The effect of cord cleansing with chlorhexidine on neonatal mortality in rural Bangladesh: a community-based, cluster-randomised trial

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Summary

Background **Up to half of neonatal deaths in high mortality settings are due to infections, many of which can originate through the freshly cut umbilical cord stump. We aimed to assess the effectiveness of two cord-cleansing regimens with the promotion of dry cord care in the prevention of neonatal mortality.**

Design **We did a community-based, parallel cluster-randomised trial in Sylhet, Bangladesh. We divided the study area into 133 clusters, which were randomly assigned to one of the two chlorhexidine cleansing regimens (single cleansing as soon as possible after birth; daily cleansing for 7 days after birth) or promotion of dry cord care. Randomisation was done by use of a computer-generated sequence, stratified by cluster-specific participation in a previous trial. All livebirths were eligible; those visited within 7 days by a local female village health worker trained to deliver the cord care intervention were enrolled. We did not mask study workers and participants to the study interventions. Our primary outcome was neonatal mortality (within 28 days of birth) per 1000 livebirths, which we analysed on an intention-to-treat basis. This trial is registered with ClinicalTrials.gov, number NCT00434408.**

Results **Between June, 2007, and September, 2009, we enrolled 29 760 newborn babies (10 329, 9423, and 10 008 in the multiple-cleansing, single-cleansing, and dry cord care groups, respectively). Neonatal mortality was lower in the single-cleansing group (22·5 per 1000 livebirths) than it was in the dry cord care group (28·3 per 1000 livebirths; relative risk [RR] 0·80 [95% CI] 0·65–0·98). Neonatal mortality in the multiple-cleansing group (26·6 per 1000 livebirths) was not statistically significantly lower than it was in the dry cord care group (RR 0·94 [0·78–1·14]). Compared with the dry cord care group, we recorded a statistically significant reduction in the occurrence of severe cord infection (redness with pus) in the multiple-cleansing group (risk per 1000 livebirths=4·2 *vs* risk per 1000 livebirths=1·2; RR 0·35 [0·15–0·81]) but not in the single-cleansing group (risk per 1000 livebirths=3·3; RR 0·77 [0·40–1·48]).**

Interpretation **Chlorhexidine cleansing of a neonate's umbilical cord can save lives, but further studies are needed to establish the best frequency with which to deliver the intervention.**

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Introduction

Neonatal deaths account for more than 40% of yearly deaths of children younger than 5 years and serious infections cause about a third of yearly neonatal deaths worldwide.[1] In high mortality settings, infections account for about half of neonatal deaths.[2,3] Although data for causes and risk factors of neonatal infections are scarce, the umbilicus is regarded as a key entry point for invasive pathogens.[4–6] Most deliveries in resource-poor settings occur at home, usually in unhygienic conditions, and are done by unskilled birth attendants. Because the umbilical stump blood vessels are exposed for the first few days after birth, they can be a route of entry for systemic infections in newborn babies;[7] such infections can rapidly lead to death. In settings where the achievement of optimum hygienic practices is challenging, elimination of exposure to the cord stump during this crucial period is impossible. Furthermore, in many communities, traditional practices involving the application of potentially harmful substances to the umbilical stump are widespread and are associated with a high risk of local infection.[8] Overall omphalitis risk varies substantially and depends on the level of direct and indirect exposures to the stump (eg, absence of hand washing and other hygiene practices by carers), and variation in definition, standardisation, and frequency of measurement. Hospital-based incidence estimates in low-resource settings have ranged from two per 1000 newborn babies to 77 per 1000 newborn babies and are probably greater in community settings. In rural Nepal,[9] moderate to severe redness around the stump was noted in about 15% of babies (incidence rate 15·2 per 100 neonatal periods), whereas in Pemba, Tanzania, 3·8% (95% CI 2·9–4·8) of babies had moderate to severe redness around the stump.[10] The presence of these local signs of infections has been directly associated with increased mortality risk.[11]

