Dry care versus chlorhexidine cord care for prevention of omphalitis. Systematic review with meta-analysis

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Objective: to compare the effect of dry care and the application of chlorhexidine to the umbilical cord of newborns at risk of developing omphalitis. Method: systematic review with meta-analysis. Clinical trials comparing dry care with the application of chlorhexidine to evaluate omphalitis were selected. Methodological quality was evaluated using the Consolidated Standards of Reporting Trials. Results: the joint analysis of the studies shows a significant decrease in the risk of omphalitis in the chlorhexidine group compared to the dry care group (RR=0.58, CI: 0.53-0.64). However, in the analysis by subgroups, chlorhexidine umbilical cord care did not reduce the risk of omphalitis in hospital births (RR=0.82, CI: 0.64-1.05), in countries with a low infant mortality rate (RR=0.8, CI: 0.5-1.28), or at chlorhexidine concentrations below 4% (RR=0.55, CI: 0.31-1). Chlorhexidine acted as a protective factor at a concentration of 4% (RR=0.58, CI: 0.53-0.64), when applied in cases of home births (RR=0.57, CI: 0.51-0.62), in countries with a high infant mortality rate (RR=0.57, CI: 0.52-0.63). Conclusion: dry cord care is effective in countries with low infant mortality rate and in hospital births. However, 4% chlorhexidine for umbilical cord care protects against omphalitis in home births, in countries with a high infant mortality rate.

Descriptors: Umbilical Cord; Chlorhexidine; Skin Care; Infection; Meta-Analysis; Infant, Newborn.

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Introduction

Omphalitis is an important cause of neonatal mortality and its prevention is of great importance for public health\(^{(1)}\). The incidence of omphalitis in newborns (NB) in developed countries is 0.7%, rising to 2.7% in developing countries\(^{(2-3)}\), and it affects both sexes equally\(^{(1)}\).

It is defined as a periumbilical acute bacterial infection with induration, erythema, bad smell, pain, and presenting or not association with purulent exudate at the base of the navel\(^{(3)}\). It is peculiar at the neonatal period, and the average age for its incidence is the third or fourth day of life\(^{(2-3)}\).

The strategies for prevention of omphalitis are: hygiene practices at delivery, aseptic material to cut the umbilical cord and hand washing every time the cord is handled\(^{(4)}\). In the 21st century there have been several studies on umbilical cord (UC) care comparing different antiseptics, and several studies have shown that the hygiene habits of bathing and drying it were not associated with an increased risk of omphalitis when compared to alcohol application\(^{(4-9)}\). Topical triple dye is a treatment used in the United States, and there are several studies comparing the topical triple dye with alcohol application for UC care, and the results of these studies show that there are no differences between the treatment groups of omphalitis\(^{(7-8)}\).

There are no studies with adequate level of evidence to establish recommendations on the most effective UC care for prevention of omphalitis in NB. Thus, a systematic review was performed to answer the question: Is the application of chlorhexidine more effective than dry cord care for prevention of omphalitis? The objective was: to compare the effect of dry care and the application of chlorhexidine to the umbilical cord of newborns at risk of developing omphalitis.

Method

A systematic review with meta-analysis was carried out, for which a bibliographic search was performed in the Cochrane, Pubmed, Scopus, CINAHL, EMBASE, Cuiden and Spanish Medical Index (EMI) databases, and a reverse search with secondary recovery. The bibliographic search was carried out by January 2017, with no previous date range limit or language restriction. In order to identify the articles describing the incidence of omphalitis in NB to which dry care or chlorhexidine cord care was used for UC care, the following descriptors were used: *umbilical cord care*, *dry care*, *newborn*, *topical umbilical cord care*, *chlorhexidine umbilical cord care*, *umbilical cord care practices*, *randomized controlled trial* and *Clinical Trial*. The following search strategy was used in the PubMed/MEDLINE database: (Umbilical cord[mh] or cords, umbilical[tiab] or umbilical cord[tiab]) and (cord care[tiab] or dry care[tiab] or dry*[tiab] or chlorhexidine[mh] or chlorhexidine cord care[tiab]) and (new-born[mh] or infant[mh]) and (omphalitis[tiab]) and (clinical trial[pt]). To plan, prepare and publish the systematic review and meta-analysis, the guidelines provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)\(^{(9)}\) were followed.

For the selection of the studies, two authors independently assessed the inclusion of the studies identified by the search strategy. In the first phase, the articles were selected according to their title and, after reading the abstracts, those that met the inclusion criteria were selected. Subsequently, an in-depth reading was carried out and their methodological quality was assessed using the Consolidated Standards Of Reporting Trials (CONSORT)\(^{(10)}\).

