\textsuperscript{1,18} Separately, CHWs visited all infants as soon as possible after birth to collect information on labor, delivery, and complications before, during, and after delivery. Date/time of birth, gender, weight of the newborn, and care after birth were collected, and signs of morbidity directly observed or reported by the mother were recorded. Blinding of the intervention was not possible.

**Cord Separation Time**

At birth assessment and follow-up visits (days 3, 6, 9, 15), CHWs recorded the separation status of the cord and the date/time of the visit. The cord was defined as fully separated when all visible parts of the cord had fallen from the stump; training procedures for all CHWs followed those used in the previous Nepal study and detailed elsewhere.\textsuperscript{21} The approach to estimating age at cord separation differed for infants whose cords separated (1) between CHW visits, (2) before the first CHW visit, or (3) after the last CHW visit. First, for infants assessed by a CHW both before and after separation (group 1), time to cord separation was defined as the midpoint between the date/time of the last visit before and first visit after cord separation was noted. Second, for infants for whom the cord had fully separated at the first visit (group 2), separation time was defined as half the age of the infant at this visit. Infants whose cord had not yet separated at the final observation (in most cases, day 15) were right-censored (ie, only a lower bound on the cord separation time can be estimated) and excluded from the primary analyses; their observation time was used in time-to-event analyses.

**Power Considerations**

The sample size for the main trial was driven by the primary outcomes of mortality and omphalitis. Assuming cord separation time parameters similar to that observed in Nepal (ie, mean = 4.60, SD = 2.0), the main study sample of 29,760 newborns provided \( >90\% \) power for detecting even small (ie, \( <3 \) hour) mean between group differences in the time to cord separation.

**Analyses**

Infant, maternal, and household-specific characteristics were compared between the 3 cord regimen groups. For consistency with previous literature on cord separation time, we followed the simplified approach of estimating mean separation time in the primary analysis. A linear regression model estimated population-average differences in cord separation time; the reference group was the dry/clean cord (ie, no chlorhexidine). A binary variable indicating separation beyond age 7 days was defined for all infants with cord separation time defined (group 1 and 2 infants) and for a subset of censored infants (group 3) whose censoring occurred beyond 7 days. This variable was examined across the trial treatment groups by using binomial regression with a log link. Time-to-event curves were constructed to include right-censored infants and further examine the distribution of times to separation. Area under the curves (ie, mean separation time) by cord care group only. The increase in risk of omphalitis for each day increase in cord separation time was estimated, along with a 95% confidence (CI) interval.

**Substudy on Maternal Perceptions and Acceptance**

Among 133 clusters, 40 were randomly selected for participation in a substudy on maternal perceptions of cord separation time and acceptance of the regimen. From each selected cluster (13 from dry and clean cord care, 14 from single cleansing, and 13 from multiple cleansing), mothers of 10 infants consecutively enrolled in the main study between October and December 2007 were eligible for inclusion. At discharge of the main trial (day 28), CHWs obtained consent to ask the mother to estimate time to umbilical cord separation, if this was “longer than usual,” her satisfaction with this time (“Were you satisfied with the time to separation?”), and her overall level of satisfaction with the cord care allocated to her infant (“Were you satisfied with the cord care provided by Pro-Jahnmo?”). Maternal report of separation time was compared across the groups using an analytical approach identical to that conducted for directly observed data. The likelihood of reporting that the cord took “longer than usual” was compared across the groups using log-binomial regression, and the proportion of mothers reporting satisfaction with separation time and/or the allocated cord care regimen was estimated. This planned sample provided \( \sim90\% \) power to detect between group differences of 24 hours in estimated separation time, and \( 80\% \) power to detect between group differences of \( \sim15\% \) for binary outcomes (ie, proportion reporting “longer than usual” or “proportion dissatisfied”).

All analyses followed an intention-to-treat approach in relation to group assignment. Standard errors estimated for between-group models were...
adjusted for the cluster-randomized design using general estimating equations. Analyses were conducted by using Stata 12.1 (Stata Corp, College Station, TX).