To reduce the risk of sepsis originating from the cord stump, WHO recommends that the cord be kept clean and that nothing should be applied to it (dry cord care).[7] In recognition of the difficulty in achieving this aim, WHO additionally recommends the use of topical antiseptics in settings where risk of infection is high. One such topical antiseptic is chlorhexidine, which has been widely used in clinical settings for more than 30 years. Studies done in high-income countries have shown that use of chlorhexidine reduces cord colonisation in newborn babies compared with dry cord care.[12,13] A randomised community-based trial in rural Nepal, which assessed cord cleansing with chlorhexidine for the reduction of cord infection and mortality, showed that in babies who received 1–7 applications of chlorhexidine cord cleansing in the first 10 days of life, omphalitis risk was reduced by 32% (15·2 per 100 neonatal periods to 10·3 per 100 neonatal periods) to 75% (1·1 per 100 neonatal periods to 0·3 per 100 neonatal periods), depending on definition of severity, and death within 28 days was 24% lower (19·3 per 1000 livebirths to 14·4 per 1000 livebirths); initiation of chlorhexidine cleansing within 24 h of birth led to 34% lower mortality risk (21·6 per 1000 livebirths to 14·4 per 1000 livebirths).[9]

After the Nepal study, an expert panel raised two questions:[14] can the findings of the study be replicated in a similar population in south Asia, and would a simpler cleansing regimen (cord cleansing only once soon after birth) be equally beneficial? To address these questions, we did a community-based cluster-randomised study in a rural area of Bangladesh and compared the effectiveness of two alternative cord cleansing regimens with 4% chlorhexidine—single cleansing of the cord as soon as possible after birth and cleansing daily for 7 days after the initial cleansing—with promotion of dry cord care.

Methods

Study design and participants

We did this study in three rural sub-districts (called upazillas) of Sylhet district in northeastern Bangladesh (Beanibazar, Zakiganj, Khanaighat), where an earlier trial of a package of community-based neonate care interventions delivered by community health workers (CHWs), including community case management of neonatal sepsis, reduced neonatal mortality by 34%.[15] The details of the design and implementation of the present study were reported previously.[16]

Briefly, 22 unions (the smallest administrative unit with a health centre) in three sub-districts (an estimated total population of 546 000 people) participated in the study (figure); the area was divided into 133 clusters on the basis of population size (mean size 4100; range 2071–5598). In each cluster, a female CHW provided a basic package of community-based neonate care interventions, including messages to keep the cord clean and avoid application of potentially harmful substances.[15] Community case management of infection in newborn babies was available in six unions, where it was implemented in the first study and was not expanded to the remaining 16 unions included in this study. In addition to CHWs, four to five local female village health workers (VHW) were trained in each cluster to deliver the cord care interventions; each VHW served a population of about 1000 people. Starting in June, 2007, the study was rolled out in phases as CHWs and VHWs were trained and deployed; the phased implementation was balanced across allocation groups. By December, 2007, all 133 clusters had initiated enrolment. Between the cluster-specific date of initiation and Sept 30, 2009, all liveborn babies delivered in these 133 clusters were eligible for enrolment. Further details on the roles of CHWs and VHWs and the phased implementation of the study are available elsewhere.[17]

Oral consent to participate was obtained from pregnant women. The study protocol was approved by the Institutional Review Board of the Johns Hopkins Bloomberg School of Public Health and the Ethical Review Committee of the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B). The study had a data safety monitoring board. Two interim analyses were done in March, 2008, with 31·3% of the data and in January, 2009, with 69·8% of the data. The DSMB recommended continuation of the trial as originally planned.