Clinical trials comparing dry care with the application of chlorhexidine solutions at all concentrations available for UC care were used as inclusion criteria. All living NB were included, without restricting the weight at birth, sex, gestational age, geographical area, level of development and delivery setting.

Using a previously developed form, two authors independently extracted the data according to: type of study, population included, length of fieldwork period, duration of follow-up, type of intervention, procedure carried out with both the dry care and the chlorhexidine cord care, and results obtained. Those authors whose articles are the subject of this study were contacted so that they could provide the data necessary for performing the meta-analysis by subgroups. A third person evaluated the discrepancies found in order to decide on the inclusion of some articles and on data extraction.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE)\(^{(11)}\) was used to evaluate the quality of the evidence, which was classified as: high, moderate, low or very low.

The results were expressed as relative risk (RR) with 95% confidence interval. The clinical heterogeneity and the homogeneity of the population were evaluated. The statistical heterogeneity and the consistency between the results of the studies were evaluated using I\(^2\) as criterion measure. I\(^2\) values of 25%, 50% and 75% were used to define heterogeneity as low, moderate and high. When this criterion was higher than 50%, a random effects model was applied to combine the results\(^{(22)}\). A sensitivity analysis of the results was carried out by performing
several meta-analyses sequentially, by subdividing them according to the methodological quality of the studies, the sample number and the concentration of chlorhexidine.

A subgroup analysis was performed for the data of the studies conducted with hospital and community NB, and dividing these data by the methodological quality of the studies, the sample number and the concentration of chlorhexidine. A subgroup analysis was carried out for chlorhexidine concentrations: 4% chlorhexidine and chlorhexidine concentrations lower than 4%.

For the statistical analysis, Review Manager 5.3\textsuperscript{(13)} and Epidat 3.1\textsuperscript{(14)} softwares were used.

**Results**

Figure 1 shows the process of selecting studies. The literature search found 511 articles, of which 468 were discarded after a reading of their titles. The analysis of the summaries led to exclusion of 28 through a complete reading of 15 articles, and 6 were eliminated for different reasons: chlorhexidine was not compared with dry cord care\textsuperscript{(15)}; be a research project\textsuperscript{(16)}; not be a clinical trial\textsuperscript{(17)}; exclusively measure the time until the umbilical cord stump falls off\textsuperscript{(18-20)}.

| Author, country, year | Methods and Participants | Interventions | Definitions | Monitoring, procedure and results |
|-----------------------|--------------------------|---------------|-------------|----------------------------------|
| Meberg et al\textsuperscript{(21)} | Norway, 1985. | Randomized clinical trial. Newborns > 37 weeks. | -Dry care. (total n=219; n included in the analysis=219).  
-Daily care with 4% chlorhexidine. (total n=217; n included in the analysis=217). | There is no definition | Monitoring for 6 weeks in 2 periods. Procedure: application of chlorhexidine for 2 minutes at the base of the umbilical cord. Results:  
-Bacterial infections in the first 6 weeks: 12.9% (pemphigus: n=52, conjunctivitis: n=23, paronychia: n=11, omphalitis: n=9).  
-Bacterial colonization: S. Aureus: 91%; Streptococcus B: 20% and E. coli: 39%. |
| Mullany et al\textsuperscript{(22)} | Nepal, 2006. | Randomized clinical trial. November 2002-March 2005. Live newborns. | Dry care (total n=5082, included in the analysis n=5021).  
-Water and soap (total n=5107).  
-4% chlorhexidine cord care (once a day for 10 days). (total n=4924, included in the analysis n=4883). | Omphalitis: Redness extending to the skin at the base of the umbilical cord. Pus with moderate or severe redness, or severe redness only. Severe redness with pus. | Visits: on the 1\textsuperscript{st}, 2\textsuperscript{nd}, 3\textsuperscript{rd}, 4\textsuperscript{th}, 6\textsuperscript{th}, 10\textsuperscript{th}, 12\textsuperscript{th}, 14\textsuperscript{th}, 21\textsuperscript{st} and 28\textsuperscript{th} days of life. Procedure: homogenous groups with previous hand washing; kit delivery was given and the same procedure was carried out for UC care, all groups had opaque plastic bottles. Results:  
-Omphalitis: the risk of infection in the chlorhexidine group was 54% lower than the dry care group.  
-Mortality: in comparison with the dry care group, the risk of mortality was 24% lower than in the chlorhexidine group. |

