Effect on nosocomial sepsis of topical oil application, skin condition, and care practice device usage in preterm neonates: A randomized controlled trial

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ABSTRACT

Introduction: Compromised skin barrier increases the susceptibility of high-risk preterm neonates to nosocomial sepsis. Thus, topical oil application may be a promising strategy for improving neonatal outcomes. **Objectives:** The objectives of the study were to study the effect of topical oil application on the incidence of nosocomial sepsis and skin condition. **Materials and Methods:** This randomized controlled trial was conducted in a referral neonatal unit. The study included consecutive preterm neonates admitted before 4 days of age with admission weight of 1000–2000 g. Computer-generated random number sequence was used for grouping neonates in sunflower oil (n=39) and control (n=39) groups. **Results:** 70 neonates (89.7%) completed the trial. At enrollment, baseline characteristics, clinical features, and lab abnormalities for sepsis evaluation were comparable in two groups. The incidence of nosocomial sepsis was 15.4% and 17.9% in oil and control group (p=0.7613). On day 10 of enrolment, in oil group, all 23 babies, and in control group, only 1 of 21 babies had normal skin (p<0.001). On multiple regression analysis, the odds ratio (95% confidence interval) for care practice device usage (v/s. randomized group and skin condition) in the causation of nosocomial sepsis was 1.189 (1.08−1.298, p=0.002). **Conclusions:** No difference in the incidence of nosocomial sepsis was observed between the oil and control groups. However, each additional day of care practice devices usage increased the risk of nosocomial sepsis by 1.19 times, despite oil application and/or improvement in the skin condition.

Key words: *Nosocomial sepsis, Oil, Preterm, Skin condition*

Nosocomial infection is an upcoming problem in developing countries as more of high-risk preterm neonates are being saved due to increasing usage of advanced technology, including care practice devices [1]. Furthermore, rate of antibiotic resistance in pathogens causing neonatal sepsis is increasing [2]. Preterm infants are particularly susceptible to infections due to high environmental load of pathogenic organisms in developing countries and their skin lacks natural protective cutaneous biofilm vernix, which is developmentally immature, easily injured, and functionally compromised due to malnutrition [3,4].

Interventions that prevent morbidity during the neonatal period that are not centered on antibiotic use have the potential to be highly cost-effective and affect health far beyond neonatal period [5,6]. Linoleate has been shown to be most potent activator of peroxisome proliferator-activated receptor alpha (PPAR a), and its application to fetal rat skin at physiologic concentrations accelerates epidermal barrier development [7]. Sunflower seed oil with high linoleate content thus appears ideal for topical application in preterm neonates. Since only limited published data from developing countries and India are available on this subject; therefore, a study was planned to evaluate the effect of sunflower oil application on nosocomial sepsis and skin condition.

MATERIALS AND METHODS

A randomized controlled trial was conducted in the referral neonatal unit of a teaching hospital for 11-month period starting March 2015. The study was approved by the Institutional Ethics Committee and written informed consent was obtained from the mother before the enrollment. All consecutive preterm neonates admitted before 4 days of age with admission weight of 1000–2000 g were included in the study. Babies with the score for neonatal acute physiology II (SNAP II) [8] >77 at 2 h of admission, major congenital malformations, generalized skin disease, infective diarrhea, and on ventilator for >12 h were excluded.

The primary outcome measure was the incidence of nosocomial sepsis during a hospital stay or 28 days of life, whichever was earlier. While the secondary outcome measure was difference in the skin condition score at enrollment and at 5 days interval until discharge (Lane and Drost) [9], and the difference in weight, length and head circumference, and serum triglycerides levels at enrollment and discharge.

Based on the past 12-month admission rate in the referral neonatal unit with requisite inclusion and exclusion criteria, a convenient sample size of 80 consecutive neonates was taken.

All consecutive neonates admitted in the unit fulfilling the inclusion criteria were enrolled. Computer-generated random number sequence after block randomization was used for group allocation. Serial numbered opaque sealed envelopes were used for allocation to oil (n=39) and control (n=39) groups.

