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Review Article

Effect of chlorhexidine cord application on prevention of neonatal sepsis in developing countries: Systematic review and meta-analysis

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ABSTRACT

Objective: The aim of this review was to identify the pooled effect of chlorhexidine cord application on prevention of neonatal sepsis in developing countries.

Methods: We have conducted systemic review and meta-analysis. Articles were searched from electronic databases such as PubMed, EMBASE, CINHAL, Cochrane central register of controlled trials (CENTRAL), and other sources such as direct Google search, Google Scholar, and POPline. Only randomized controlled trial studies were considered for this review. The effect of chlorhexidine cord application on prevention of neonatal sepsis and mortality was assessed as compared to dry cord care.

Results: Five studies from developing countries were included in the review with a total of 129,293 participants. Pooled result of meta-analysis showed that chlorhexidine cord application reduces neonatal sepsis by 32% as compared to dry cord care (relative risk [RR] 0.68, 95% confidence interval [CI] 0.57–0.81, random effect model, I^2 =93%). It also indicated that chlorhexidine cord application reduces severe sepsis by 77% (RR 0.23, 95% CI 0.11–0.48, random effect model, I^2 = 63%) and neonatal mortality reduction by 13 % as compared to dry cord care (RR 0.87, 95% CI 0.79–0.97, random effect model, I^2 = 0%). **Conclusions:** Chlorhexidine cord application significantly reduces neonatal sepsis and mortality in developing countries. Therefore, we stress the importance of including chlorhexidine cord application into the essential newborn care in the setting with high burden of neonatal mortality. The review protocol was registered at PROSPERO with registration number CRD 42018089204.

Keywords: Chlorhexidine, neonatal mortality, neonatal sepsis, umbilical cord care

Introduction

Globally, about 2.6 million newborns loss their life in the first 4 weeks of age.[1] A majority of this mortality were accounted from low- and middle-income countries (LMIC).[2,3] Almost all, 99% of newborn death are from the developing countries and most of which are considered to be preventable.[4,5] Evidence showed that three major causes of neonatal mortality (NMR) were related to preterm birth (28%), severe infections (26%), and asphyxia (23%).[6,7]

Over the past two to three decades, neonatal mortality reduction remains a sluggish in developing countries and its burden accounts around 46% of all under-five mortality.[1] The achievement of sustainable development goals for neonatal mortality reduction to <12/1000 life birth in every country by 2030 demands doubling of the current rate of neonatal mortality reduction.[8] To increase current neonatal mortality reduction, focusing on cost effective interventions is crucial.[9,10]

Neonatal sepsis was identified as one of major causes of newborn morbidity and mortality in the developing world accounting for one third of neonatal death.[11-14] Most of these deaths could be prevented by implementing cost-effective measures such as infection preventions and hygienic newborn care practices.[7,15,16]

Umbilical cord is the main portal of entry for microorganisms that cause newborn sepsis.[17,18] Optimal umbilical cord care practices during the first week of life have significant potential to reduce neonatal death secondary to sepsis.[19-21]

Multiple published studies showed that chlorhexidine cord application/cleansing significantly reduces neonatal sepsis.[22-25] Chlorhexidine is cost effective and easy to apply on umbilical cord by health workers or caregivers.[26]

To produce concrete evidence related to the effect of chlorhexidine cord application on prevention of neonatal sepsis/

cord infection in developing countries, it is important to conduct a systematic review and meta-analysis. Even though there were certain studies, systematic review, and meta-analysis, they were not specific to developing countries and some review did not included some randomized controlled trial (RCT) studies from African countries. Reviews which were published in Cochrane in 2015 were not specific to developing countries and did not included the two RCTs from African counties.[27,28] The review conducted by Imdad *et al*. in 2013 was only limited to community setting studies. Moreover, two RCTs from African countries were also published after this review.[27,28] Thus, the current review produces concrete evidence on the benefit of chlorhexidine cord application for the prevention of neonatal sepsis and mortality. The objective of this review is to identify the pooled effect of chlorhexidine cord application on prevention of neonatal sepsis in developing countries.

Methods

Search strategies and evaluation of studies

We have conducted this review to assess a pooled effect of chlorhexidine cord application on prevention of neonatal sepsis/cord infections and mortality in developing countries. Articles were searched from electronic databases such as PubMed, EMBASE, CINHAL, a Cochrane Central Register of Controlled Trials (CENTRAL), and other sources such as direct Google search, Google Scholar, and POPline. We have also searched other sources such as direct Google search, Google Scholar, and POPline. The following search strategies were used; Newborn OR Infant AND Chlorhexidine AND Sepsis OR Infection AND Umbilical Cord AND Developing Countries AND Developing Countries. Three stages of search strategies were employed to access all available relevant articles. Initial search was performed on electronic databases and followed by analysis of titles, abstracts, and index terms to retrieve all relevant papers. Then, identified keywords and index terms were used across all databases. Finally, after identifying relevant articles, their reference lists were also looked (ancestor searching strategy was followed), and in the same way, other studies which cited them were looked online (descendent search strategy). Finally, all articles relevant to the review titles were retrieved and imported to EndNote software. Then, all studies which fulfill pre-determined inclusion criteria were included in the systematic review.