Figure 1 – Process of selecting studies

Figure 2 shows the characteristics of the sample of each study, interventions and outcome measures.
| Author, country, year | Methods and Participants | Interventions | Definitions | Monitoring, procedure and results |
|-----------------------|--------------------------|---------------|-------------|----------------------------------|
| Kapellen et al[22], Germany, 2009. | Randomized clinical trial. November 2003-August 2005. Full-term newborns; 37-42 weeks. Weight greater than 2500gr. | Dry care (total n=332, included in the analysis n=332). -1% chlorhexidine powder (once a day for at least 3 days after stump falls off. (total n=337, included in the analysis n=337)). | Omphalitis: erythema, edema, secretion, sepsis or umbilical cellulitis. | Visits on the 10th-14th days after birth. Procedure: Chlorhexidine application every diaper change. Daily monitoring by parents with evolution reporting. Results: -Stump fall off time: 7.0±2.5 days in the chlorhexidine group and 7.8±2.9 days in the dry care group. Adverse events: ulcers, granulomas, omphalitis, erythema, edema, secretion. Incidence of adverse events: chlorhexidine group: 32.3% of NB; dry care group: 44.9%. -Satisfaction with the treatment: chlorhexidine group: 98.9% were satisfied or very satisfied; dry care group: 91.4% were satisfied or very satisfied. |
| El Arifeen et al[23], Bangladesh, 2012. | Randomized clinical trial. June 2007-September 2009. Live newborns. | Dry care (total n=10,006, included in the analysis n=9,924). -A single application of 4% chlorhexidine. (total n=9,923). -A daily application of chlorhexidine for 7 days. (total n=10,329, included in the analysis n=10,254). | Omphalitis: Redness extending to the skin or pus. Redness extending to the skin. Redness with pus or severe redness. Severe redness with pus. | Visits: on the 1st, 3rd, 6th, 9th and 15th days. Another visit between on the 28th and 35th days. Procedure: all groups used opaque plastic bottles; in the daily chlorhexidine group, the solution was applied once after birth, and once a day for 7 days. The recommendations of the WHO were followed in the dry care group. At each visit, UC condition and the care procedure were checked. A sterile instrument was used to cut the cord in 93% of NB. Results: -Onfalitis: when compared with the multiple chlorhexidine group, the dry care group showed a lower risk of redness or pus, and a lower risk of severe redness with pus. -Mortality: there are no statistically significant differences in the relative risk of neonatal mortality between multiple chlorhexidine group and the dry care group. |
| Soofi et al[24], Pakistan, 2012. | Randomized clinical trial. January 2008-June 2009. Live newborns. | -4% chlorhexidine for cord care once a day for 14 days after birth and hand washing with soap. (total n=2827, included in the analysis n=2214). -Dry care with previous hand washing. (total n=2822, included in the analysis n=2475). -4% chlorhexidine for cord care once a day for 14 days after birth without previous hand washing. (total n=3131). -Control group: Care without previous hand washing. (total n=3106). | Omphalitis: No omphalitis: no redness, swelling or pus. Mild onfalitis: redness, swelling, or pus in the cord area. Moderate onfalitis: redness, swelling or pus extending for less than 2 cm to the skin from the base of the cord stump. Severe omphalitis: inflammation extending for more than 2 cm from the cord, with or without pus. | Visits: on the 1st, 3rd, 5th, 7th, 14th and 28th days. Procedure: the midwives were trained, and each participant was given a birth kit and hand washing instructions in all groups. During the visits, care performance and signs of omphalitis were observed. Results: -Onfalitis: the risk of omphalitis (any degree) in the three treatment groups was lower than in the control group. -Neonatal mortality: 29.4 per 1,000 live births. |
| Gathwala et al[25], India, 2013. | Randomized clinical trial. June 2010-November 2011. Newborns > 32 weeks and 1500gr of weight. | -2.5% chlorhexidine gluconate, 3 times a day for 3 days. (total n=70, included in the analysis n=70). -Dry care and fold the diaper below the cord (total n=70, included in the analysis n=70). | Probable sepsis. Culture-proven sepsis. | Monitoring at hospital admission. Procedure: dry care group: UC was maintained clean and dry and the diapers were folded under the umbilical stump; in the chlorhexidine group, chlorhexidine was applied to the UC three times a day (once per nursing shift) for 3 days after the stump falls off. The cord was observed twice a day for signs of omphalitis. Results: - Cord fall off time. In the chlorhexidine care group: average: 8.5±2s(2.77); in the dry care group: average: 10.3±1(3.23). -Onfalitis: The absolute risk of sepsis proven by culture was 21.43% and 2.86% in the dry care group and in the chlorhexidine group, respectively. -Mortality: chlorhexidine group: n=0; dry care group, n=4. |

