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Methylated spirit versus 4% chlorhexidine gel in neonatal umbilical cord infection: A short report of a randomized, open-labelled, parallel-group trial

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Abstract: *Background:* Neonatal sepsis is a known leading cause of neonatal morbidity and mortality.
Aim: To compare the efficacies of 96% methylated spirit and 4% chlorhexidine (CHX) gel in the treatment of umbilical stump of neonates.
Method: This was a randomized, open labelled, parallel group trial of CHX gel and Methylated spirit for neonatal umbilical cord care in Jos, between 2/6/17 and 16/7/17. Inclusion criteria were term, newly born 0 to 6 hours old, with no known risk for sepsis and written informed parental consent. Eligible subjects were randomized to receive methylated spirit or 4% CHX gel. Outcome measures were cord separation time, omphalitis, neonatal sepsis and neonatal mortality by day 28.
Results: A total sample of 51 of 58 met enrolment criteria. Thirty-two (62.7%) where delivered in JUTH, 33(64.7%) were males with a mean birth weight of 3.7kg (CI 3.04 – 3.30). Mean cord separation times were 7.96 ± 4.07)days in the methylated spirit group vs 6.43 ± 3.13days in the CHX comparator group, (p=0.078). Omphalitis was0% *vs*2(8.3%) and NNS 2 (7.4%)*vs*2(8.3%) in methylated spirit and CHX treatment groups respectively. There was 1(3.7%) mortality in the methylated spirit treatment group.
Conclusion: Methylated spirit and 4% CHX gel have comparable umbilical stump treatment efficacy. Methylated spirit may be a safe alternative in clinical settings where topical 4% CHX gel is unavailable or unsafe.

Key words: Methylated spirit, 4% Chlorhexidine gel, mortality, Cord separation time, Neonatal sepsis, Omphalitis

Introduction

Neonatal sepsis (NNS) is a public health burden in sub-Saharan Africa (sSA). In 2015, the World Health Organization (WHO) Global Health Observatory (GHO) reported 2.7 million neonatal deaths of which 7% was attributable to NNS.[1] Omphalitis is significant focus for NNS particularly in developing countries.[2,3,4]
Four percent ethyl alcohol, commonly identified as methylated spirit (surgical spirit) is a denatured alcohol which has been in use for the care of umbilical cord for a long time, perhaps partly because is effective, readily available and affordable in most parts of the world. [5, 6]
Recent studies seem to suggest that, use of topical 4% chlorhexidine gel (CHX) is superior to methylated spirit in reducing incidence of omphalitis among newborns.[7] Consequently, WHO advocated and deployed wide spread use of topical 4% CHX for the care of umbilical cord stump in settings of poor environmental hygiene or where neonatal mortality is high.[8] On November 17th, 2016, the Federal Ministry of Health, Nigeria published and rolled-out a 5 year National Strategy for Scale –up of CHX gel for the care of umbilical cord in Nigeria.[9] However, the wide spread use of CHX has been grossly made difficult by its unavailability, acceptability and effectiveness in Nigeria. To the best of our knowledge, there are few studies comparing its efficacy with methylated spirit which has been in use in our clinical setting for a very long time.

At the moment, topical 4% CHX gel is the goal standard for the care of umbilical cord of newborns and thus, presents a strong challenging comparator to other topical agents. Therefore, this short report aims to compare the efficacies of methylated spirit and 4% CHX in the umbilical cord care for prevention of omphalitis and or

NNS in healthy hospital born neonates in Jos, Plateau State, Nigeria.

Methodology

Study design: A Randomized, open-labelled, Parallel-group Trial of methylated spirit and topical 4% CHX gel.
Study participants: Apparently healthy term hospital born neonates with no known risk factors for NNS were identified for enrollment.
Study locations: The study was conducted in the Jos University Teaching Hospital (JUTH) and Fertile Ground Hospital (FGH), both of which are located in the cosmopolitan city of Jos, Plateau State, and provide maternal and newborn health services.
The Jos University Teaching Hospital is a 500 bed capacity tertiary centre with an average of 2809 deliveries per annum. Fertile Ground Hospital on the other hand, is a privately owned 29 bed capacity and multi-specialist hospital which in addition, provides in-vitro - fertilization (IVF) services. It has an average of 296 annual deliveries.