Randomisation and masking

The CHW clusters (n=133) were randomly allocated to either 4% aqueous chlorhexidine solution once at birth, chlorhexidine at birth plus daily cord cleansing with

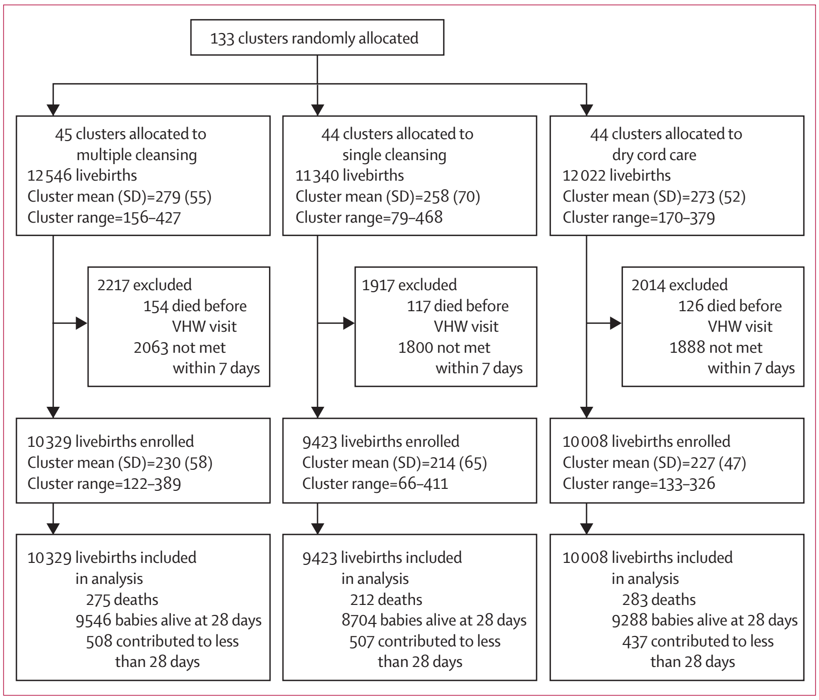

Figure: **Study profile**
VHW= village health workers

chlorhexidine for 7 days, or dry cord care (comparison group).[18] Randomisation was stratified on the three groups of the previous Projahnmo project[15] (33, 32, and 40 clusters) and the 28 newly added CHW clusters, to achieve balance in underlying neonatal mortality risk. Randomisation was done by generating random allocation sequences in Stata (version 9.2). Because of the nature of the interventions, we could not mask intervention workers and study participants to the study interventions.

Procedures

Mothers and newborn babies in all three groups received postnatal home visits from VHWs for 7 days after enrolment. These visits differed in only the cord application across the three study groups. The chlorhexidine solution used in the trial was prepared by diluting a 20% stock solution of aqueous chlorhexidine digluconate (ACI Limited, Dhaka, Bangladesh) with distilled water. The prepared 4% chlorhexidine solution was packaged into 70 mL and 10 mL opaque bottles and distributed to the VHWs in the multiple and single cleansing areas, respectively. Five bottles were randomly selected from each dilution batch and were tested in a laboratory to check for the chlorhexidine concentration.

In the single chlorhexidine cleansing group, the VHWs cleansed the cord with 4% chlorhexidine only at the first visit as soon as possible after birth. In the multiple chlorhexidine cleansing group, the VHWs cleansed the cord as soon as possible after birth and once a day for 7 days. In the dry cord care group, the VHWs promoted cord care messages during home visits that are recommended by WHO, and did not apply chlorhexidine to the cord. The first home visit by the VHW was recommended to be made within 6 h of delivery. At every visit, the VHW recorded the visit date and time, the newborn babies' vital status (alive or dead), and intervention status for that day (provided or refused) with a pictorial form.

The CHWs visited all households in their catchment area every 2 months to update a list of married women of reproductive age. Consent to participate was obtained from pregnant women, and sociodemographic information was collected for age, parity, date of last menstrual period, birth history, occupation, literacy, and household assets. CHWs visited participating pregnant women twice during pregnancy and provided birth and neonatal care preparedness counselling, clean birthing kits, and referral for antenatal care.