Inclusion and exclusion criteria

We searched for both published and unpublished articles from 2000 to May 15, 2018. Our search was limited to articles reported in English because of inability to read and understand other languages. Only RCT studies were considered for this review. All studies which assessed the effect of chlorhexidine cord application on prevention of neonatal sepsis and/or mortality in developing countries were included.

All observational studies were excluded from this review. Studies from developed countries were also excluded from the study. The main purpose of focusing on study from developing country is to evaluate the effect of chlorhexidine-based cord care in low-resource setting with high burden of NMR. Studies in which exposure and outcome variables clearly not indicated were also excluded. In addition, studies that did not use appropriate sample size determination or sampling methods were also excluded.

For articles screening process first, we have considered titles and abstracts of articles for inclusion. Then, all articles which fulfill inclusion criteria were retrieved as full text and read thoroughly for further assessment. While reading the full text, those articles which fail to present clearly the exposure (chlorhexidine cord application/chlorhexidine-based cord care) and outcome (neonatal sepsis/omphalitis and/or NMR) were excluded from the review. Studies that clearly report the above criteria were included for further methodological quality assessment.

Definition of exposure and outcome variables

In this review, an exposure variable is chlorhexidine cord application with an aim to prevent neonatal sepsis/omphalitis and/or mortality as compared to dry cord care. In this review, outcome variable is challenged due to different ways of its definition (definition of neonatal sepsis or cord infection/omphalitis and NMR varies across the studies).

Critical appraisals and data abstraction

This systematic review was conducted from February to May 15, 2018. The review of records was done in accordance with Preferred Reporting Items for Systematic Review and Meta-Analysis.[29] Joanna Briggs Institute (JBI) critical appraisal tool for randomized control trial (RCT) study was used for methodological quality screening of included articles.[30] This screening process was conducted by two independent reviewers and for any discrepancy agreement was reached by discussion. Based on JBI critical appraisal results, any studies which had unsatisfactory methodological quality were excluded [Appendix 1 and 2]. Finally, for all included studies, authors and year of publication, study setting and country, number of study participants/sample size (both for intervention and control groups), major findings such as incidences of neonatal sepsis and mortality, and reported relative risk (RR) with 95% CI were extracted and presented [Tables 1 and 2].

Review Results

Database search provided a total of 1229 articles. After removal of duplicates, 829 potentially relevant articles were identified. By reviewing titles, a total of 143 articles were included for evaluation of abstracts. Following evaluation of the abstracts, 34 articles were identified for full-text screening. Of the full-text articles screened, 28 were excluded because they did not meet the inclusion criteria. After screening full-text, a total of six articles were retained for methodological quality assessment

Table 1: Data abstraction for primamry outcome (neonatal sepsis or infections)

Author, year	Country, study setting and design	Groups or arms of studies and measurement of outcomes	Live births/ sample size	Outcome of interests	Risk per 1000 live births	RR (95% CI)
Arifeen et al., 2012	Bangladesh, Community-based RCT	Redness extending to skin or pus				
		Multiple chlorixedine	10254	1406	137.1	0.89 (0.62–1.26)
		Single chlorixedine	9354	1252	133.8	0.89 (0.62–1.26)
		Dry cord care	9924	1545	155.7	
		Redness extending to skin				
		Multiple chlorixedine	10254	327	31.9	0.78 (0.5–1.22)
		Single chlorixedine	9354	339	36.2	0.93 (0.61–1.43)
		Dry cord care	9924	403	40.6	
		Redness with pus or severe redness				
		Multiple chlorixedine	10254	151	14.7	0.58 (0.31–0.95)
		Single chlorixedine	9354	211	22.6	0.90 (0.55–1.46)
		Dry cord care	9924	258	26.0	
		Severe redness with pus				
		Multiple chlorhexidine	10254	16	1.6	0.35 (0.15–0.81)
		Single chlorhexidine	9354	31	3.3	0.77 (0.4–1.48)
		Dry cord care	9924	42	4.2	
Sazawal, 2016	Tanzania, community-based RCT	Any redness or pus				
		Chlorhexidine	18015	1413	78.4	0.65 (0.61–0.7)
		Dry cord care	18896	2183	115.5	
		Any redness without pus				
		Chlorhexidine	18015	1051	58.4	0.76 (0.7–0.82)
		Dry cord care	18896	1427	75.5	
		Moderate redness with pus or severe redness				
		Chlorhexidine	18015	166	9.2	0.61 (0.5–0.73)
		Dry cord care	18896	286	15.1	
		Severe redness with pus				
		Chlorhexidine	18015	2	0.1	0.06 (0.02–0.25)
		Dry cord care	18896	33	1.8	
Soofi et al., 2012	Pakistan, Community-based RCT	Treatment group analysis				
		Handwashing and chlorhexidine cleansing (Group A)	2214	82	37.03	0.53 (0.53–0.88)
		Handwashing only (Group B)	2475	127	51.3	0.67 (0.48–0.93)
		Chlorhexidine cleansing only (Group C)	2653	84	31.66	0.44 (0.29–0.67)
		Control (Group D)	2399	182	75.86	
		Factorial analysis (handwashing vs. no handwashing)				
		No handwashing (Groups C and D)	5052	266	52.65	0.67 (0.48–0.93)
		Handwashing (Groups A and B)	4689	209	44.57	0.44 (0.29–0.67)
		Factorial analysis (chlorhexidine cleansing vs. no chlorhexidine cleansing)				
		No chlorhexidine cleansing (Groups B and D)	4874	309	63.39	0.83 (0.61–1.13)
		Chlorhexidine cleansing (Groups A and C)	4867	166	34.1	0.58 (0.41–0.82)
Mullany et al., 2006	Nepal, community-based RCT	Moderate or severe redness				
		Chlorhexidine 4.0%	4703	438	93.13	0.64 (0.58–0.8)
		Soap/water	4883	660	135.13	1.03 (0.87–1.22)