Baseline characteristics included age, sex, gestational age, weight, length, and head circumference. Antenatal risk factors for sepsis were elicited. Birth history included place and type of delivery, time to first cry, and resuscitation. Usage of care practice devices on neonate was also recorded. Assessment at enrollment and during a hospital stay for suspected sepsis included clinical features such as toxic appearance, cyanosis, feeble pulses, low/high axillary temperature, skin bleed, seizures, or full fontanel. Lab evaluation included sepsis screen and blood culture. Lumbar puncture was done if sepsis screen was positive.

Following enrollment, neonates in oil group received sunflower oil (procured as Saffola oil from Kendriya Bhandar) application over entire body below neck by the principal investigator 3 times daily (each application for 1–2 min) for initial 7 days. The amount of oil used was 4 ml/kg body weight/application. During this period, mother (caregiver, if mother not available) was trained by the principal investigator in hand washing and oil application techniques. Subsequently, during hospital stay, mother applied oil 3 times daily under the supervision of principal investigator. Neonates in control group were handled and cared in similar manner except oil application. The intervention could not be blinded due to operational reasons. Every effort was made to prevent contamination between randomized groups and mothers were physically separated as far as possible. Cultures of oil samples were taken every 7–10 days to check for the colonization. The temperature was recorded before and after the intervention to prevent hypothermia. Oil application was temporarily discontinued if neonate developed shock requiring inotropic support or ventilated or had apneas requiring continuous positive airway pressure.

All neonates were observed daily for the clinical feature of sepsis, if present, sepsis screen, and blood cultures were done. Skin surface culture was taken from axilla and abdomen (1 cm radius area around umbilicus) at enrollment and every 5 days to detect surface colonization. Assessment of skin condition over abdomen, and dorsum of hand and foot was done at enrollment and 5 days interval during the study period by the principal investigator. The enrolled neonates were followed up after 3–5 days of discharge by evaluating clinical features and/or sepsis screen to detect any incubating infections at the time of discharge. All neonates with diagnosed sepsis were started on antibiotics according to unit protocol.

Statistical analysis was done using Epi-info 6 software, by both intention to treat and per-protocol (minimum 4 days of intervention) methods; $p<0.05$ was considered significant.

RESULTS

During study period 1339 neonates were admitted in referral neonatal unit and total 78 consecutive neonates satisfying inclusion criteria were enrolled. Of these, 70 neonates completed trial defined as an intervention or hospital stay of ≥4 days after enrollment (Fig. 1).

Table 1 depicts the baseline characteristics of study subjects. While 53.8%, 15.4%, and 30.8% neonates in oil group were late, moderate, and very preterm, respectively, the numbers of these babies in the control group were 59%, 18%, and 23%, respectively. Further, the number of low birth weight (LBW) and very LBW (VLBW) babies in oil group was 38.5% and 61.5%

