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Original Article

Impact of different antiseptics on umbilical cord colonization and cord separation time

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Abstract

Introduction: There is still some uncertainty on cord care practices all around the world, especially in developing countries. The aim of our study was to investigate the effects of six different umbilical cord care practices on the rate of colonization and cord separation time.

Methodology: A total of 516 newborns were randomly allocated to the following six umbilical cord care groups: group 1 received dry care; groups 2–4 received a single application of 70% alcohol, 4% chlorhexidine, or povidon-iodine in the delivery room, respectively, which were discontinued thereafter; groups 5 and 6 received a single application of 70% alcohol or 4% chlorhexidine, respectively, starting in the delivery room and continuing every six hours until discharge. Umbilical cords were examined on the second and third days and between the fifth and seventh day for signs of omphalitis. Swab cultures were taken on the second or third day from all cases.

Results: Cord separation time (median [interquartile range]) was the shortest for group 1 (7 [6–7] days) and the longest for group 3 (10 [7–12] days) and group 6 (10 [8–12] days) ($p < 0.001$). The cord colonization in the swab cultures was significantly lower in groups 3 and 6 ($p < 0.001$). Omphalitis was detected in eight (1.5%) patients among the study population, and there was no significant difference between the groups.

Conclusions: Our study showed that chlorhexidine application was the most effective agent in decreasing colonization, though it increased cord separation time significantly in both groups.

Key words: newborn; cord care; colonization; cord separation time; omphalitis.

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Introduction

In countries with limited resources, umbilical cord infection continues to be a major cause of neonatal morbidity and poses significant risk of mortality [1-3]. The idea of preventive treatment evolved from the assumption that bacterial growth in the umbilicus is harmful. This resulted in routine umbilical cord care with disinfectants and antimicrobial agents to prevent systemic infection [4].

Since 1998, the World Health Organization has recommended promotion of clean and dry cord care for newborns, while noting that topical antiseptics may be used where risk of infection is high; however, controversy still exists in the literature [5]. A Cochrane review by Zupan *et al*. [6] reported studies mainly conducted in hospitals in high-income countries; the results cannot be generalized to community settings in low-income countries, where achieving clean and dry cord care is difficult [7-10]. A recent meta-analysis that included studies from both developing and developed countries reported that 4% chlorhexidine significantly reduced omphalitis in community settings [11]. However, the effect of chlorhexidine compared to dry cord care on neonatal mortality in hospital settings remains largely unknown.

Turkey is a middle-income country, and cord care practices differ widely depending on the hospital's policy. The aim of our study was to investigate the effects of the most frequently used umbilical cord care practices in our hospital setting and to propose the most appropriate antiseptic agent for cord care. The primary outcome of the study was the rate of colonization and the time of cord separation.

Methodology

This was a prospective randomized clinical trial to study the above objectives and to analyze the outcomes specified on an intention-to-treat basis. The study was conducted on all infants who were born consecutively between December 2008 and June 2010 in the obstetric wards of the Marmara University Hospital, with the approval of the institutional ethics committee. Written informed consent from one or both parents was obtained prior to enrollment.

Participants

The eligibility criteria included term healthy newborn infants. The flow chart of the study is shown in Figure 1. The criteria for exclusion were prematurity (less than 37 weeks of gestation), birth weight less than 2,500 grams, any congenital anomaly, meconium-stained amniotic fluid, and respiratory distress after birth. In this study, the time of discharge was set at between 48 and 72 hours.

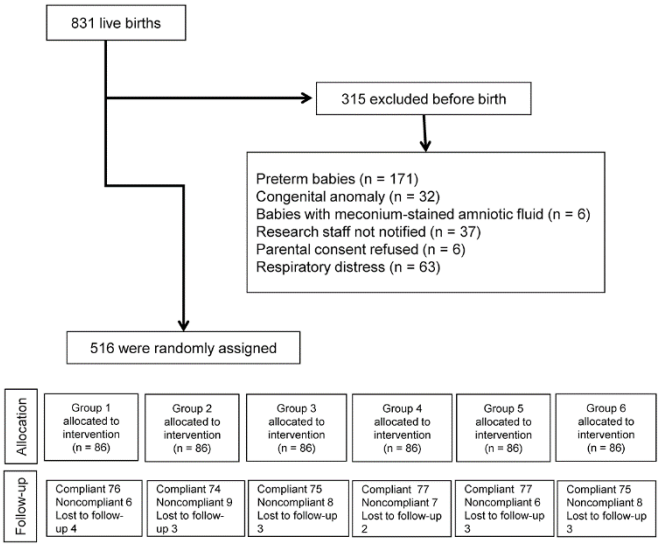
Intervention

The eligible infants were randomly allocated to one of the six different umbilical cord care groups per the opaque envelope method. The study subjects were randomized by means of consecutively numbered opaque envelopes on which a sticker indicating instructions for each group was placed. The babies were enrolled in one of the following groups. Group 1 was the dry cord care group; the umbilical cord was kept clean and dry. In groups 2, 3, and 4, a single application of 70% alcohol, 4% chlorhexidine, or povidone-iodine, respectively, was applied in the delivery room. In groups 5 and 6, a single application of 70% alcohol or 4% chlorhexidine, respectively, was applied in the delivery room, and the same agent was applied every six hours until discharge.