(Contd...)

Table 1: *Continued*

Author, year	Country, study setting and design	Groups or arms of studies and measurement of outcomes	Live births/ sample size	Outcome of interests	Risk per 1000 live births	RR (95% CI)
		Dry cord care	4859	638	131.3	
		Moderate or severe redness with pus				
		Chlorhexidine 4.0%	4883	147	30.1	0.46 (0.36–0.59)
		Soap/water	5029	280	55.67	0.88 (0.69–1.12)
		Dry cord care	5021	315	62.74	
		Severe redness with pus				
		Chlorhexidine 4.0%	4930	13	2.64	0.25 (0.12–0.53)
		Soap/water	5096	53	10.4	1.01 (0.58–1.77)
		Dry cord care	5076	52	10.24	
Semrau et al., 2016	Zambia, facility-based RCT	Intention-to-treat analysis				
		Chlorhexidine	18510	82	4.43	0.73 (0.47–1.13)
		Dry cord care	19346	118	6.1	
		As practised analysis				
		Chlorhexidine	16660	77	4.62	0.76 (0.48–1.18)
		Dry cord care	19346	118	6.1	

RCTs: Randomized controlled trials, RR: Relative risk, CI: Confidence interval

Table 2: Data abstraction for secondary outcome (NMR)

Author, year	Country, study setting and design	Groups or arms of studies and measurement of outcomes	Live births/ sample size	Outcome of interests/ (NM)	NM per 1000 live births	RR (95% CI)
Arifeen *et al*., 2012	Bangladesh, community-based RCT	All enrolled babies				
		Multiple chlorixedine	10,329	275	26.6	0.94 (0.78–1.14)
		Single chlorixedine	9423	212	22.5	0.8 (0.65–0.98)
		Dry cord care	10,008	283	28.3	
		Deaths in the 1st week of life in enrolled babies				
		Multiple chlorixedine	10,329	182	17.6	0.91 (0.71–1.18)
		Single chlorixedine	9423	149	15.8	0.83 (0.64–1.09)
		Dry cord care	10,008	193	19.3	
Sazawal *et al*., 2016	Tanzania, community-based RCT	Overall				
		Chlorhexidine	18,015	189	10.5	0.9 (0.74–1.09)
		Dry cord care	18,896	221	11.7	
Soofi *et al*., 2012	Pakistan, community-based RCT	Treatment group analysis				
		Handwashing and chlorhexidine cleansing (Group A)	2214	45	20.3	0.64 (0.39–1.06)
		Handwashing only (Group B)	2475	95	38.4	1.23 (0.82–1.83)
		Chlorhexidine cleansing only (Group C)	2653	66	24.9	0.74 (0.5–1.08)
		Control (Group D)	2399	81	33.8	
		Factorial analysis (handwashing vs. no handwashing)				
		No handwashing (Groups C and D)	5052	147	29.1	
		Handwashing (Groups A and B)	4689	140	29.9	1.08 (0.79–1.48)
		Factorial analysis (chlorhexidine cleansing vs. no chlorhexidine cleansing)				
		No chlorhexidine cleansing (Groups B and D)	4874	176	36.1	
		Chlorhexidine cleansing (Groups A and C)	4867	111	22.8	0.62 (0.45–0.85)

(Contd...)

Table 2: *Continued*

Author, year	Country, study setting and design	Groups or arms of studies and measurement of outcomes	Live births/ sample size	Outcome of interests/ (NM)	NM per 1000 live births	RR (95% CI)
Mullany *et al*., 2006	Nepal, community-based RCT	Treatment group				
		Chlorhexidine 40%	4924	72	14.6	0.76 (0.55–1.04)
		Soap/water	5107	98	19.2	1 (0.76–1.31)
		Dry cord care	5082	98	19.3	
Semrau *et al*., 2016	Zambia, facility-based RCT	Intention-to-treat analysis				
		All-cause NMR (including day 0 deaths)				
		Chlorhexidine	18,510	282	15.2	1.12 (0.88–1.44)
		Dry cord care	19,346	263	13.6	
		All-cause NMR (excluding day 0 deaths)				
		Chlorhexidine	18,424	200	10.9	1.12 (0.86–1.47)
		Dry cord care	19,266	186	9.7	
		As practised analysis				
		All-cause NMR (including day 0 deaths)				
		Chlorhexidine	16,645	141	8.5	0.88 (0.66–1.16)
		Dry cord care	19,266	186	9.7	
		All-cause NMR (excluding day 0 deaths)				
		Chlorhexidine	16,400	132	8	0.94 (0.72–1.22)
		Dry cord care	16,400	141	8.6	