Approvals
The main trial and the nested cord separation substudy were approved by the Institutional Review Board of Johns Hopkins University, Baltimore, Maryland, and the Ethical Review Board of the International Centre for Diarrheal Disease Research, Bangladesh.

RESULTS
Participants
Among 29,760 live births enrolled in the main study, ≥1 observations of the cord separation status were available for 29,532 (99.2%; Fig 1). In the majority of cases (26,129, or 88.5%), observations of the cord both before and after separation were available, and for an additional 1252 (4.2%) infants, the cord had already separated when the infant was first met, resulting in 27,831 data points for the primary analysis. The other 2151 infants (7.3%) were right-censored (ie, all observations of the cord occurred before separation), but half (1128, 52.2%) of the right-censoring occurred after 7 days and thus these observations were additionally available for the analysis of the binary indicator ≥7 day separation. Substudy data on maternal estimation of cord separation time and satisfaction were available from 380 infants. Randomization balance was assessed on the data set used for the primary analysis; the 3 groups were well balanced on household, infant, and maternal characteristics (Table 1).

Cord Separation Time
A summary of parameters of the cord separation time distribution, including mean, SD, and interquartile range, both overall and by cord care regimen is shown in Table 2. Mean age at separation was 6.36 days but differed substantially between the 3 cord-care regimens. Infants not receiving chlorhexidine applications to the cord were on average 4.78 days old at separation; this increased to 6.90 days (difference 2.10; 95% CI: 1.85–2.35) and 7.49 days (difference 2.69; 95% CI: 2.44–2.95) in the single and multiple cleansing groups, respectively. When restricting to only the 26,129 (88.5%) infants with

FIGURE 1
Participant flowchart.
direct observations both before and after separation, results were similar (data not shown). The age at separation exceeded 7 days in 38.3% of all infants (10,921 of 28,509), but variation between groups was substantial. Although 13.5% of cords separated between 7 and 14 days, the likelihood was substantially greater in the single cleansing (45.9%, relative risk [RR] = 3.37; 95% CI: 2.88–3.94) and multiple cleansing (55.7%, RR = 4.09, 95% CI: 3.51–4.77) groups. Application of nonstudy substances to the cord did not differ between infants with extended (ie, beyond 7 days) separation time using the survival-function based estimate of mean separation time increased for these 2 groups (7.23 and 8.52 days, respectively).

**Cord Separation Time and Infection**

Given the strong correlation between treatment and both separation time shown here and cord infection risk shown previously, we restricted analysis of this relationship to infants in the no-chlorhexidine group. Risk of moderate or severe omphalitis (ie, redness around the stump with pus or redness extending around the base of the stump) was 3.1% (RR = 1.03; 95% CI: 0.97–1.09) higher for each additional day the cord did not separate, and 13.8% (RR = 1.14; 95% CI: 0.82–1.58) higher among infants whose cords separated beyond 7 days; neither of these estimates was statistically significant.

**Maternal Report and Satisfaction**

Age at separation estimated by mother at the end of the neonatal period followed a similar trend as those estimated through CHW direct observations. The mean times (SD) were 5.33 days (1.88), 7.25 days (2.33), and 7.54 days (3.05) for the dry and clean cord care, single-cleansing, and multiple-cleansing groups, respectively. Mothers estimated ages at separation in single
and multiple-cleansing groups that exceeded the no-chlorhexidine group by 1.93 days (95% CI: 0.98–2.89) and 2.28 days (95% CI: 1.31–3.24), respectively. Mothers in the multiple cleansing group were 2.55 (95% CI: 1.23–5.28) times more likely to report that separation occurred “longer than usual” than mothers of infants in the no-chlorhexidine group, and the likelihood of reporting “longer than usual” increased ∼18.3% (95% CI: 13.6–23.1) for each 24-hour increase in directly observed separation time. Overall satisfaction with the time to separation (336 of 376, 89.4%) was high, but dissatisfaction, when expressed, was more frequent in the single and multiple chlorhexidine cleansing groups (11.1% and 17.6%) than the no-chlorhexidine group (2.5%). Among 40 women dissatisfied with cord separation time and 364 women overall, 4 (10%) and 14 (3.8%), respectively, told the CHW that she was not satisfied with the cord-care regimen received (i.e., randomly allocated) to her infant. There were no significant differences between the groups in reported dissatisfaction with cord care (1.7%, 6.5%, and 2.4% in the no-chlorhexidine, single-cleansing, and multiple-cleansing groups, respectively).