VHWs accompanied the CHWs during the pregnancy visits to meet the family, explain her role, and encourage early and rapid notification of onset of labour or birth. Once notified, the VHW did her first of seven home visits, and contacted her supervising CHW who visited the newborn baby as soon as possible (preferably within 24 h of birth). At this first visit, the CHWs collected information about the labour and delivery, and about any complications before, during, and after delivery. She also collected information on date and time of birth, sex, weight, and care after birth. At the initial visit and each of the follow-up visits (days 3, 6, 9, and 15), the CHW recorded the newborn baby's vital status and examined the umbilical cord stump, recording signs of redness, pus, and swelling. Whereas pus was defined as either present or absent, redness and swelling were classified into four categories: none, mild (restricted to the stump), moderate, or severe (moderate and severe classifications required extension to the skin around the base of the stump of <2 cm or ≥2 cm, respectively). Cord infection was then defined for analysis with combinations of these

	Dry cord care	Single chlorhexidine cleansing	Multiple chlorhexidine cleansing
Mother's age (years; mean [SD])	27·9 (5·6)	28·0 (5·6)	27·7 (5·6)
Mother's education (years; mean [SD])	6·3 (2·3)	6·3 (2·3)	6·3 (2·2)
Any antenatal care	4087 (41%)	4268 (45%)	4745 (46%)
Iron supplementation during pregnancy	938 (9%)	1128 (12%)	1108 (11%)
Household wealth quintile			
1st (poorest)	1963 (20%)	1995 (21%)	2013 (20%)
2nd	2098 (21%)	1831 (19%)	2115 (21%)
3rd	1929 (19%)	1845 (20%)	2098 (20%)
4th	1898 (19%)	1886 (20%)	2152 (21%)
5th (wealthiest)	2120 (21%)	1866 (20%)	1951 (19%)
Household size (mean [SD])	6·9 (3·5)	6·9 (3·5)	6·8 (3·4)
Religion			
Islam	9652 (96%)	8953 (95%)	9837 (95%)
Hinduism	346 (4%)	465 (5%)	486 (5%)
Others	10 (<0·5%)	5 (<0·5%)	6 (<0·5%)
Parity			
First child	1777 (18%)	1676 (18%)	1928 (19%)
Second or third child	3629 (36%)	3430 (36%)	3767 (37%)
Fourth or higher	4602 (46%)	4317 (46%)	4634 (45%)
Singleton or multiple birth			
Singleton	9752 (97%)	9213 (98%)	10 084 (98%)
Twin	247 (3%)	204 (2%)	239 (2%)
Triplet	9 (<0·5%)	6 (<0·5%)	6 (<0·5%)
Sex			
Male	5140 (51%)	4881 (52%)	5389 (52%)
Female	4868 (49%)	4542 (48%)	4940 (48%)
Neonatal weight			
<1500 g	71 (1%)	54 (1%)	74 (1%)
1500–1999 g	471 (5%)	402 (4%)	456 (5%)
2000–2499 g	2516 (26%)	2717 (30%)	2844 (28%)
≥2500 g	6713 (69%)	6010 (66%)	6728 (67%)
Missing	237 (2%)	240 (3%)	227 (2%)
Weight (g; mean [SD])	2677 (449·4)	2653 (437·7)	2667 (446·9)
Preterm (<37 weeks)	2073 (21%)	1933 (21%)	2188 (21%)
Gestational age (weeks; mean [SD])	39·1 (3·1)	39·1 (3·0)	39·1 (3·1)

Data are n (%) unless otherwise stated.

Table 1: **Baseline neonatal, maternal, and household characteristics**

signs, in varying severity. During the first week of a baby's life (days 1, 3, and 6), CHWs and VHWs often visited together. The CHW recorded the final neonatal vital status of the newborn baby at a home visit made between 28 days and 35 days after birth.