None of the patients were given any antiseptic solutions after discharge unless indicated. There was no blinding during allocation, as it was not possible to mask the intervention received, but the physician who followed the babies after birth until discharge was blind to all the cases.

The clean cord care at birth was performed in accordance with the recommendations of the World Health Organization [5]. All the study subjects were rooming with their mothers. In this study, the mothers were instructed to fold diapers below the level of the umbilicus and to avoid giving their infants tub baths until the cord fell off. Meticulous hand-washing was emphasized for the caregivers.

Figure 1. The flow chart of study.



The umbilical cord was examined and swab cultures were taken at the second or third day of life during discharge. After discharge, at the fifth or seventh day of life, all newborns were re-examined for signs of omphalitis. A second swab culture was taken when signs of omphalitis were detected. If the umbilical cord was not separated at the fifth or seventh days of life, families were called weekly by phone, in order to record the cord separation time and signs of omphalitis. Specimens were obtained with a sterile cotton swab from the cord-cutaneous junctions and were placed immediately in Stuart's transport medium (bioMeriéux, Marcy-l'Etoile, France). Swabs were inoculated onto blood agar (bioMeriéux, Marcy-l'Etoile, France) and MacConkey's agar (bioMeriéux, Marcy-l'Etoile, France) using the streak plate method. Plates were incubated aerobically for 24–48 hours at 37°C. Isolates were identified by Vitek 2 (bioMeriéux, Marcy-l'Etoile, France). The results were recorded by the same research fellow in microbiology.

Definitions

Omphalitis and colonization were diagnosed based on the criteria of the Centers for Disease Control [12] and was defined as follows. Omphalitis in a newborn (≤ 30 days of age) must meet at least one of the following criteria: (1) The patient has erythema and/or serous drainage from umbilicus and at least one of the following: (a) organisms cultured from drainage or needle aspirate; or (b) organisms cultured from blood; or (2) The patient has both erythema and purulence at the umbilicus. Colonization was defined as the presence of microorganisms on skin, on mucous membranes, in

open wounds, excretions, or secretions that were not causing any adverse clinical signs or symptoms.

The cord detachment time was the length of time necessary for the cord to detach completely.

Sample size

To determine the sample size, a power analysis with 95% confidence level (1-α) and 80% power (1-β) was performed. For the cord separation time, the sample size was calculated as 36 babies for each group if the shortest and the longest cord separation times were accepted as six (with a variance of 2) and eight days (with a variance of 16), respectively [13,14]. The sample size was calculated as 49 for each group, considering that the percentage of colonization for dry cord care would be 60% and 30%, respectively, for chlorhexidine application [15,16].

Statistical analysis

Descriptive statistics were used to report sample characteristics. All continuous data were analyzed using the Kolmogorov-Smirnov test for normality testing. Descriptive statistics were presented as mean, standard deviations and median, and inter-quartile ranges. The cord separation time between the groups was compared using the Kruskal-Wallis test and *post hoc* Bonferroni correction analysis, and the descriptive analysis was presented as median and inter-quartile range. The categorical data were presented with percentages (%), and Pearson's Chi-squared test was used for statistical analysis. Comparisons between groups for normally distributed continuous variables were evaluated using one-way analysis of variance (ANOVA) test with *post hoc* Tukey honest significant difference (HSD) comparisons. The differences were considered statistically significant at a level of probability of $p < 0.05$. SPSS version 13.0 (IBM, Armonk, USA) was used for statistical analysis.

Results

There were 44 babies who were noncompliant with the assigned study group, and 18 babies were lost during follow-up (Figure 1). The distribution of the noncompliant and lost follow-up babies was not significantly different across the study groups. The demographic characteristics were not significantly different among the six groups (Table 1). The cord separation time was significantly shorter in the dry care group (7 [6–7] days) compared to other groups ($p < 0.001$).In the post-hoc analysis, the cord separation time in both 4% chlorhexidine groups (group 3: 10 [7–12] days; group 6: 10 [8–12] days) was significantly longer than that in groups 1, 2, and 5 ($p < 0.001$), but there was no statistically significant difference when compared with the povidone-iodine group. The cord separation time was found to be 7 (6-10) days, 8 (6-11) days, and 7 (6-10) days in groups 2, 4, and 5, respectively, without any statistical differences (Table 2).