**DISCUSSION**

In this community-based study of cord separation time in rural Bangladesh, increases of 2.1 and 2.7 days in mean separation time were observed for single and multiple chlorhexidine cleansing of the cord, respectively, compared with dry and clean cord care. These represent relative increases of ∼44% to 56%, and the average increase was greater when taking into account right censoring of observations. The likelihood of separation after 7 days was 3.4 to 4.1 times greater in the cleansing groups. The increases observed here are consistent and slightly greater than those reported in the community-based trial in Nepal. Unlike that trial, however, a group with a single-chlorhexidine application applied as soon as possible after birth was included in the current study. Although the rightward shift in cord separation time was slightly lesser in magnitude in the single compared with multiple-cleansing groups, the similarity between the intervention groups is more striking than the difference. The fact that a single cleansing exerted a similar impact on time to separation as multiple cleansing likely reflects the well-documented residual effect of chlorhexidine; the compound binds tightly to the skin, and persistent reductions in bacterial colonization of the cord among the infants in this current study have been shown. Given the similarity shown here, cord separation time should not be among the factors considered when comparing the relative benefit or feasibility of single versus multiple cleansings.

There was no evidence of an association between cord separation time and the
risk of umbilical cord infection. This too is consistent with the previous study in Nepal and is understandable given that, with the exception of rare cases in which leukocyte adhesion deficiency is the underlying cause, delayed cord separation more frequently indicates improved hygiene and less exposure of the cord. When the increase in cord separation time is a direct result of the reduced bacterial colonization and infection arising from chlorhexidine applications, those without infection will tend to have longer separation times. In fact, there is consistent and statistically strong evidence that 4.0% chlorhexidine cleansing reduces omphalitis risk substantially; in all 3 published community-based trials, the most serious cord infections were reduced by 49% to 75%.1–3

Mothers of infants in the cleansing groups could detect this increase in cord separation time, despite having, at most, a single point of reference (ie, their first infant to receive chlorhexidine vs any infants born before this study). On average, these mothers reported separation times that were increased beyond nonchlorhexidine infants by about the same magnitude as that directly observed by workers; they also more frequently reported that separation time was “longer than usual.” However, although intervention group mothers were subsequently also more likely to report dissatisfaction with this time, there was no evidence that this resulted in less acceptance of or satisfaction with the umbilical cord regimen provided to their infant.

In hospital-based studies in high-resource settings, caretaker’s concern with separation time has been noted.27–30 With substantially reduced or even nonmeasurable risk of infection and mortality in those studies, expressed dissatisfaction with longer separation times has been a justifiable basis for discontinuing topical antiseptics. It is possible that nonaqueous formulations of chlorhexidine (eg, powder) might not delay separation to the same degree as aqueous formulations and thus mitigate some of these concerns.31 Regardless, where infection and mortality risk is high, formulating guidelines for optimal care on the basis of caretakers’ or providers’ concerns with separation time would be mistaken. Rather, such decisions should be based on the evidence, provided currently by 3 randomized trials in South Asia, that chlorhexidine cord cleansing can improve survival and reduce the risk of omphalitis. Any implementation of chlorhexidine cleansing should recognize that mean cord separation times will increase and that, if detected by caretakers, this might be viewed negatively. To ensure that these legitimate concerns do not reduce overall compliance, especially where topical applications of antiseptics have not been the norm, appropriate behavior change communications should be incorporated into the implementation approach; setting-specific qualitative research may be necessary to develop these communications. We suggest that such messaging emphasize that chlorhexidine cord cleansing can improve survival and reduce infection risk; should begin as soon as possible after birth; will help achieve clean and hygienic cord care; and, although possibly increasing the time to normal healing and separation of the cord by a few days, the increase is not harmful to the infant and indicates that chlorhexidine is keeping the infant’s cord clean.

REFERENCES

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