Statistical analysis

The sample size calculation was made on the basis of an expectation that both single-cleansing and multiple-cleansing with 4% chlorhexidine solution would reduce mortality in enrolled babies by about 25%. Because our study area had a fixed number of clusters, we first estimated the required sample size under an assumption of individual-randomisation, and then adjusted the required sample size upward by incorporating an estimated design effect.[19] With data from the previous study, our estimate of overall neonatal mortality rate in the study population after implementation of the basic neonatal care package was 36 per 1000 livebirths and design effect of 1·2. We set type 1 and type 2 error rates at 5% and 80%, respectively, and assumed 20% of neonatal mortality would occur shortly after birth, before enrolment, and 5–10% loss to follow-up. The estimated required total sample size was 28797 newborn babies. We planned for about 2·3 years of enrolment, expecting about 12500 births per year.

Babies were defined as enrolled if they were alive at the time of the first VHW home visit and if the first VHW visit occurred within 7 days after birth. Descriptive statistics were calculated on enrolment rates, timing, frequency and coverage of cord care interventions, coverage of the basic package of interventions, and neonatal care practices, as well as characteristics of the newborn baby, mother, and household. Balance in these variables across the three groups of the study was assessed with multinomial, binomial, and linear regression models, with SEs adjusted to account for the clustered-design with the Huber-White sandwich estimator.[20,21] The intention-to-treat analysis included all enrolled babies, including those born in a facility, irrespective of whether or not they received the intervention. The primary outcome for this analysis was death within 28 days after birth per 1000 livebirths. The risk of mortality in the multiple-cleansing and single-cleansing intervention clusters was compared relative to the dry cord care cluster. The proportion of liveborn babies enrolled who died within 28 days were compared with binomial regression with a log link to estimate relative risk. To account for the clustered allocation, SEs were adjusted with the generalised estimating equation approach.[22] The analyses of outcome included an assessment of intervention effect stratified by birthweight, gestational age, and timing of intervention initiation. We also estimated the overall effect of the intervention on mortality in all livebirths, including enrolled and non-enrolled births. We analysed cord infection outcomes with the same approach.

Role of the funding sources

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between June, 2007, and September, 2009, we identified 35908 liveborn infants in the study area, of whom 29760 (83%) were enrolled into the study (figure). Final vital status at 28 days of life was available in 95% of the enrolled newborn babies (28308 of 29760), and the proportion available for analysis did not differ between study groups. Baseline household, maternal, and newborn baby characteristics were much the same between the three study groups (table 1). Rates of antenatal care visits, and iron-folate supplementation during pregnancy were low (table 1). Mothers of 67% of newborns (19794 of 19760) received both planned birth and neonatal care home visits (webappendix). The proportion of enrolled newborn babies who received the postnatal home visits on days 1, 3, 6, 9, and 15 varied between 86·6% (25769 of 29760) and 91·5% (27235 of 29760) (day 1 visit being the lowest). About 7% (1978 of 29760) of deliveries were in facilities and about 9% (2673 of 29760) of babies were delivered by a skilled birth attendant. High intervention coverage was achieved for enrolled newborn babies, with most babies receiving the cord-cleansing intervention within 24 h of birth (table 2).

See Online for webappendix

A sterile instrument was used to cut the cord of 93% of babies (27677 of 29760) (webappendix). Non-study applications on the cord were uncommon in all study groups both at the time of cord cutting

	Dry cord care	Single chlorhexidine cleansing	Multiple chlorhexidine cleansing	p value
Coverage of cord intervention*				
Received seven interventions	8358 (84%)	7962 (85%)	8677 (84%)	<0·0001
Received six interventions	394 (4%)	329 (4%)	449 (4%)	<0·0001
Received five interventions	372 (4%)	321 (3%)	369 (4%)	<0·0001
Received four interventions	202 (2%)	171 (2%)	211 (2%)	<0·0001
Received three interventions	193 (2%)	150 (2%)	146 (1%)	<0·0001
Received two interventions	240 (2%)	193 (2%)	185 (2%)	<0·0001
Received one intervention	236 (2%)	237 (3%)	189 (2%)	<0·0001
Received no intervention	13 (<0·5%)	60 (1%)	103 (1%)	<0·0001
Number of cord interventions (mean [SD])	6·5 (1%)	6·5 (1%)	6·5 (1%)	0·89
Timing of cord intervention				
Within 24 h of birth	8621 (86%)	8113 (86%)	8694 (87%)	0·91
Between 24 h and 48 h	597 (6%)	593 (6%)	603 (6%)	0·91
After 48 h (or none)	790 (8%)	717 (8%)	762 (7%)	0·91