NMR: Neonatal mortality, RCTs: Randomized controlled trials, RR: Relative risk, CI: Confidence interval

and they were critically appraised by the two independent reviewers [Appendix 2]. Subsequently, one publication was excluded because of unsatisfactory methodological quality.[31] Finally, five publications were maintained for data abstraction and systematic review [Figure 1].[23,27,28,32,33]

Data processing and analysis

In this review, only RCT studies were included. After all necessary information were extracted from the included articles, double data entry method was followed to transfer all results to Review Manager Version 5.3 for meta-analysis. A random effect model was used to estimate pooled effect size as RR with 95% confidence interval (CI). Analysis was conducted using Mantel-Haenszel as the default because all included data were dichotomous. Statistical heterogeneity was assessed through standard Chi-square with $P < 0.1$ for statistical significance. Level of heterogeneity was defined based on I^2 (I square) ($I^2 = 0\%$ no heterogeneity, $I^2 < 50\%$ low heterogeneity, $I^2 = 50$–75% medium heterogeneity, and $I^2 > 75\%$ high heterogeneity). Moreover, sensitivity analysis was conducted using random and fixed effect models alternatively. We have also checked the consistence of pooled effect by computing analysis with and without inclusion of poor quality articles.

Description of included studies

In this review, a total of five studies were included (four community-based and one facility-based RCTs). In all included studies, a main intervention or treatment was 4% chlorhexidine cord application as compared to standard care (dry cord care). Among the total included studies, two RCTs were conducted in Africa. One facility-based study was done in Zambia[28] and the other community-based study was conducted in Tanzania.[27] Other three studies included in this review were conducted in Bangladesh,[34] Nepal,[32] and Pakistan.[33]

A facility-based Zambian study was included a total of 37,758 newborn babies; 18450 (99.7%) chlorhexidine and 19308 (99·8%) dry cord care groups were followed up to 28 days of post-partum. Both intention-to-treat (ITT) and per-protocol analysis were conducted. The author was also considered a baseline comparability of study subjects, but the study participants and research workers were not blinded. This study did not show any significant effects of chlorhexidine-based cord care on NMR (RR 1.12, 95% CI 0.86–1.47) and sepsis (RR 0.73, 95% CI 0.47–1.13).[28] For the primary outcome of the study, analysis was done with and without neonatal deaths which occurred before day zero, and in both cases, no significant effect was reported. Nine adverse events related to chlorhexidine were reported (one ocular exposure and eight local skin irritation) and none was sever.[28]

A community-based RCT from Tanzanian was included 36911 newborn babies (18,015 chlorhexidine and 18,896 dry cord care groups). This study had two phases (phases 1 and 2). In the first phase, the study had three arms (7292, 7321, and 7484

