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A review of studies with chlorhexidine applied directly to the umbilical cord

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Abstract

Infection-related neonatal mortality due to omphalitis in developing country home births is an important public health problem. Three cluster randomized trials of 4% chlorhexidine applied to the umbilical cord stump from 1 to multiple times in the days following a home birth have evaluated this intervention compared to other types of cord care on the development of omphalitis and neonatal mortality. Each of the 3 studies showed significant reductions in either omphalitis, neonatal mortality, or both with the 4% chlorhexidine. However, the optimal dosing schedule remains uncertain. While further studies are needed to clarify this issue, from the 3 studies it is now clear that with a minimum of one application of 4% chlorhexidine to the umbilical cord stump following delivery, the incidence of omphalitis and neonatal mortality can be reduced, especially in preterm newborns. This intervention, which is safe, inexpensive and requires minimal training and skill, should strongly be considered for adoption wherever home births occur.

Introduction

Each year, world-wide, there are approximately 3.3 million neonatal deaths in the first 28 days of life. Ninety-eight percent of these neonatal deaths occur in developing countries, with over half associated with a home birth; a third are believed to be due to infection.(1,2) Newborns are especially prone to infections for a number of reasons including a relatively immature immune system and exposure to maternal vaginal organisms during the birth process. Exposure to various pathogens in the first days of life, often transmitted by physical contact with the caregivers, provides another source of infection. While all newborns are at risk of infection, those born prematurely or who experience asphyxia or other serious neonatal conditions are at even greater risk of acquiring an infection in the neonatal period. Compared to term infants, preterm infants have thinner and more vulnerable skin, are at increased risk for respiratory distress, and are more likely to receive various invasive interventions, thereby allowing pathogens easier entrance. One vulnerable area for infection for all infants is the umbilical cord stump. Usually cut and then tied shortly after birth, for nearly a week until it detaches spontaneously, the cord stump provides necrotic tissue for organisms to colonize and a point of easy access for entrance to the neonate. Some 2 to 7% of infants born in low-income countries develop an infection of the umbilical cord stump known as omphalitis with about 10% of these characterized as severe, usually characterized as the presence of pus and redness extending more than 2 cm from the stump. (3) Of all

neonates with omphalitis, from 2 to 15% die of a systemic infection or neonatal sepsis. One reason for the high prevalence of omphalitis and the high case fatality rate in many developing countries is the practice of applying potentially harmful substances such as animal dung to the cord stump after it is cut. (4,5)

Many studies have attempted to reduce the incidence of neonatal infections using various methodologies. Use of clean birth kits to provide a sterile field for the baby at birth and a clean razor to cut the cord, as well as providing soap and instructions for care-giver hand-washing has been shown in some studies, but not all, to significantly reduce neonatal sepsis and mortality. (6,7)

Chlorhexidine is an antiseptic used for many years to reduce risk of acquiring infections in various health care settings. Wherever it is used, it reduces bacterial colony counts and in many instances infection rates as well. (8,9) It has an excellent safety record and little evidence of bacterial resistance. Since many newborn infections appear to arise from organisms acquired from the maternal genital tract during labor, during the 1990's attempts were made to reduce newborn infections by using a vaginal and newborn wash with chlorhexidine. Two non-randomized studies of this intervention in developing countries showed promise; (10,11) however, two recent randomized trials, one in Pakistan and one in South Africa, failed to show a reduction in neonatal mortality, although the Pakistan study did show a significant reduction in skin infections in the chlorhexidine group. (12,13) The concentration of chlorhexidine used in the first two studies was 0.25%, and in the latter two, 0.5% and 0.6%.

A review of three studies

Another approach to reduce neonatal infections focused on the use of a 4% chlorhexidine solution placed directly to the umbilical cord stump in the hope of reducing omphalitis and neonatal mortality. The first large cluster randomized study in Nepal involving over 15,000 infants delivered at home compared the use of 4% chlorhexidine to the umbilical cord stump on 7 of the first 10 days of life to cord stump cleansing with soap and water or dry cord care. (14) They found a 75% reduction in severe omphalitis (incidence rate ratio 0.25, 95% CI 0.12–0.53) and a 24% reduction in neonatal mortality (RR 0.76, 95% CI 0.55–1.04) in the chlorhexidine group compared to the dry cord care group. Neither severe omphalitis nor neonatal mortality was reduced by soap and water treatment of the cord stump compared to dry umbilical cord care. Much of the impact of chlorhexidine was in low birth weight infants. A second recently published study done in Pakistan involving 9,741 infants, also delivered at home, used a factorial design to evaluate daily umbilical cord chlorhexidine treatment over 14 days and hand washing. (15) They found no impact of hand washing on either the incidence of omphalitis or neonatal mortality, but a substantial reduction in both omphalitis (RR = 0.58, 95% CI 0.41–0.82) and neonatal mortality (RR = 0.62, 95% CI 0.45–0.85) in the chlorhexidine arm. In the most recently published three arm cluster randomized study from Bangladesh focusing on home births, the investigators compared dry cord care, one application of 4% chlorhexidine to the cord stump soon after birth, and multiple chlorhexidine (up to 7) applications. (16) Using the dry cord care group as the control (rate of 4.2/1000 for severe omphalitis and 28.3/1000 for neonatal mortality), one application of chlorhexidine reduced the neonatal mortality to 22.2/1000 ($p=0.002$), but did not have a significant impact on severe omphalitis (3.3/1000), while repeated applications of chlorhexidine reduced the incidence of severe omphalitis (1.2/1000, RR 0.35, 95% CI 0.15–0.81) but did not have a significant impact on neonatal mortality (26.6/1000, RR 0.94, 95% CI 0.78–1.14). There is no clear explanation as to why there was a significant reduction in mortality only in the single application group and a significant reduction in severe omphalitis only in the multiple application group. Furthermore, the impact on neonatal mortality appeared to be significant only for preterm infants.

Commentary

Omphalitis is an important cause of neonatal mortality and preventing this condition and its associated neonatal mortality is of high public health importance. While the use of clean birth kits, hand washing and careful attention to cleanliness in the days after birth may all be important components of a program to reduce neonatal sepsis, none of these interventions have to date provided unequivocal evidence that they can reduce sepsis-related neonatal mortality. The three studies briefly reviewed here, taken together, provide substantial evidence that umbilical cord stump treatment with 4% chlorhexidine reduces both omphalitis and neonatal mortality, with the impact likely greater in preterm and low birth weight infants. It is rare to have 3 large cluster randomized trials evaluating a single intervention - especially for births occurring at home in the poorest countries - available to inform public health policy.

The Bangladesh study, of course, raises questions about effectiveness of the two chlorhexidine treatment schedules, especially because of the divergence in effects on severe omphalitis and mortality. If this were the only study available, because of these discrepancies, it is unlikely one could recommend this treatment for use throughout the developing world. However, with three large randomized studies showing positive results, this intervention, which is especially attractive because of its low cost, safety, and its ability to be used in home settings with minimal training, should be strongly considered for widespread adoption for home births in low-income countries.

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