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**Definitions:**
- **Interventions:**
- **Definitions:**
  - Omphalitis: erythema, edema, secretion, sepsis or umbilical cellulitis.
  - Onfalitis: The absolute risk of sepsis proven by culture was 21.43% and 2.86% in the dry care group and in the chlorhexidine group, respectively. -Mortality: chlorhexidine group: n=0; dry care group, n=4.
The meta-analysis was performed using the 9 selected studies and 118,903 NB in total, of which 50.61% underwent dry umbilical cord care (60,182 NB). In total, there were 1,863 cases of omphalitis in both groups, and 64.03% of these cases of omphalitis belong to the dry cord care group.

Figure 3 shows the biases of the different studies included in the meta-analysis, with no study considered to be invalid.

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Regarding the risk of omphalitis, the 9 included studies show a significant decrease in the risk of omphalitis in the chlorhexidine group compared to the dry cord care group, with a RR of 0.58 (CI: 0.53-0.64), with moderate heterogeneity ($I^2=45\%$, $\chi^2=14.51$, $p=0.07$). This may be due to the clinical heterogeneity and, therefore, a subgroup analysis was performed. The result of the Egger’s test was 0.4556 ($p=0.6625$), which indicates that there is no publication bias. The data with which the meta-analysis was carried out (Figure 4) come from studies in which chlorhexidine was applied multiple times. According to the GRADE system, this level of evidence is rated as moderate. It can be seen in the tree graph (Figure 4) that four studies do not show a significant decrease in the risk of omphalitis with the use of chlorhexidine for cord care when compared with dry care.

When a subgroup analysis was performed, it is observed that in countries with NMR<10 there was a RR of 0.80 (CI: 0.5-1.28), so there are no significant differences between the two types of care for prevention of omphalitis. However, there is a significant decrease in the risk of omphalitis in the subgroup with NMR>10 (RR=0.57, CI: 0.52-0.63), as show in Figure 5. Countries with NMR<10 are those in which the studies are conducted with NB older than 36 weeks. According to the GRADE system, the level of evidence is moderate for those studies with NMR>10 and low for the present research with NMR<10.
In the community births group there is a significant decrease in the risk of omphalitis using chlorhexidine for umbilical cord care (RR=0.57, CI: 0.51-0.62), and a moderate heterogeneity of data was obtained ($I^2=45\%$, $\chi^2=7.3$, $p=0.12$). In the community births group there is a significant decrease in the risk of omphalitis using chlorhexidine for UC care (RR=0.57, CI: 0.51-0.62), and a moderate heterogeneity of data was obtained ($I^2=45\%$, $\chi^2=7.3$, $p=0.12$). These data from the meta-analyses by subgroups correspond to a level of evidence rated as moderate, according to the GRADE system.

The sensitivity analysis shows that the risk of omphalitis remains the same for all studies by excluding the studies in which blinding is not performed (RR=0.54, CI: 0.47-0.61). When studies not presenting selection bias are analyzed, the risk increases, but there is still a significant decrease in the risk of omphalitis with the use of chlorhexidine for UC care (RR=0.63, CI: 0.55-0.72), and in this case, the statistical heterogeneity obtained is low ($I^2=23\%$). When sensitivity was analyzed by eliminating studies, it is observed that if a study is eliminated$^{(22)}$, the resulting relative change is 6.18%, and this is the research whose confidence interval is more distant from 1.

Regarding the different concentrations of chlorhexidine used in the studies, when the meta-analysis is performed only with the studies in which a 4% chlorhexidine concentration was used in the intervention group, the result is a RR=0.58; CI: 0.53-0.64. By jointly analyzing the studies in which concentrations lower than 4% were used, a RR=0.55 is obtained; CI: 0.31-1. The high heterogeneity of the studies prevents an independent analysis for chlorhexidine concentrations of 1% and 2.5%.

**Discussion**

In a joint analysis, with the inclusion of the latest published studies, the current evidence showed a significant decrease in the risk of omphalitis with the use of multiple applications of chlorhexidine when compared with dry cord care. In countries with high neonatal mortality rates, such as Nepal, with 22 deaths per 1,000 live births$^{(31)}$, the risk of omphalitis is lower with the application of chlorhexidine when compared with dry cord care. In contrast, in countries with very low neonatal mortality rates, such as Germany, with 2 deaths per 1,000 live births$^{(31)}$, application of chlorhexidine does not differ from dry care in relation to the risk of omphalitis, although these studies investigated a small sample when compared with those whose NMR>10.