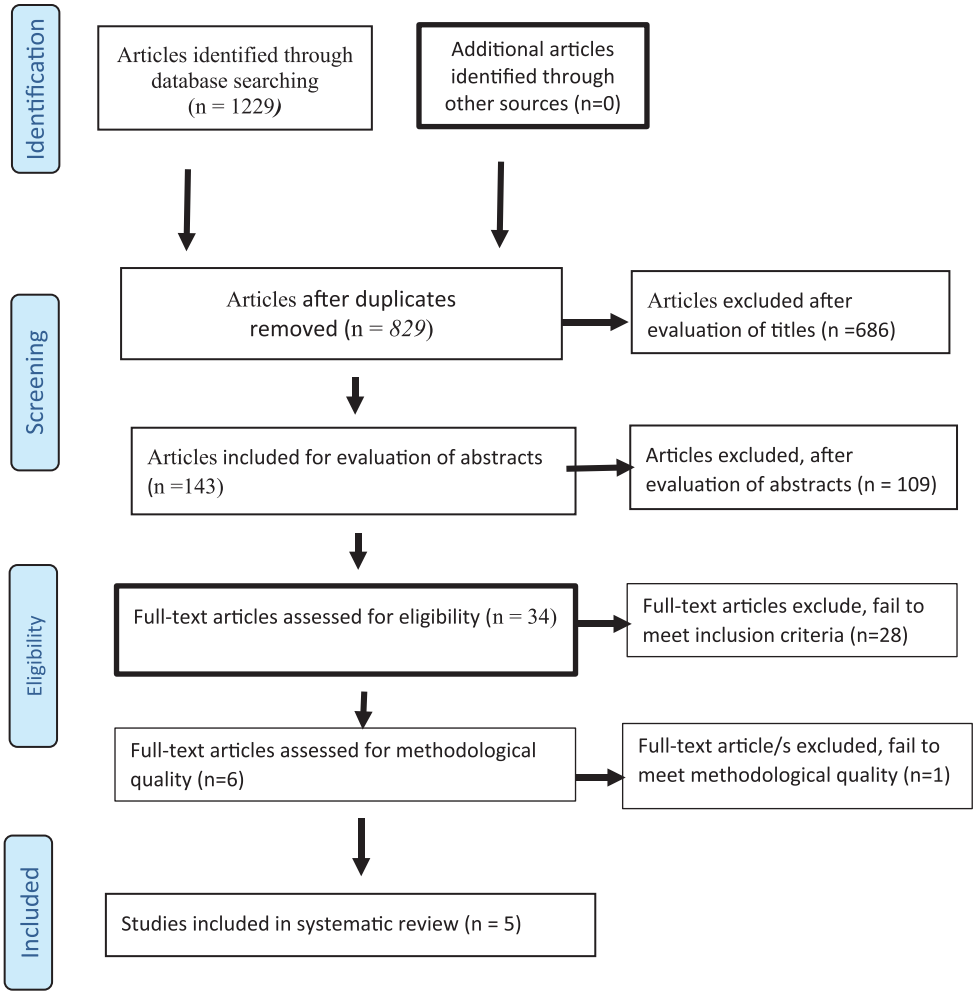

Figure 1: Preferred reporting items for systematic review and meta-analysis, flow diagram showing the identification of articles

newborn babies were assigned to chlorhexidine, placebo, and dry cord care, respectively). In phase 2 of the study, placebo group was discontinued and baseline comparability of study participants was clearly reported. In trial, study participants and research workers were not masked during phase 2 of the study. An ITT analysis was done for both primary and secondary outcomes (neonatal and cord infection/sepsis). This RCT reported a significant reduction of omphalitis among chlorhexidine group as compared to dry cord care group (RR 0.65, 95% CI 0.61–0.7), but there was no significant difference in NMR among chlorhexidine group as compared to dry cord care group (RR 0.9, 95% CI 0.74–1.09).[27]

A cluster RCT from Bangladesh was enrolled 29,760 newborn babies using three different arms (10,329, 9423, and 10,008 multiple chlorhexidine cord cleansing, single chlorhexidine cord cleansing, and dry cord care, respectively). The author was considered baseline comparability of study participants among the three arms, but the study subjects and research workers were not masked. In this study, a primary outcome was reported as a death of infants per 1000 live births within 28 days. An ITT analysis was done for both primary and secondary outcome (NMR and omphalitis). The risk of NMR in multiple and single chlorhexidine cord cleansing groups was compared relative to the dry cord care cluster. The study showed that multiple chlorhexidine cord cleansing reduces any umbilical cord redness or pus by 42% (RR 0.58, 95% CI 0.31–0.95) and sever umbilical cord redness with pus by 65% (RR 0.35, 95% CI 0.15–0.81) as compared to dry cord care. Risk of NMR was significantly lower among single chlorhexidine group as compared to dry cord care (RR 0.8, 95% CI 0.65–0.98), but multiple chlorhexidine cord cleansing did not reduce NMR (RR 0.94, 95% CI 0.78–1.14). In this study, no adverse effect of chlorhexidine was reported.[23]

Community-based clustered RCT study from Nepal was enrolled 15,123 newborn babies in three different groups (4934, 5107, and 5082 newborn babies as chlorhexidine, soap and water, and dry cord care groups, respectively). In this study, the author was considered baseline comparability of study subjects and double-blinded approach was followed. An incidence of cord infection was reported per 100, but for the review purpose, we have changed a risk of umbilical cord infection into cases per 1000 live births. The analysis

was conducted based on ITT approach and cluster effect was considered using design effect for each group in the study. This study showed that chlorhexidine reduces severe cord infection by 75% (RR 0.25%, 95% CI 0.12–0.13) as compared to dry cord care, but there was no protective benefit from soap and water-based cord care as compared to dry cord care. The study was also showed that chlorhexidine cord application within 24 hrs reduces NMR by 34% (RR 0.66, 95% CI 0.46–0.95) and indicated that a time to start chlorhexidine cord application after birth is important factor.[32]

A community-based RCT from Pakistan was enrolled 9741 newborn babies and allocated them into four different groups (2165, 2378, 2578, and 2312 chlorhexidine with handwashing, handwashing only, chlorhexidine only, and dry cord care groups, respectively). Baseline comparability of the study subjects was considered. Data collectors and implementation teams were masked. A primary outcome of the study was incidence of omphalitis and NMR. The result from this study showed that chlorhexidine significantly reduces risk of omphalitis by 42% (RR 0.58, 95% CI 0.41–0.82) and NMR by 38% (RR 0.62, 95% CI 0.45–0.85) as compared to dry cord care but handwashing has no effect in both cases.[33]

Meta-analysis of included studies

Effect of chlorhexidine cord application on neonatal sepsis/cord infection

We did meta-analysis using five RCTs which compared the effects of multiple chlorhexidine cord application with dry cord care.[23,27,28,32,33] There were a total of 8089 cord infections/neonatal sepsis in two groups (chlorhexidine and dry cord care groups). A pooled results from the five trial studies showed that chlorhexidin reduces neonatal sepsis/cord infections by 32% (RR 0.68, 95% CI 0.57–0.81; Random effect model, $I^2 = 93\%$) [Figure 2].

Sensitivity analysis

Sensitivity analysis was conducted by limiting the analysis to three studies.[27,28,32] This analysis remove two studies which have inconsistance (statistical heteroginity $I^2 = 93\%$). The combined results showed that chlorhexidine reduces neonatal sepsis/cord infection by 31% (RR 0.69, 95% CI 0.65–0.73; random effect model, $I^2 = 0\%$) [Figure 3].