Enrolment criteria

Inclusion criteria: Apparently healthy term hospital born, male and female newborns ≥ 0 to ≤ 6 hours
With written informed consent of parent or legally acceptable representative (LAR) and their willingness for return visits to delivery hospital or telephone interview per study protocol.
Exclusion criteria: Structural birth defects where topical application of test agent is impossible (e.g. omphalocele, gastroschisis), clinical or laboratory evidence of sepsis, maternal peripartum pyrexia, prolonged rupture of fetal membranes or evidence of chorioamnionitis, HIV/HBV/HCV seropositive mothers and known hypersensitivity to any of the topical test agents.

Intervention

Test agents

Topical Chlorhexidine digluconate 7.1% (equivalent to 4% chlorhexidine gel): 4% CHX (25g of 4% Chlorxy-G Gel, Batch N0 CGH2, manufactured date: 08/15 and expiry date: 07/18) for application on cord stump according to manufacturer's instructions.
Topical 96% methylated spirit: This was obtained from the Compounding Pharmacy Unit of the Jos University Teaching Hospital.
Subjects identification, screening and enrollment procedures
Prior to enrollment, full clinical history was obtained and thorough physical examination carried out. Relevant medical information obtained (age, sex, gestational and mode of delivery, risk for sepsis, history of sensitivity to test agent, maternal age, parity, vaccination status, weight, temperature, structural defect) were documented on case report forms (CRF). Care-givers were taught in addition to clinical demonstration, the procedure for topical application of test agents and proper hand-washing technique.
Four per cent topical CHXgel was applied generously on the umbilical stump and spread around the abdominal wall area that comes into contact with the stump using the index finger. This was carried out twice daily and any other times of the day the stump appeared wet. On the other hand, clean piece of cotton wool soaked in dispensed 50mls container of 96% methylated spirit was used in cleaning of stump and the cord clamp every two hours. Cleansing procedure started from the tip of the stump towards the cord clamp and proximally to the base of the stump. Care-givers were also provided with more test agents whenever they were exhausted.
Eligible enrollees were then allocated to one of the treatment groups by simple random technic (1:1).

Caregivers had telephone interviews on day 2 following enrolment into the study. Information of interest on the checklist were: fever, redness around cord stump, bleeding, bad odor or purulent discharge, swelling, frequency of cord care, cord separation time, evidence of omphalitis and or sepsis. Questions were also solicited for use of other agents out of study protocol. Enrollees had returned visits on days 7, 14 and 28 or any other days within study protocol when there were study related concerns. On each clinic visit, clinical evaluation was carried out for evidence of cord separation, omphalitis or sepsis. In the event of diagnosis of probable sepsis, based on WHO Guidelines for omphalitis (erythema, foul smelling discharge around the cord), the patient were hospitalized in the respective health facility. Blood culture, cord swab and lumber puncture for cerebrospinal fluid microbiological diagnosis were carried out. The affected neonates received our hospital's standard of care for NNS therapy.

Cord separation time: This was defined as the time (days) taken for the umbilical cord to dry and completely fall off from the cord stump.
Solicited adverse reactions such as dermatitis, anaphylaxis were recorded on CRF.[11,12] Any study subject who developed such reactions were given alternative treatment.
Protocol violation: A study subject was judged to have violated protocol if there is evidence to suggest: Use or application of a different treatment agent outside study protocol, umbilical stump was cut manually for any reason and or did not apply treatment agent according to protocol.

Outcome measures

The primary out come measure was cord separation time (days). The secondary outcomes were development of omphalitis, NNS and occurrence of mortality until D28.Adverse reactions to test agents were documented.

Statistical Analysis

Primary analysis was performed on Day 28 per protocol population (PP) of neonates. The intention to treat (ITT)

study subjects were all treatment allocated neonates who had at least one topical application of test medication. Per protocol population was a subset of the ITT as well as those who did not violate the study protocol. The difference in the efficacy and the 95% confidence interval (CI) was calculated by normal estimates of binomial distribution.

Statisticala analysis was done using Stata 14.1 copyright 1985-2015 Stata Corp, 4905 Lake way Drive, College Station, Texas 77845 USA. Serial N0:301406310375

Ethical and confidentiality consideration

Ethical approval was received from JUTH'S Ethics Committee (JUTH/DCS/ADM/127/XXV/162).

