Published in final edited form as:

Pediatr Infect Dis J. 2017 October ; 36(10): 1011–1013. doi:10.1097/INF.0000000000001617.

Impact of Chlorhexidine Cord Cleansing on Mortality, Omphalitis, and Cord Separation Time Among Facility-Born Babies in Nepal and Bangladesh

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Abstract

Guidance is needed regarding potential extension of the WHO recommendation for cord cleansing with chlorhexidine to babies born in facilities. Among 3,223 facility-born babies from Nepal and Bangladesh, mortality was approximately halved among those allocated to the intervention clusters (10.5/1000 vs. 19.4/1000, RR=0.54; 95% CI: 0.30 – 0.97). In high-mortality settings, a single policy for home and facility births is warranted.

Keywords

chlorhexidine; umbilical cord; neonatal mortality; omphalitis; bacterial colonization; cord separation time

Introduction

In 2013, the World Health Organization provided updated guidance for umbilical cord care, advising use of 4.0% chlorhexidine (7.1% chlorhexidine digluconate) cord cleansing for home births in settings with high neonatal mortality [1]. These updated guidelines focused on home births because the South Asian trials that formed the basis of new recommendations were dominated by home births (>90%)[2-4] and the neonatal mortality rate (NMR) in those trials exceeded 30/1000. Two recent studies [5,6] in substantially lower risk settings in Tanzania and Zambia (NMR <11/1000 and <15/1000, respectively) provided no evidence that the intervention would improve survival in settings where mortality was already low. In high-mortality settings, however, policymakers need further guidance on whether or not to extend their emerging chlorhexidine cleansing programs to facility births.

Such guidance is critical as the proportion of facility births in many low-resource areas of South Asia and sub-Saharan Africa is increasing rapidly, without sufficient evidence that survival rates among these babies are improving [7]. In this brief report, we pool data from our two large population-based trials in Nepal and Bangladesh, and summarize the impact of chlorhexidine for cord cleansing on mortality, omphalitis, and cord separation time among babies born in first-level rural health facilities.

Methods

Study Design and Data Collection

The details of the design and the results of our two trials have been previously published [2,3]. Briefly, in both settings (Sarlahi District, Nepal and Sylhet District, Bangladesh), we enumerated households and women of child bearing age, identified pregnancies through routine community-based (i.e. household visits) surveillance, and followed pregnant women through 28 days post-partum. Babies (facility or home births) met alive by community health workers were provided with a cord care regimen to which the geographic cluster of their home had been randomly allocated. In Nepal, a multiple-day chlorhexidine cleansing regimen (days 1,2,3,4,6,8,10) was compared to soap and water cleansing or dry cord care (no cleansing). In Bangladesh, two separate chlorhexidine regimens – a single day (day 1) and a multiple-day regimen (days 1-7) – were compared with dry cord care. In both settings, a data collection team visited all babies at home on a fixed visit schedule to collect signs of omphalitis (pus, redness, swelling), status of cord separation, and vital status. Field workers were trained on signs of omphalitis (by LCM) using a previously validated standard protocol and a set of training images of the cord stump and infection [8].

Analysis

The primary outcome of interest was death within 28 days after birth. We also examined risk of omphalitis using three infection definitions (mild [pus or redness limited to cord stump], moderate [pus and redness extending to the base around the stump], severe [pus and redness more than 2 cm from the base]). Time to cord separation was defined as the age of the baby at the mid-point between the first visit at which the cord was observed to have fallen, and the prior visit. The definitions, risk factors for, and burden of omphalitis in these settings, along with descriptions of population-based cord separation time are available [9-11]. Here, we restrict our analysis to the subset of enrolled babies that were born in facilities; these occurred predominately in low-level public facilities (health posts/primary health centres in Nepal; Family Welfare Centres in Bangladesh), service provision sites that often struggle to provide basic but essential maternal and neonatal services, such as hygienic delivery, emergency obstetric services, or implement standard infection control procedures. In the primary analysis, we combined chlorhexidine regimens regardless of frequency, and compared these clusters to those where chlorhexidine was not provided; in addition, we examined chlorhexidine impact when comparing multiple-days cleansing vs. dry cord care, and any chlorhexidine vs. dry cord care. We examined comparability of the groups by assessing a range of household, maternal, and child characteristics. Comparative risk for mortality and omphalitis was estimated using binomial regression with log link functions; simple linear regression was used to compare mean time to cord separation. In all cases,

standard errors were adjusted for clustered randomization, using generalized estimating equations. We did not account for multiple comparisons. Analyses were done utilizing STATA 14.2.

Results

A total of 3,223 babies were born in facilities (Nepal: 1,245; Bangladesh: 1,978) during the study period and enrolled in the trials. Of these 1,728 (53.6%) were male, 887 (27.9%) were low birth weight (missing for 40 babies), and 424 (13.2%) were preterm (<37 weeks); the majority of babies (57.1%) were born to mothers less than 25 years of age. Within this sub-analysis of facility births, the original randomization schemes achieved balance on most variables. When comparing clusters allocated to chlorhexidine cleansing regimens with clusters allocated to non-chlorhexidine regimens, babies were evenly distributed in terms of sex, low birth weight, preterm status, breastfeeding initiation time and provision of colostrum, hand washing of birth attendant prior to delivery, maternal literacy/education, and caste and ethnicity (variable for Nepal only). Mothers of babies in chlorhexidine clusters were less likely to have received two doses of tetanus toxoid in the prior 2 years (26.9% vs. 41.8%), were slightly older (25.6 vs 24.4 years), and less likely to report that their baby's cord was cut with a sterile instrument (29.5% vs. 39.7%).