Effect of chlorhexidin on severe cord infection/ neonatal sepsis

Three cluster-randomized trials also assessed the effect of chlorhexidin on sever cord infections/neonatal sepsis as compared to dry cord care.[23,27,32] There were a total of 158 sever cord infections/neonatal sepsis. A pooled result from the three studies showed that chlorhexidine cord cleansing reduces severe cord infections/neonatal sepsis by 77% (RR 0.23, 95% CI 0.11–0.48; random effect model, $I^2 = 63\%$) [Figure 4].

Effect of chlorhexidine cord application on NMR

The five cluter-radomised trials also evaluated the effect of multpile chlorhexidine-based cord care on neonataal mortality/death.[23,27,28,32,33] A total NMR among both groups (chlorhexidine and dry cord care) was 1375. Pooled result from the five trials showed that multiple chlorhexidin-based cord care reduces NMR by 13% as compared to dry cord care (RR 0.87, 95% CI 0.79–0.97; random effect model, $I^2 = 0\%$) [Figure 5].

Discussion

Summary of main findings: Prevention of neonatal sepsis and mortality

The current systematic review identified five cluster RCT studies which meet pre-set inclusion criteria and methodological quality. These studies include a total of 129,293 newborn babies. A major finding from meta-analysis suggested that chlorhexidine cord application has significant effect on prevention of neonatal sepsis/cord infection. Meta-analysis of five studies showed that chlorhexidine cord application reduces risk of infection by 32% as compared to

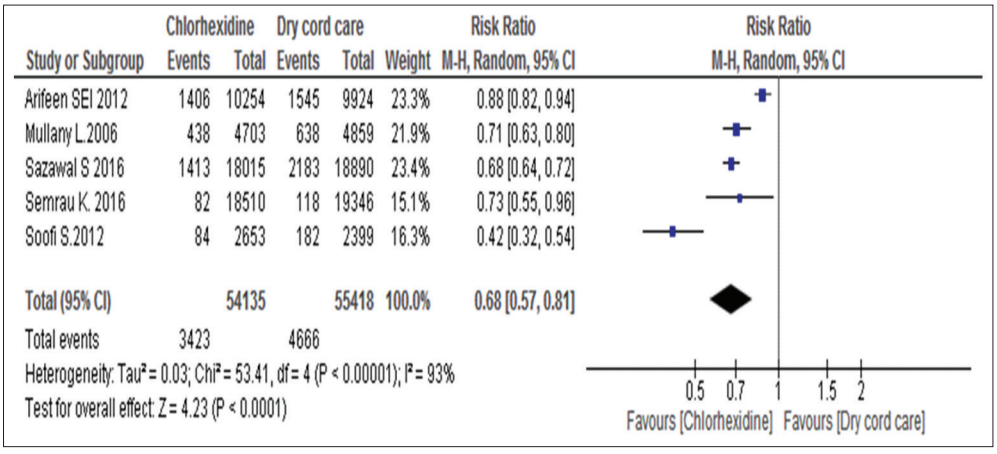

Figure 2: Forest plot of comparison: Chlorhexidine versus dry cord care, outcome: Any cord redness or pus

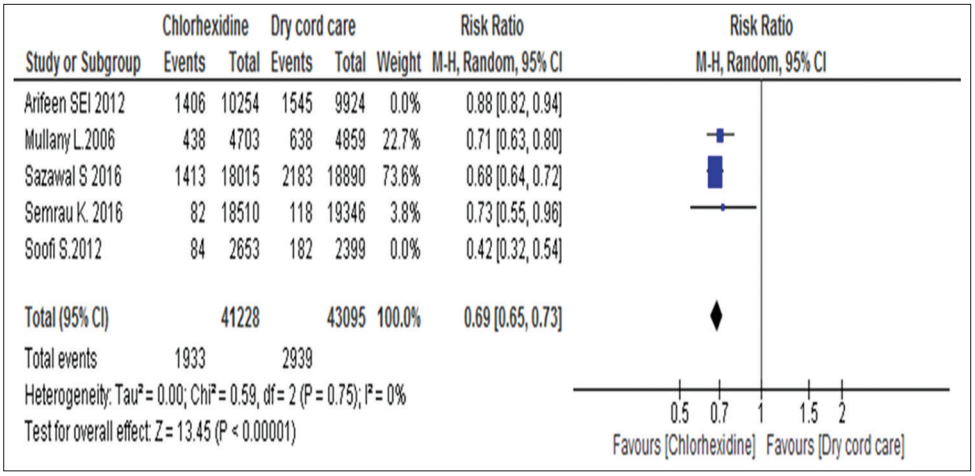

Figure 3: Sensitivity analysis forest plot of comparison: Chlorhexidine verus dry cord care, outcome: Any cord redness or pus