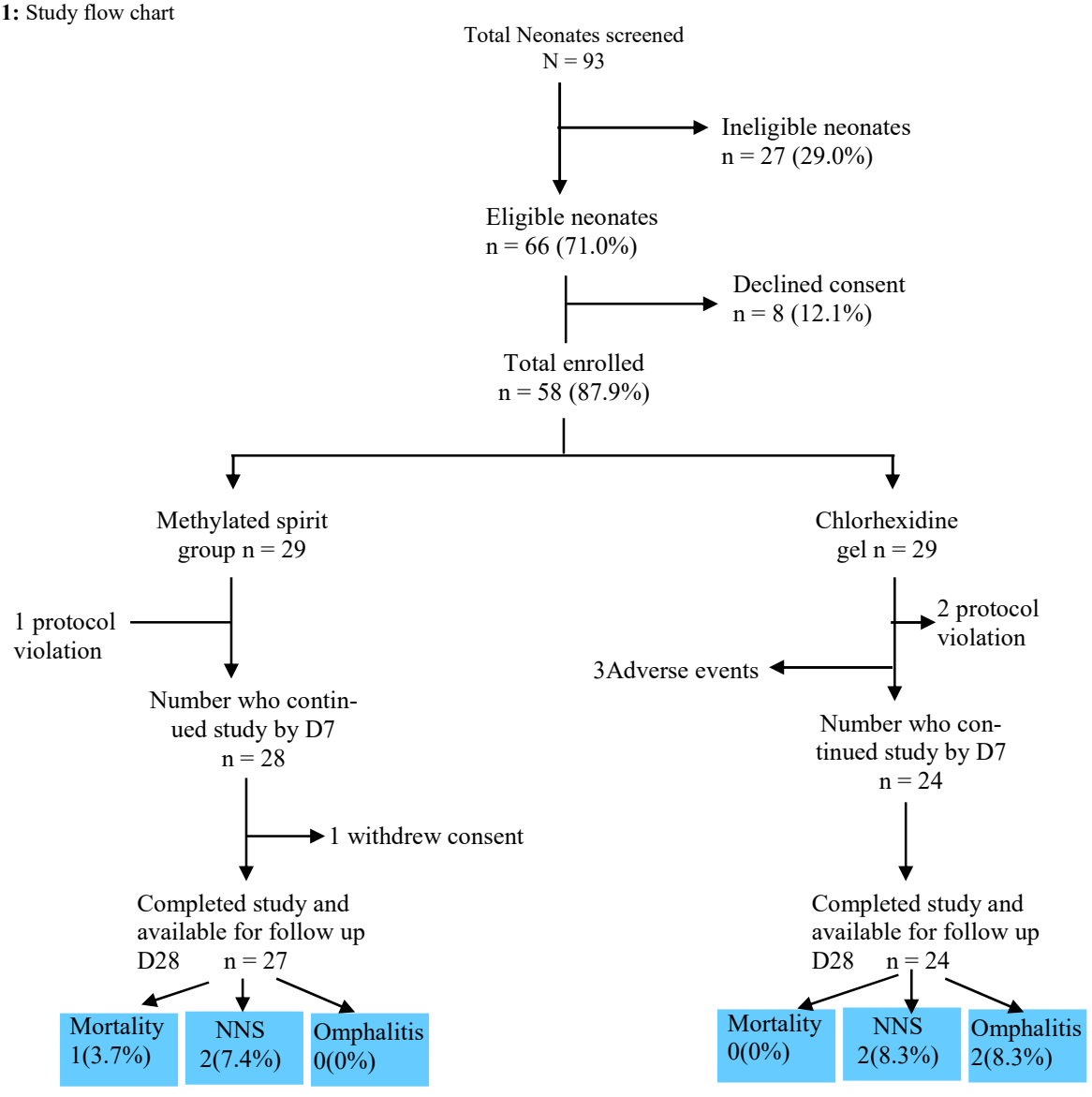
Written informed consent was received from parents of student subjects.

Results

Between 1st June, 2017 and 17th July, 2017, 260 deliveries were conducted (224 in JUTH and 36 in FGH). Of the 93 newborns screened for study,66 (71.0%) were eligible. Twenty-nine eligible subjects were allocated into one of the treatment groups to receive 96% methylated spirit or 4% chlorhexidine gel. Two subjects (6.9%)and 1(3.4%) from CHX gel and methylated spirit groups respectively violated study protocol. In addition, 1(3.4%) subject from methylated spirit group withdrew consent on day 2 for reasons unconnected to the study. Another3(10.3%) developed adverse events to 4% chlorhexidine gel. These reactions were in the form of periumbilical bullous skin eruptions that extended to pubic regions which were in direct contact with the gel. Bullous fluid swabs microbiological assay were sterile. These were therefore, excluded from final data analysis but were given alternative treatment agents per study protocol and then followed up for safety in line with Good Clinical Practice Guidelines. Their cord stumps healed, fell off and exited the study. Twenty-seven study subjects (93.1%) and 24(82.9%) from methylated spirit and CHX treatment groups respectively completed the study and were available for analysis at D28. (Figure 1).