In total, 49% (253/516) of the study cases were colonized. Most cases were colonized with normal skin flora including coagulase-negative staphylococci

Table 1. Demographic characteristics of the study groups.

	Group 1 (n = 86)	Group 2 (n = 86)	Group 3 (n = 86)	Group 4 (n = 86)	Group 5 (n = 86)	Group 6 (n = 86)	p
Gender (M)* n (%)	44 (51.1)	43 (50.0)	44 (51.1)	36 (41.8)	43 (50.0)	38 (44.2)	[b]0.62
Gestational age (weeks) Mean ± SD	38.7 ± 0.8	38.8 ± 0.9	38.9 ± 0.9	38.7 ± 0.8	38.7 ± 1.0	39.1 ± 1.0	[a]0.06
Birth weight (g) Mean ± SD Median (IQR)	3,417.1 ± 364.5 3,300 (2,750–4,360)	3,375.2 ± 372.3 3,340 (2,540–4,300)	3,352.4 ± 375.8 3,280 (2,600–4,400)	3,247.9 ± 312.2 3,190 (2,700–4,080)	3,380.7 ± 383.1 3,250 (2,670–4,400)	3,412.1 ± 375.2 3,350 (2,680–4,350)	[a]0.28
Delivery mode (VD) † n (%)	30 (34.8)	21 (24.4)	22 (25.6)	25 (29.1)	19 (22.1)	23 (26.7)	[b]0.39
Maternal age (years) Mean ± SD Median (IQR)	29.4 ± 5.3 29 (17–42)	30.1 ± 5.0 29 (19–42)	30.2 ± 6.1 30 (17–45)	29.9 ± 5.3 30 (18–42)	29.6 ± 5.0 28 (20–42)	29.3 ± 5.5 29 (20–46)	[a]0.85

[a] One-way ANOVA test; [b] Pearson's Chi-squared test † VD: vaginal delivery; *M: male; Group 1: Dry care; Group 2: A single application of 70% alcohol in the delivery room; Group 3: A single application of 4% chlorhexidine in the delivery room; Group 4: A single application of povidone-iodine in the delivery room; Group 5: A single application of 70% alcohol in the delivery room that continued until discharge (every six hours with in the first two to three days); Group 6: A single application of 4% chlorhexidine in the delivery room that continued until discharge (every six hours with in the first two to three days).

Table 2. Cord separation time of the study groups.

	Group 1 (n = 86)	Group 2 (n = 86)	Group 3 (n = 86)	Group 4 (n = 86)	Group 5 (n = 86)	Group 6 (n = 86)	P
Cord separation time (days) Median (IQR)	7 (6–7)	7 (6–10)	10 (7–12)	8 (6–11)	7 (6–10)	10 (8–12)	[a]**0.001***

* $p < 0.01$; [a] Kruskal-Wallis test.

Table 3. Colonization results of the study groups.

	Group 1 n (%)	Group 2 n (%)	Group 3 n (%)	Group 4 n (%)	Group 5 n (%)	Group 6 n (%)	[a]p
Normal skin flora†	47 (54.7)	42 (48.8)	12 (14.0)	42 (48.8)	36 (41.9)	12 (14.0)	0.001*
Pathogenic microorganisms‡	12 (14.0)	11 (12.8)	4 (4.7)	17 (19.7)	13 (15.1)	5 (5.8)	0.35
Total bacterial colonization	59 (68.6)	53 (61.6)	16 (18.6)	59 (68.6)	49 (56.9)	17 (19.7)	0.001*
No growth	27 (31.4)	33 (38.3)	70 (81.4)	27 (31.4)	37 (43.0)	69 (80.2)	0.001*

[a] Pearson's Chi-squared test; * $p < 0.01$; † Including coagulase-negative *Staphylococcus*; ‡ *Staphylococcus aureus*, group B *Streptococcus*, *Enterococus faecalis*, *Escherichia coli*, *Klebsiella*, *Enterobacter*, *Serratia marcescens;* Group 1: Dry care; Group 2: A single application of 70% alcohol in the delivery room: Group 3: A single application of 4% chlorhexidine in the delivery room; Group 4: A single application of povidone-iodine in the delivery room; Group 5: A single application of 70% alcohol in the delivery room that continued until discharge (every six hours with in the first two to three days); Group 6: A single application of 4% chlorhexidine in the delivery room that continued until discharge (every six hours with in the first two to three days).