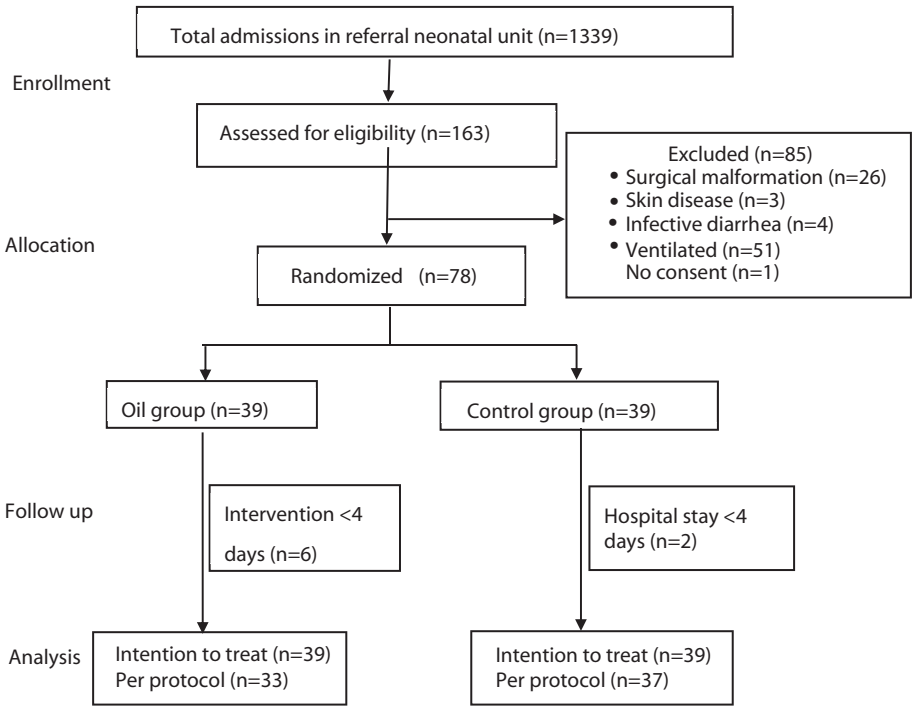

Figure 1: Study flowchart

Table 1: Baseline characteristics and intervention for oil and control groups

Baseline variables	Oil group (n=39)		Control group (n=39)
Age at enrollment (h)			
Mean (SD)	16.7 (22.3)		26.3 (29.2)
Median (range)	18 (4,97)		20 (3,102)
Sex female, n (%)	9 (23.1)		13 (33.4)
Gestational age (w), mean (SD)	33 (2.36)		33.5 (2.25)
Enrollment weight (g), mean (SD)	1433 (218)		1520 (277)
Maternal fever, n (%)	6 (15.4)		6 (15.4)
Foul smelling liquor, n (%)	1 (2.5)		1 (2.5)
Frequency/burning micturition (%)	4 (10.2)		2 (5.1)
Prolonged leaking per vaginum n (%)	8 (20.5)		6 (15.3)
Obstetric procedures, n (%)	1 (2.5)		1 (2.5)
Home delivery, n (%)	13 (33.3)		8 (20.5)
Vaginal delivery, n (%)	37 (94.9)		37 (94.9)
Need for resuscitation, n (%)	3 (7.7)		4 (10.2)
Care practice device usage (days)			
Median (range)	6 (1,31)		8 (0,29)
Mean (SD)	8.8 (7.25)		9.3 (6.79)
Antibiotics usage at enrollment (n=19) (days) mean (SD) (a)	6.1 (4.13)		8.2 (4.71)
Intervention	**Intention to treat**	**Per protocol**	
Duration of oil applications/baby (days) mean (SD)	9.94 (5.8)	11.2 (5.2)	(b)
Number of applications/baby mean (SD)	31 (17.6)	34.6 (15.8)	
Amount of oil used (ml/baby/application), mean (SD)	6.15 (0.84)	6.21 (0.86)	

(a) P=0.039, (b) neonates in control group had routine skin care practices for mean duration of 11.1 days, SD: Standard deviation

while in control group, 56.4% and 43.6% of neonates were LBW and VLBW, respectively. Almost 70% of babies in both groups were small for gestational age [10]. While 17 mothers in oil group had any one or more of the risk factors of sepsis, 11 mothers in control group had one or more risk factor. During the study period all 39 babies in oil group and 38 of 39 in control group had intravenous cannula. Umbilical catheter was placed in four babies in oil group while none in control group. Eight babies each in both groups had endotracheal tube inserted. Device days, defined as sum of days for which each device was used in a neonate, were (median [range]) 6 (1, 31) and 8 (0, 29) in oil and control groups. All babies were exclusively breastfed and if indicated, were given additional nasogastric feeds with expressed breast milk. None of the babies received parenteral nutrition during a hospital stay.

At enrollment, 14 babies in oil group and 12 babies in control group were symptomatic, most common symptom being a toxic appearance in eight neonates in each group. Again, at enrollment sepsis screen (defined as abnormal any two of four laboratory criteria, *viz*., total leucocyte count <5000 or >20,000 cells per cubic mm, IT ratio >0.2, C-reactive protein >6 mg/L, or abnormal micro erythrocyte sedimentation rate) was positive in 19 neonates in each group. In oil Group 3 babies had blood culture positive with growth of methicillin-resistant coagulase-negative *Staphylococcus aureus*, *Enterococcus,* and *Acinetobacter*. In control group organisms were *Pseudomonas*, *Acinetobacter*, and methicillin-resistant *S. aureus* (two neonates). 19 babies each in oil and control groups received antibiotics for treatment of sepsis diagnosed at enrollment.