The results also show that community births present a lower risk of omphalitis with the application of chlorhexidine, a finding that corroborates the data from a review conducted in 2015, in which RR=0.48; CI: 0.4-0.57$^{(32)}$, and from another one carried out in 2016, in which RR=0.4; CI: 0.25-0.63, with an $I^2$ of 68%$^{(33)}$. This situation is not consistent with the findings of studies with a group of hospital births, in which there were no differences between the application of chlorhexidine and dry care. The findings of other
studies also do not show differences in the incidence of omphalitis depending on the type of cord care, although they did not compare solely dry care with the application of chlorhexidine\(^\text{[22-33]}\) for UC care.

Several systematic reviews have shown similar results, in which chlorhexidine was found to reduce the risk of omphalitis\(^\text{[23-35]}\), especially in countries with high NMR. In this sense, our results support that UC care with the use of 4% chlorhexidine protects against omphalitis in home births in countries with high NMR. The application of chlorhexidine in concentrations lower than 4% did not act as a protection factor against omphalitis, although it must be emphasized that the studies using these concentrations of chlorhexidine evaluated hospital births.

Depending on where the birth takes place, the UC cutting technique is performed with the use of a new or boiled razor blade\(^\text{[35-36]}\), and this, together with the lack of hand washing before the intervention\(^\text{[35]}\) increases the risk of infection, especially in home deliveries. Researchers are aware that efforts to promote hand washing, cut the umbilical cord with the use of clean instruments and avoid unclean domestic interventions can reduce exposure to infectious agents and improve neonatal outcomes\(^\text{[37]}\).

Limitations: This systematic review with meta-analysis needs to be interpreted with caution due to the included clinical trials and their own limitations. In at least 5 of these studies, it was not possible to mask the intervention of participants and professionals, although it is unlikely that the results were biased, as proven by the sensitivity analysis.

There is variation in the interventions carried out in the different studies such as: in 4 research studies\(^\text{[22,24,27-28]}\), training was provided to the mothers so that they could perform a correct hand hygiene. Regarding hygiene for cutting of the UC, 5 studies\(^\text{[22,24-25,27-28]}\) specify that a delivery kit was given to achieving maximum cleanliness.

There were 3 studies\(^\text{[22,24,25]}\) in which the delivery took place in community settings, 2 in community and hospital settings\(^\text{[27-28]}\) and four in hospital settings\(^\text{[21,23,26,29]}\).

In 6 studies, the chlorhexidine concentration used for cord care was 4%\(^\text{[21,22,24-25,27-29]}\), and the concentrations used in the remaining three studies\(^\text{[23,26,29]}\) were 2.5% and 1%\(^\text{[23,26,29]}\). The sensitivity analysis performed considering the different chlorhexidine concentrations used, suggests that the use of chlorhexidine in concentrations lower than 4% is not associated with a greater protection against omphalitis than that provided by dry umbilical cord care.

Another limitation of the present analysis is that no data on low birth weight and premature babies are shown. The analysis only used data available from studies whose inclusion criteria specified NB at more than 36 weeks gestation.

The criteria used to perform the analysis on the studies classifying omphalitis into several categories were: Redness with pus or severe redness and severe redness with pus, which correspond to moderate and severe omphalitis.

There is no conflict of interest or funding in this study.

**Conclusion**

Application of 4% chlorhexidine in NB significantly decreases the incidence of omphalitis in home births in countries with a NMR higher than 10 deaths per 1,000 live births. The inclusion of newly published studies reinforces the level of evidence so that the use of chlorhexidine is recommended for UC care in developing countries. This meta-analysis provides important information for the policies aiming at the care for NB in home births and in high-risk situations where hygiene conditions are not appropriated.

There are no significant differences between dry cord care and the use of chlorhexidine in concentrations lower than 4% for UC care in countries with low NMR and in hospital births. It was evidenced that dry cord care is an effective intervention in these contexts and it may be recommended for prevention of omphalitis because it is less expensive. Therefore, it is convenient to expand the knowledge through double blind clinical trials in these contexts to evaluate both interventions and thus improve the care practice provided to the newborn.

In full term NB, there are no statistically significant differences between the two groups of UC care. It is necessary to carry out more studies according to the gestational age to know what proportion of preterm newborns have omphalitis regardless of the type of cord care.

It would be useful to conduct studies with qualitative methodology to know the experiences in the UC care and consider them for the development of more effective and efficient health strategies aiming at reducing the incidence of omphalitis.

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