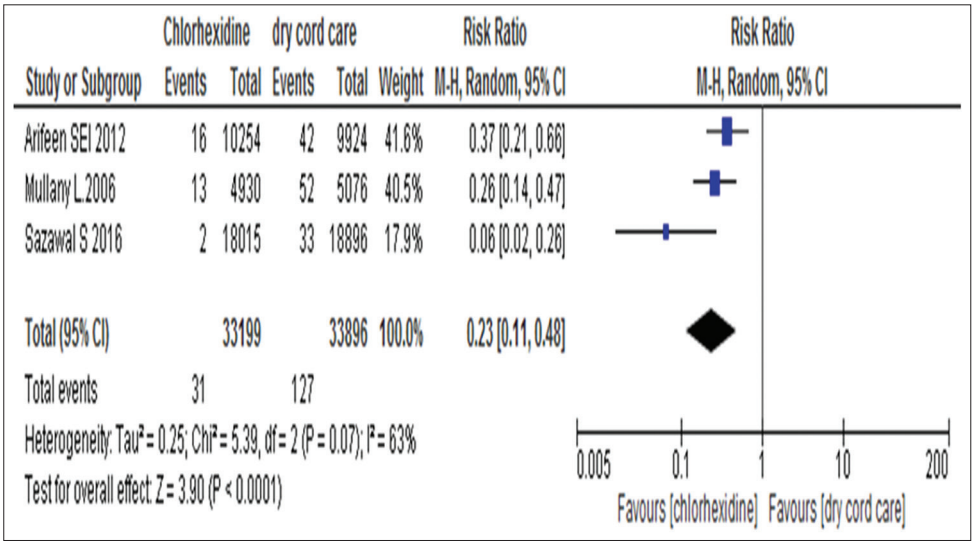

Figure 4: Forest plot of comparison: Chlorhexidine versus dry cord care, outcome: Severe redness with pus

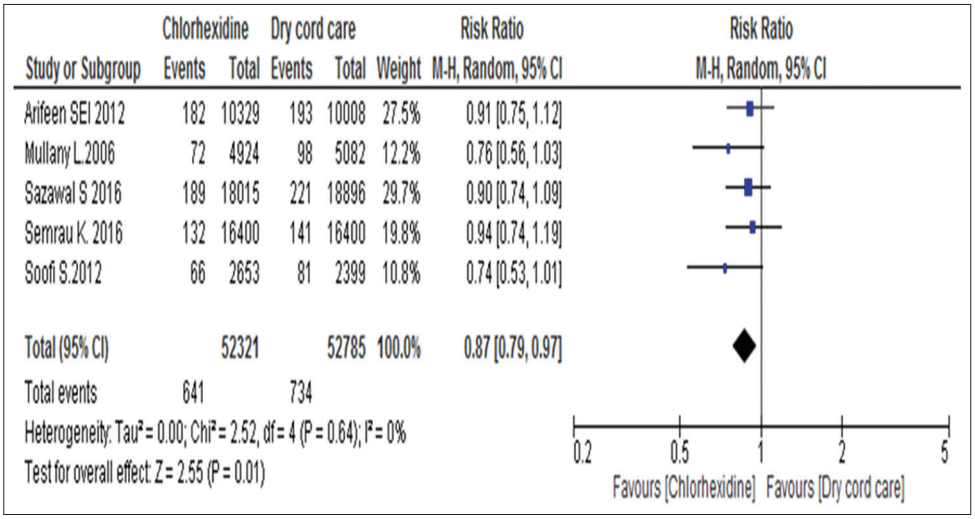

Figure 5: Forest plot of comparison: Chlorhexidine versus dry cord care, outcome: Neonatal mortality

dry cord care or standard cord care. The analysis also showed that chlorhexidine cord application reduces the risk of severe cord infection/sepsis by 77% as compared to dry cord care. This finding is consistent with other reviews which suggested that the use of chlorhexidine for cord care significantly reduces NMR and sepsis/cord infection.[35,36]

We have also conducted meta-analysis to assess a pooled effect of chlorhexidine cord application on NMR. This analysis indicated that chlorhexidine cord application significantly reduces NMR by 13% as compared to dry cord care in the developing countries. This finding is also in line with previous systematic review which showed that the use of chlorhexidine for umbilical cord care has significant benefit for neonatal mortality reduction.[35-37]

With low-to-moderate quality of evidence, it is suggested that using chlorhexidine for newborn umbilical cord care in the developing countries helps prevent neonatal cord infection/sepsis and reduces mortality. The World Health Organization is also recommended that 4% chlorhexidine daily cord application is useful in the setting with high burden of NMR and home delivery.[38] Accordingly, it can be proposed that chlorhexidine cord application should be integral part of essential newborn care in the developing countries where the burden of NMR and home delivery is very high.

Quality of the evidence

We have evaluated the quality of evidence using GRADE approach. A quality of evidence assessment was conducted by two independent reviewers. Rating of evidence quality was started at high level and then downgraded one level for serious concerns or two level for very serious concerns related to risk of bias, inconsistency, indirectness, imprecision, and publication bias.

Our review has shown different quality of evidence for both primary and secondary outcomes. Analysis conducted using five studies to assess the effect of chlorhexidine-based cord care showed low quality of evidence in reducing sepsis/cord infection. The quality of evidence was downgraded two level because of very serious detection and performances and inconsistency. Moderate quality of evidence was seen for the reduction of severe cord infection/sepsis and NMR. The quality of evidence was downgraded by one level because of serious detection and performance bias [Appendixes 3 and 4].