Data are n (%) unless otherwise stated. *Intervention was a home visit by a village health worker with or without cord cleansing as per protocol.

Table 2: **Coverage and timing of intervention**

(6%, 1666 of 29 280) and follow-up (3%, 945 of 29 386). Rates of drying and wrapping of newborn babies within 5 min of birth was low in all three groups (webappendix). Breastfeeding was initiated within 1 h of birth in 56% (5131 of 9212), 62% (6334 of 10 166), and 66% (6484 of 9849) of the newborn babies in the single cleansing, multiple cleansing, and dry cord care groups, respectively; these differences between the study groups were not statistically significant.

Compared with babies in the dry cord care group, babies in the multiple chlorhexidine group had lower risk of any redness in the umbilical stump or pus, and a lower risk of severe redness with pus (table 3). In babies with cord infections, redness was most prevalent between visits on day 3 and day 6. The mean time to first observation of redness of a moderate extent (ie, extending to the base of the stump) was 81·2 h (3·4 days) of age. For pus, the mean time to first observation was about 150 h (6·3 days) after birth.

The risk of neonatal mortality was lower in the single-cleansing group than it was in the dry cord care group (table 4). We recorded no statistically significant difference for the relative risk of neonatal mortality between the multiple chlorhexidine and the dry cord care group, nor did we record a difference between either of the chlorhexidine groups and the dry cord care group when restricting analysis to death within the first week of life (table 4). In all newborns, including those not enrolled, overall neonatal mortality in the single-cleansing group (31·3 per 1000 livebirths) was 15% (95% CI 0–28; p=0·050) lower than it was in the dry cord care group (36·8 per 1000 livebirths). The mortality effect in all enrolled babies was greater in babies with a low birthweight (<2500 g) and preterm (<37 weeks) babies (webappendix), but when analysis was done with data from individual groups the effect was only statistically significant in preterm infants in the single-cleansing group (35%, 95% CI 14–50; p=0·002). We recorded no adverse events during this study.

	Livebirths	Cases	Risk per 1000 livebirths	Relative risk (95% CI)
Redness extending to skin, or pus				
Multiple chlorhexidine	10 254	1406	137·1	0·89 (0·62–1·26)
Single chlorhexidine	9354	1252	133·8	0·89 (0·62–1·26)
Dry cord care	9924	1545	155·7	1·00
Redness extending to skin				
Multiple chlorhexidine	10 254	327	31·9	0·78 (0·50–1·22)
Single chlorhexidine	9354	339	36·2	0·93 (0·61–1·43)
Dry cord care	9924	403	40·6	1·00
Redness with pus, or severe redness				
Multiple chlorhexidine	10 254	151	14·7	0·55 (0·31–0·95)
Single chlorhexidine	9354	211	22·6	0·90 (0·55–1·46)
Dry cord care	9924	258	26·0	1·00
Severe redness with pus				
Multiple chlorhexidine	10 254	16	1·6	0·35 (0·15–0·81)
Single chlorhexidine	9354	31	3·3	0·77 (0·40–1·48)
Dry cord care	9924	42	4·2	1·00