During the entire study period, all 39 neonates in oil group received oil application for a total duration of 388 days while in a subgroup of 33 babies receiving oil application for >4 days as per protocol schedule total intervention days were 370 (Table 1). There were no adverse events of oil application during the study period. A total of 36 cultures of stock oil sample done were sterile. There was no growth of pathogenic organisms such as *Escherichia coli*, and *Klebsiella*, on surface cultures of the skin of abdomen or axilla in study subjects.

The skin was assessed periodically; with a skin condition score of 0 depicting normal skin and gradual deterioration in skin condition and with advancing score 9 depicting erythematous, crusting, and oozing skin involving entire body surface areas. A comparable number of neonates had normal skin with zero score at enrollment (oil group=58.9% and control group=66.6%), (Table 2). On day 10 of intervention, babies with "normal" skin condition were significantly higher in oil group compared to control group ($p<0.001$). Skin condition score kept on improving in oil group as duration of hospital stay increased while it deteriorated in control group. On day 10 of enrolment, in oil group, all the 23 babies had normal skin, and in control group, only 1 of 21 babies had normal skin ($p<0.001$).

Nosocomial sepsis was defined as either positive sepsis screen and/or positive blood or cerebrospinal fluid (CSF) culture ≥4 days following enrollment. The presence of any clinical feature was an indication for sepsis screen and blood culture. 17 babies in oil and 13 babies in control groups were symptomatic and thus evaluated

for nosocomial sepsis. Sepsis screen was positive in six subjects each, blood culture in two subjects each, and CSF was abnormal in one subject each, thus incidence of nosocomial sepsis was 15.4% (6/39) and 17.9% (7/39) (p=0.7613) in oil and control groups, respectively (14 episodes per 1000 patient days in oil group and 16 episodes in control group [p=0.4278]). Organisms grown were *E. coli* and *Pseudomonas* in oil group while in control group were *E. coli* and *Enterococcus*. No baby had multiple episodes of nosocomial infection.

During study period neonates in oil group lost a mean weight of 41.4 g/kg while babies in control group lost 39.3 g/kg (p=0.8922). The mean gain in length and head circumference over study period in oil group was 1.47 (1.45) and 0.82 (0.75) cm while in control group was 1.1 (1.2) cm (p=0.2234) and 0.66 (0.66) cm (p=0.9880), respectively. At enrollment, mean serum triglyceride level in oil and control group (61 v/s. 57.5 mg/dL) was comparable; however, the mean increase in levels during the study period was greater in oil group as compared to control group (54.3 v/s. 38.5 mg/dL, p=0.2922).

DISCUSSION

Use of topical cream and its benefits in the improvement of neonates' skin condition have a proven history; many studies have compared and shown the skin scores and its effects on the skin [9]. The present randomized clinical trial was designed to evaluate the effect on nosocomial sepsis of topical application of sunflower oil and skin condition in outborn preterm LBW neonates. The incidence of nosocomial sepsis in oil group was comparable to control group (p=0.4278).

The study conducted by Darmstadt *et al.* [3] in Egypt demonstrated significantly reduced incidence of nosocomial infections in sunflower oil group compared to control group (29% vs. 47%, p=0.007).

In subsequent year, Darmstadt *et al.* [11] carried out another study in Bangladesh which again revealed the reduced incidence of nosocomial sepsis (10.8 episodes/100 patient days in control group v/s. 6.95 episodes/100 patient days in sunflower oil group). Salam *et al.* [12] from Pakistan used coconut oil as emollient and showed that significantly fewer infants developed culture-proven sepsis in the intervention group (39.5 vs. 219.1 episodes per 1000 patient days). However, the decreased incidence of nosocomial sepsis in intervention group as observed in all these three studies is in contrast to the observation by Edwards *et al.* [13] who have found increased incidence of nosocomial sepsis in prophylactic ointment group, possibly due to significantly increased use of care practice devices, including assisted ventilation (p=0.04) and systemic antibiotics (p=0.06).