Limitations of the study

In this review, the outcome of interest (neonatal sepsis/cord infection) was challenged by inconsistent definition and classification of umbilical cord infection/sepsis among different studies. No study was reported sepsis-specific NMR. Our search was only limited to articles which were published in English language. Other limitations of the review was related to risk of detection and performances bias as study participants and outcome assessors were not masked in different included studies.

Conclusions

In general, this review indicated that 4% chlorhexidine cord application appears to be effective for the prevention of neonatal sepsis/cord infection and reduces NMR in developing countries. Therefore, we emphasize the importance of including chlorhexidine cord application into the essential newborn care in the developing countries.

Implication for practices

Our review concluded that there is benefit of 4% chlorhexidine cord application/cleansing for the prevention of neonatal sepsis/cord infection and reduction of NMR. Moreover, all five cluster RCTs included in this review were from developing countries and used 4% chlorhexidine for umbilical cord care as treatment. Therefore, the result can be generalized to the context of all developing Courtiers. Thus, we suggest incorporation of 4% chlorhexidine cord application as essential newborn component in this setting.

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List of Appendix

Appendix 1: Summary of critical appraisal of included studies using JBI critical tools for RCTs

Included study	Q_1	Q_2	Q_3	Q_4	Q_5	Q_6	Q_7	Q_8	Q_9	Q_{10}	Q_{11}	Q_{12}	Q_{13}
Arifeen *et al*., 2012	y	n	y	n	n	y	y	y	y	y	y	y	Y
Mullany *et al*., 2006	y	u	y	y	y	y	y	y	y	y	y	y	Y
Sazawal *et al*., 2016	y	y	u	n	u	u	y	y	y	y	y	y	Y
Semrau *et al*., 2016	y	n	u	n	n	n	y	y	y	y	y	y	Y
Soofi *et al*., 2012	y	u	u	u	y	y	y	y	y	y	y	y	Y
Total score (%)	100	20	40	20	40	60	100	100	100	100	100	100	100

JBI: Joanna Briggs Institute, RCTs: Randomized controlled trials

Appendix 2: Summary of critical appraisal of exclude study using JBI critical tools for RCTs

Excluded study	Q_1	Q_2	Q_3	Q_4	Q_5	Q_6	Q_7	Q_8	Q_9	Q_{10}	Q_{11}	Q_{12}	Q_{13}
Prabha *et al*., 2014	n	n	u	n	n	n	u	u	y	y	y	y	Y
Total score (%)	0	0	0	0	0	0	0	0	1	1	1	1	1

JBI: Joanna Briggs Institute, RCTs: Randomized controlled trials

Appendix 3: Summary of quality of evidences review: Effect of chlorhexidine cord application for prevention of neonatal sepsis/cord infection as compared to dry cord care in the developing countries

Grade criteria	Rating (circle one)	Explain reasons for down- or up-grading	Quality of the evidence
Study Design	RCT (starts as high quality non-RCT (starts as low quality)	All the five included studies are randomized control trial	High quality
Risk of bias	No Serious (−1) Very serious (−2)	Downgraded one level (from high to low) because of three studies have high risk of detection and performance bias	Moderate quality*
Inconsistence	No Serious(−1) Very serious (−2)	Downgraded one level because of considerable statistical heterogeneity (I^2=93%)	Low quality**
Indirectness	No Serious(−1) Very serious (−2)	No indirectness	Low quality**
Imprecisions	No Serious(−1) Very serious (−2)	No imprecisions	
Publication bias	Undetected Strongly suspected	No	
Other (Upgrading factors circle all that apply)	Large effect(+1 or+2) Dose response(+1 or+2) No plausible confounding (+1 or+2)		

High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

*The quality of evidence was downgraded from high to moderate because of high risk for detection and performance bias. **The quality of evidence was downgraded from moderate to low because of considerable statistical heterogeneity (I^2=93%). RCTs: Randomized controlled trials

Appendix 4: Summary of quality of evidences review: Effect of chlorhexidine cord application for prevention of NMR as compared to dry cord care in the developing countries

Grade criteria	Rating (circle one)	Explain reasons for down-or upgrading	Quality of the evidence
Study Design	RCT (starts as high quality) Non-RCT (starts as low quality)	All the five included studies are randomized control trial	High quality
Risk of bias	No Serious (−1) Very serious (−2)	Downgraded one level (downgraded from high quality to moderate) because of likely risk of detection and performance biases	Moderate quality*
Inconsistence	No Serious (−1) Very serious (−2)	No inconsistence	Moderate quality
Indirectness	No Serious(−1) Very serious (−2)	No indirectness	
Imprecisions	No Serious (−1) Very serious (−2)	No imprecisions	
Publication bias	Undetected Strongly suspected	No Inconsistence	
Other (Upgrading factors circle all that apply)	Large effect (+1 or+2) Dose response (+1 or+2) No plausible confounding (+1 or+2		

High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

The quality of evidence was downgraded one level because of serious concerns of risk detection and performance bias. NMR: Neonatal mortality, RCTs: Randomized controlled trials