Table 3: Cord infections

	Livebirths	Neonatal deaths	Mortality risk per 1000 livebirths	Relative risk (95% CI)
All enrolled babies				
Multiple chlorhexidine	10 329	275	26·6	0·94 (0·78–1·14)
Single chlorhexidine	9423	212	22·5	0·80 (0·65–0·98)
Dry cord care	10 008	283	28·3	1·00
Deaths in the 1st week of life in enrolled babies				
Multiple chlorhexidine	10 329	182	17·6	0·91 (0·71–1·18)
Single chlorhexidine	9423	149	15·8	0·83 (0·64–1·09)
Dry cord care	10 008	193	19·3	1·00

Table 4: Neonatal deaths and mortality risks

Discussion

In our study, neonatal mortality was lower in neonates who received a single cord cleansing with 4% chlorhexidine than it was in those who received dry cord care. We recorded no reduction of neonatal deaths in the multiple-cleansing group, but did record a reduced risk of serious cord infection in this group compared with babies in the dry cord care. Our finding that multiple cord cleansing with chlorhexidine did not reduce mortality contrasts with the finding of the Nepal study, in which cleansing of the umbilical stump with 4% chlorhexidine on 7 of the first 10 days of life resulted in 24% lower neonatal mortality compared with dry cord care.[9]

Several explanations exist for the absence of mortality effect in the multiple-cleansing group. First, although this study group was possibly different in some aspects that resulted in an increased underlying risk, we did not find any differences between the three groups. Rates of enrolment of newborn babies into the study were high (82–83%) and were much the same in all three groups, and the cluster-randomisation procedure achieved balance in the three groups in terms of household, maternal, and newborn baby characteristics and in the coverage of the basic neonatal health intervention package. One factor that differed across the study groups was the mean number of livebirths per cluster (figure), a result of slightly lower crude birth rate and slightly smaller population in the single-cleansing group. However, important indicators that are predictive of neonatal mortality such as proportion preterm or low birth weight, or breastfeeding practices were much the same between the three groups.

A second possibility is poorer delivery of the intervention in the multiple-cleansing group. However, we recorded no difference between the three groups in the timing of initiation of the interventions with 86–87% starting interventions within 24 h of birth. The mean number of intervention days was exactly 6·5 in all three groups in this trial. The proportion of individuals who received all 7 days of intervention was much the same between the single and multiple chlorhexidine groups. These proportions did not statistically differ in terms of the risk of any umbilical redness or pus; however, the incidence of severe cord infection was substantially lower in the multiple-cleansing group compared with the control group.

A third possibility is that the results seen in either the multiple-cleansing or single-cleansing group arose by chance. Assuming a probable design effect of 1·20, we originally powered the trial at 80% for a 25% reduction in mortality risk in enrolled babies. However, we recorded an actual design effect for mortality of 1·36 and the observed 20% reduction in the single-cleansing group was lower than expected. Thus, if the true benefit for multiple cleansing was similar to that recorded for single cleansing, our actual power to detect such an effect was diminished and could have been missed by chance. Alternatively, the recorded effect in the single-cleaning group could have been due to chance. However, we believe that this is less likely in view of the lower risk of umbilical cord infection and lower cord colonisation[23] in the multiple-cleansing group and the data from Nepal showing that chlohexidine cleansing reduces neonatal mortality risk. Furthermore, the chance of missing a true effect is much higher (type 2 error of 20%) than erroneously seeing an effect (type 1 error of 5%).