A recent meta-analysis based on some of these trials showed a significantly higher incidence of infection in infants treated with emollient (total trials=6, n=1551, risk ratio=1:20 [1.01–1.42]) in high-income countries whereas in low-income or middle-income countries (total trials=2, n=535, and risk ratio=0.91 [0.65–1.28]) the incidence of sepsis with or without emollients use was comparable [14].

Since the present study has comparable incidence in oil and control groups, further analysis of possible confounders on nosocomial sepsis was attempted by developing a logistic regression model. Risk factors significant on univariable analysis were entered into a multiple logistic regression model. The group of babies with/without intervention (oil application) was used as categorical variable in model. Duration of various care practice devices (in days), significant on univariable analysis (mean rank in nosocomial sepsis v/s. no nosocomial sepsis group was 71 and 37, p=0.0002), was used both as a continuous variable and categorical variable (defined as cumulative care practice device usage for > vs < 10 days) (Table 3). Skin condition (normal v/s. abnormal) on day 10 of enrollment was used as categorical variable. The group of babies (nosocomial sepsis v/s. no nosocomial sepsis) was used as a dependent variable. On multiple regression analysis, the relative risk (95% confidence interval) for care practice device usage, when analyzed as continuous variable was 1.189 (1.08–1.298, p=0.002) and as categorical variable was 6.193 (4.759–7.627,

Table 2: Skin condition score

Day of enrollment	Skin condition in oil group		Skin condition in control group	
	Normal	Abnormal	Normal	Abnormal
Day 0, n/total (%)	23/39 (58.9)	16/39 (41)	26/39 (66.6)	13/39 (33.3)
Day 5, n/total (%)	32/35 (91.4)	3/35 (8.5)	12/37 (32.4)	25/37 (67.5)
Day 10, n/total (%)	23/23 (100)	0/0	1/21 (4.7)	20/21 (95.2)
Day 15, n/total (%)	12/12 (100)	0/0	0/0	11/11 (100)
Day 20, n/total (%)	5/5 (100)	0/0	0/0	5/5 (100)
Day 25, n/total (%)	0/0	0/0	0/0	2/2 (100)

Table 3: Multivariable regression analysis

Variable	Care practice device usage used as continuous variable				Care practice device usage used as categorical variable			
	Coefficient B	SE	OR (95% CI)	p	Coefficient B	SE	OR (95% CI)	p
Randomization (oil and control)	−0.66	0.77	0.52 (−0.10, 2.03)	0.394	−0.79	0.74	0.45 (0.10, 1.90)	0.286
Care practice device usage	0.17	0.06	1.19 (1.08, 1.30)	0.002	1.82	0.73	6.19 (4.76, 7.63)	0.013
Skin condition	0.11	0.54	1.11 (0.05, 2.18)	0.844	−0.34	0.47	0.71 (−0.22, 1.64)	0.475

CI: Confidence interval, OR: Odds ratio, SE: Standard error

p=0.013). Thus, each additional day of care practice devices usage increased the risk of nosocomial sepsis by 1.19 times, despite oil application and/or improvement in skin condition.

The strength of present trial is that it is first such study on Indian neonates with a trial compliance of 90%. Having small sample size and availability of limited information at enrollment in outborn neonates for both risk factors of sepsis and antibiotics received at referral center are its limitations. Therefore, a randomized controlled trial with adequate sample size in neonates with lower care practice device usage and antibiotics is suggested to evaluate interplay of improved skin condition and breach in its integrity on nosocomial sepsis.

CONCLUSIONS

A higher device usage causing breach in integrity of skin and/or mucous membrane might have nullified the beneficial effect of significantly improved neonatal skin condition with oil application, thus predisposing these neonates to an increased chance of nosocomial sepsis in the presence of a high microbial environmental load in developing country.

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