(CoNS) (37%; 191/516), while 12% (62/516) were colonized with pathogenic organisms (*Staphylococcus aureus*, group B *Streptococcus*, Gram-negative microorganisms), mainly *Staphylococcus aureus* (52%) (Table 3). Total bacterial colonization rate of cases with normal skin flora (including CoNS) was significantly lower in the third and sixth groups in the swab cultures ($p < 0.001$). The percentage of *Staphylococcus aureus*, the leading agent in the pathogenic group, was not different among the groups. The rate of *Staphylococcus aureus* colonization in groups 1, 2, 3, 4, 5, and 6 was 7.6%, 9.3%, 3.4%, 8.9%, 8.1%, and 5.2%, respectively. Of 516 newborns, 8 (1.5%) developed omphalitis. The results of the swab cultures are shown in Table 4. There was no significant difference in the rate of omphalitis when compared between the study groups ($p = 0.375$). Colonization with pathogenic organisms was present at the first swab culture in two of the eight infants with omphalitis (one infant with *Staphylococcus aureus* and one infant with *Serratia marcescens*), and three of the infants with omphalitis had positive colonization at the second swab cultures (three infants with *Staphylococcus aureus*) (Table 4).

Discussion

Different methods of umbilical cord care have been applied over the years in efforts to reduce the risk of neonatal infection; however, the recent evidence does not support one regimen over another for the prevention of omphalitis [6]. Previously, colonization of the umbilical cord was considered to be a risk factor for omphalitis. The umbilicus is recognized as the first site of colonization after birth, and colonization usually occurs 48–72 hours after birth [16]. The infection-colonization relationship has been investigated in several studies, and there is still controversy among reported studies [6]. In a community-based study from Bangladesh, the authors showed that cord cleansing with 4% chlorhexidine immediately after birth reduces overall and organism-specific colonization of the stump, and also reduces neonatal infection in developing countries [20]. Mullany *et al.* reported that

Table 4. Clinical findings and culture results of the babies with omphalitis.

Patient no.	Groups	First colonization (Days 2 and 3)	Second colonization (Days 5 to 7)	Clinical findings
1	1	No growth	*Staphylococus aureus*	Erythema and pus
2	1	Normal skin flora	No growth	Erythema and pus
3	1	Normal skin flora	No growth	Erythema and pus
4	2	No growth	No growth	Erythema and pus
5	2	Normal skin flora	*Staphylococus aureus*	Erythema and pus
6	4	*Serratia marcescens*	CONS	Erythema
7	4	*Staphylococus aureus*	Normal skin flora	Erythema
8	6	Normal skin flora	*Staphylococus aureus*	Erythema and pus

although the cord separation time was longer with chlorhexidine compared to other antiseptics, it did not increase subsequent morbidity or infection [21]. A recent meta-analysis showed that there was significant evidence to suggest that topical application of chlorhexidine to the umbilical cord reduces neonatal mortality and omphalitis in community and primary care settings in developing countries [11]. In contrast to that study, a meta-analysis including 21 studies mostly from developed countries with low rates of omphalitis, reported that antiseptic solutions did not decrease the rate of omphalitis when compared to dry cord care, although they reduced bacterial colonization compared to dry cord care. It must be kept in mind that most of the studies in this meta-analysis were hospital based [6]. In our study, both chlorhexidine groups were less colonized with normal skin flora, including CoNS, compared to all the other groups. However, the longest cord separation time was measured in both groups receiving 4% chlorhexidine (groups 3 and 6). Cord separation time was significantly shorter in the dry cord care group. This was in accordance with the current literature [4,13,22,23]. Although the cord separation time was increased in both 4% chlorhexidine groups in our study, only one of the cases with omphalitis was in the chlorhexidine group (group 6).

The incidence of omphalitis has decreased in industrialized countries over the years due to aseptic delivery techniques and clean cord care, and the incidence has been reported to be between 0.2% and 0.7% [5,24,25]. The rate of omphalitis was 1.5% in our study, which is higher than the rates reported from developed countries, but lower than in the developing world where this rate may be as high as 6%–10% [24-26]. We found no significant difference in the rate of omphalitis between the study groups. As the targeted number of cases for this outcome could not be reached according to the power analysis, this result should be interpreted cautiously.

Conclusions

The aim of our study was to compare the effect of different antiseptic solutions on colonization and cord separation time. In that aspect, chlorhexidine application appeared to be the most effective agent in decreasing colonization, though it significantly increased the cord separation time. Further studies are needed to reach a conclusion about routine cord care practices, particularly in the developing world, where omphalitis is a significant issue.

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