Among babies enrolled in the trials, overall mortality within 28 days for those born in a facility was 14.9/1000, and was substantially lower (RR = 0.54, 95% CI: 0.30 – 0.97) in chlorhexidine clusters (10.5/1000) compared to non-chlorhexidine clusters (19.4/1000). This observed impact on mortality did not differ when comparing multiple-days chlorhexidine arms to dry cord care (RR=0.50 95%CI: 0.25-1.02), or any chlorhexidine vs dry cord care (0.47 95%CI: 0.26 – 0.87). Similarly, among babies in the chlorhexidine arms, risk of mild (RR = 0.60 [0.41 – 0.89]) or moderate (RR = 0.54 [0.32 – 0.93]) omphalitis (as defined above), was lower compared to babies not receiving chlorhexidine applications; severe omphalitis did not differ between the groups, but risk was uniformly low (<1% in both groups). Age at cord separation was higher among babies exposed to chlorhexidine (6.5 days) compared to non-chlorhexidine groups (5.1 days), a difference of 1.36 days (95% CI: 1.14 – 1.58). All estimation models were re-run including covariates that were imbalanced (maternal age, use of sterile cord cutting instrument, and tetanus toxoid coverage) in addition to low birth weight and gestational age, and the results did not change (data not shown).

Discussion

Our pooled analysis demonstrates that cord cleansing with chlorhexidine can reduce mortality and infection risk among facility births, with magnitudes similar to the previously published population-based estimates forming the basis of the WHO's 2013 guideline update. Furthermore, the overall mean time to cord separation, which is inversely proportional to the level of bacterial exposure and colonization of the cord stump tissues, was low (5.8 days), and was increased by 1.36 days, similar to population-level increases in these sites.

Two issues should be considered when interpreting these results. First, while this analysis provides information on more than 3,000 facility births, approximately half of which received chlorhexidine, the overall impact on neonatal mortality will be lower than observed here, as live born babies that died prior to being met (i.e. died in facility or after discharge, but prior to being visited by study workers) were not enrolled. Unfortunately, we did not have complete individual-level information on birth-location for babies not enrolled. For the subset where this is available, however, NMR was 30.3/1000, which was similar to home births in Bangladesh (35.4/1000) and Nepal (34.2/1000) during the trial period. Second, the chlorhexidine group in our primary analysis comprises three varying chlorhexidine regimens (single day cleansing, daily for first 7 days, or 7 cleansings over first 10 days). Thus, in this or other pooled- or meta-analyses of chlorhexidine studies, decisions regarding if and how to combine slightly varying cord care regimens are required. Here, for our primary analysis we compared any chlorhexidine to non-chlorhexidine groups, as was previously conducted for a meta-analysis of all South Asian trials [12]; the specific choice made here did not affect our conclusion.

That chlorhexidine cleansing interventions would work similarly among babies born in facilities in these settings should not be surprising. In these districts, as in many low resource settings achieving remarkable gains in rate of facility delivery, the circumstances surrounding birth that might affect risk of neonatal mortality through pathogens colonizing the patent, freshly cut vessels of the cord stump, are unlikely to differ between home and facility births. The latter overwhelmingly occur in first-level facilities where reliable supplies of electricity and clean, running water are often unavailable, basic distribution of medical equipment and medicines are often disrupted, staff are commonly under-resourced or insufficiently trained, and mothers and babies are discharged within hours of delivery [7]. In such situations, extending a simple and cost-effective means to reduce infection risk and improve survival with chlorhexidine should be considered. In addition to the direct effect that use of chlorhexidine cleansing can have for facility births, overall coverage and reach of national programs to home births may be facilitated through uniform recommendations for cord care. Instead of attempting to promote different care regimens by place of delivery, a distinction that may not correlate substantively with underlying risk, a single uniform policy should be implemented. Additionally, policy makers should carefully consider the wisdom of adhering to a strict threshold (e.g., 30/1000) for decision-making regarding chlorhexidine cleansing programs. While the absolute and relative efficacy of chlorhexidine cord cleansing likely diminishes as underlying risk of mortality decreases, there is little reason to believe the benefit immediately decreases to zero as NMR passes below that threshold. At the national level, where policy decisions are made, a strict quantitative threshold is also problematic in light of sub-national geographic and seasonal differences in risk, and inherent uncertainty in estimates of NMR. Given the low cost and high potential for improved survival and reduced morbidity, those most proximally responsible for steering neonatal health programming should implement a single chlorhexidine cleansing policy, regardless of birth location and level of mortality, until the health system can achieve clean and hygienic conditions at all levels.

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