Thirty-three (64%) were male with mean birth weight 3.7kg (CI 3.04 – 3.30).The mean enrollment temperature was 36.7 ± 0.20^{O}C).Mean maternal age 31.5 years CI (29.92 – 32.99) with mean parity 2.7 CI (2.25 – 3.15). See Table 1 below:

Fig 1: Study flow chart



Two (7.4%) and 2(8.3%) cases of neonatal sepsis (NNS) from methylated spirit and 4% chlorhexidine gel (CHX) treatment arms respectively. There were 2(8.3%) cases of omphalitis from CHX treatment group. One study subject (3.7%) of neonatal mortality (NNM) was recorded from methylated treatment. This subject developed severe jaundice, presumably from G6PD deficiency and died on the D3 of study. Parents declined autopsy.

The mean cord separation time in (days) in the methylated spirit and CHX gel treatment groups were 7.96 ± 4.07, (CI 6.28 – 9.64) and 6.43 ± 3.13, CI (5.08 – 7.79) respectively, p= 0.078.

Discussion

Within the limitations of a short report and small sized dataset, the mean cord separation time in the methylated spirit treatment group was longer compared to the CHX gel treatment group. The difference was not statistically significant. Mean cord separation time in the methylated spirit group was shorter than 9.5 ± 3.8[5] days but longer than 4.54 ±1.846 [6] days reported from Ibadan and Kano respectively. The differences in the mean cord separation time in studies cited above may be due to differences in the instrument used in the studies. Both studies cited above relied heavily on recall information from respondents which could have potentially compromised the exact details of cord care pattern and the precise strength of alcohol based agents that were used by caregivers, compared to the present study which 96% alcohol applied two hourly intervals were used as a comparator treatment group.

However, our find in the CHX group was comparable with 6.41 and 6.90 days reported by Mousa *at al* and Mullany *et al*[10,11] respectively. Similar to other reports, [5] male study subjects in the methylated spirit treatment group appeared to have shorter cord separation time. This find contrasted those in the CHX treatment group. It also sharply contrasted earlier reports from Kano [6] in which, it clearly showed no significant sex difference in cord separation time. The mechanisms for umbilical cord separation is not completely understood. It is thought that, the umbilical cord dries and becomes mummified. A zone of demarcation between the normal skin of the anterior abdominal wall and the drying umbilical cord stump is formed. This pathophysiologic process is consistent with histological section that clearly shows polymorphonuclear leukocyte infiltrates at this zone.[12, 13, 14]

In contrast to reported findings, there were more cases of omphalitis in the CHX compares to the methylated spirit treatment group.[15]Streptococcus *spp*. was isolated in one study subject and Pseudomonas *spp*. in the other. They both received appropriate antibiotic therapy. Conversely, there were comparable proportions of neonatal sepsis (NNS) in both treatment arms, respectively. Thus, suggesting that, 96% alcohol could be a safe alternative when CHX is unavailable.

Mortality rates in the methylated spirit treatment group was high compared to the CHX group. This study subject died on day 3 from severe neonatal jaundice, presumably of G6PD deficiency.

One-tenths of study subjects in the CHX treatment group developed adverse reactions. These adverse reactions manifested as bullous eruptions on anterior abdominal wall around the umbilical stumps and on the pubis areas which were in contact with CHX gel. Skin and bullous fluid swab microbiological investigations were sterile. They were therefore, given alternative agents (methylated spirit) to clean the cord stump. No recorded cases of anaphylactic reactions as reported from previous studies.[16]

Conclusions

Methylated spirit and 4% CHX gel have comparable umbilical stump treatment efficacies. Methylated spirit could be a safe alternative in clinical settings where CHX gel is unavailable and or with unsure safety profile.

Limitations of the study

The small sized dataset could not favor advanced statistics to compare several perinatal factors that may potentially influence the outcomes of interest.

Conflict of interest: None
Funding: None

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