The Bangladesh population was similar to Nepal in terms of low birthweight rate (32% *vs* 30%) and overall neonatal mortality (35·3 per 1000 livebirths *vs* 32·0 per 1000 livebirths). However, our study and the Nepal study differed in several ways. The faster time to enrolment in Bangladesh (86–88% within 24 h) than in Nepal (62–64% within 24 h) led to a higher recorded mortality rate in enrolled babies in the control group in Bangladesh (28·2 per 1000 livebirths) than in Nepal (19·3 per 1000 livebirths). The difference in mortality levels in enrolled babies in Bangladesh and Nepal was substantial and suggests differences in the distribution of causes of deaths. In particular, the timing and number of infection-related deaths are likely to be different in the two study-enrolled populations. For example, compared with the study population in Nepal, the study population in Bangladesh included a greater proportion of early deaths, which would be due to both non-infectious causes[3] and early-onset sepsis, both of which would be expected to reduce the effect of chlorhexidine cord cleansing. Moreover, our trial interventions were implemented alongside a maternal and neonatal health programme, which had previously shown a large effect on neonatal mortality[15] and had a strong postnatal neonatal care component. In Nepal, however, chlorhexidine cleansing was delivered in the context of a less intensively delivered set of antenatal and postnatal interventions. The presence of the maternal and neonatal health programme in our study, although some components of the programme were not optimally implemented, could have lessened the effect of the chlorhexidine intervention, but measurement of the additional effect of chlorhexidine cleansing was the specific intent in this study.

The overall degree of exposure of the cord stump to pathogens in the immediate post-partum period is likely to dictate the extent to which chlorhexidine cleansing is an effective intervention. In our study area in Bangladesh, non-study applications to the cord were substantially less frequent, compared with in the Nepal study, and the types of substances applied also differed.[9,15] This low frequency of non-study applications during the trial period differed substantially from pre-study measures in this population,[24] possibly owing to the effectiveness of the basic set of messages about the avoidance of harmful practices—messages that were given to all three groups. These differences in cord care practices (relative to Nepal), and the reduced absolute risk of cord infection in Bangladesh probably indicates lower underlying exposure of the cord in this setting, and might also explain the lower overall effect of chlorhexidine.

We have presented the results from the second study in low-resource settings in south Asia on the effect of topical chlorhexidine cleansing of umbilical cord. Our study was done in rural Sylhet, Bangladesh, which is typical of the countries in south Asia, especially in terms of the low rates of facility delivery or skilled attendance at birth, poor neonatal care practices and care seeking, and high mortality rates. The evidence presented here provides an estimate of the effect of the chlorhexidine intervention beyond the effect of a basic package of neonatal care interventions. Although the results of this study are

Panel: Research in context

Systematic review

One community-based trial of chlorhexidine cord cleansing was done in Nepal between 2002 and 2005,[1] and showed reduced mortality and omphalitis risk in babies receiving immediate and repeated cleansing applications. The rationale and design of our trial builds directly on this previous trial, and was guided by published reviews on the potential effect of chlorhexidine interventions on neonatal health outcomes.[2,3]

Interpretation

Our trial adds to existing evidence about the potential effect of chlorhexidine cleansing of the umbilical cord in low-resource settings. We recorded a reduction of 20% in mortality risk in babies receiving one application of chlorhexidine as soon as possible after birth. A second group, receiving chlorhexidine daily through the first week of life did not have lower mortality risk. These data, along with results from a third south Asian trial (done in Pakistan),[25] provide evidence that chlorhexidine cleansing reduces risk of neonatal mortality and omphalitis; further randomised trials in sub Saharan-African settings are needed.

mixed, we note that chlorhexidine has an excellent safety record[8] and it is simple and inexpensive to deliver. The intervention can thus be rapidly incorporated into existing health programmes. Programmatic implementation of chlorhexidine cord care intervention will be especially attractive for countries with restricted resources and high neonatal mortality. We are aware of no other trial designed to assess the effect of a single cleansing of the umbilical cord (panel). We recommend that additional studies are done in other settings to confirm that single cleansing is indeed effective, because this intervention would simplify programme logistics and aid the achievement of high intervention coverage in real-life settings.

Contributors

All investigators participated in the research and intervention design. RS and SMR were responsible for detailed planning and implementation of the interventions. IM and MRRT were responsible for detailed planning and implementation of data collection. NB was responsible for data management and preliminary analysis. AHB, SEA, and LCM provided oversight to planning and implementation of intervention and data collection. LCM, SEA, and AHB did the analysis and wrote the first draft of the paper. All authors reviewed the paper and approved the final version.

Conflicts of interest

We declare that we have no conflicts of interest.

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