Pediatric Dermatology Vol. 25 No. 2 174–178, 2008

The Effect of Daily Treatment with an Olive Oil/Lanolin Emollient on Skin Integrity in Preterm Infants: A Randomized Controlled Trial

Ursula Kiechl-Kohlendorfer, M.Sc., M.D., Cindy Berger, R.N., and Romy Inzinger, R.N.

Division of Neonatology, Neuropediatrics and Metabolic Disorders, Department of Pediatrics, Innsbruck Medical University, Innsbruck, Austria

Abstract: **To date, appropriate skin therapy for premature infants has not been clearly defined. Emollient creams are often used without solid evidence for a benefit to the neonate. The aim of the current study was to investigate the cutaneous effects of two different topical ointment therapies. Between October 2004 and November 2006 we prospectively enrolled 173 infants between 25 and 36 weeks of gestation admitted to a neonatal intensive care unit. Infants were randomly assigned to daily topical treatment with water-in-oil emollient cream (Bepanthen®), olive oil cream (70% lanoline, 30% olive oil), or to a control group. Each neonate was continuously treated for a maximum of 4 weeks. Skin condition (skin score reflecting degree of dermatitis) in these groups was compared at weeks 1, 2, 3, and 4. Neonates treated with olive oil cream showed statistically less dermatitis than did neonates treated with emollient cream, and both had a better outcome than those in the control group ($p < 0.001$ in weeks 2–4). Treatment effects persisted throughout the study period and applied to infants of all gestational ages. This study demonstrates that topical skin therapy lowers the risk of dermatitis. Olive oil cream was superior to water-in-oil emollient cream.**

Skin surface of the full-term neonate is drier than that of adults (1). During the first year of life, the skin develops increased hydration, possibly related to greater functional maturity of eccrine sweat glands (2). In preterm infants, especially in those with less than 32 weeks of gestation, the stratum corneum, the barrier function of the skin, is not fully developed (3–6). Acceleration of the maturation process occurs after birth, with most preterm infants having a functionally mature stratum corneum by 2 weeks postnatal age (4). In addition, transepidermal water loss measurements showed that infants born at 25 weeks or less of gestation had immature skin barrier function for longer than 4 weeks, in some infants even 8 weeks (6), resulting in an increased risk of electrolyte imbalance, dehydration, and thermal instability.

Preterm neonates often develop peeling and scaling dermatitis. Moisturizers help restore the natural barrier properties of the skin (7), but appropriate therapy and duration of therapy for the dry, fissured skin of preterm infants has not yet been clearly defined. Choice of an

Address correspondence to Ursula Kiechl-Kohlendorfer, M.Sc., M.D., Division of Neonatology, Department of Pediatrics, Innsbruck Medical University, Anichstrasse 35, 6020 Innsbruck, Austria, or e-mail: ursula.kohlendorfer@i-med.ac.at.

DOI: 10.1111/j.1525-1470.2008.00627.x

appropriate emollient is essential, as some oils increase skin functional barrier (8,9) whereas others could damage the integrity of the skin barrier (8). We conducted a prospective study to evaluate the long-term effects of prophylactic skin therapy on neonates' skin and compared two different topical skin emollients.

MATERIAL AND METHODS

Between October 2004 and November 2006, all infants between 25 and 36 weeks of gestation who were admitted to a neonatal intensive care unit (NICU) were prospectively enrolled. Infants were excluded if survival was expected to be <48 hours, or if they had manifest skin disease or life-threatening congenital anomalies. The study was approved by the local ethics committee.

Once informed consent was obtained, neonates were randomly assigned to group A (Bepanthen®; Bayer Healthcare, Wuppertal, Germany), group B (olive oil cream), or group C (control). Bepanthen is a proprietary ointment including dexpanthenol and phenoxyethanol. Olive oil is a natural and widely available oil; in the current study a mixture of 30% olive oil and 70% lanoline produced in our pharmacy was used. The control group received routine skin care without topical emollients or other measures to prevent skin breakdown or modulate skin-barrier function. In the treatment groups, therapy commenced within the first 24 hours of life. The body, except the face and scalp, was treated either with a thin coat of the Bepanthen or with olive oil cream.

Topical emollient was dispensed to each neonate in tubes containing 10 g that contained enough emollient for 1 day. Each neonate was continuously treated for a maximum of 4 weeks. Infants who were transferred out of the NICU before day 28 were followed up on the intermediate care unit. Skin therapy was applied twice a day. At baseline and at weeks 1 through 4 each neonate was evaluated by two investigators, who were blinded to the neonates' therapy. Evaluation of the skin condition was performed 8 to 12 hours after the preceding application of skin therapy and at comparable times in the control group. Skin condition was graded on a 4-point scale (1–4) modified from the one published by Lane and Drost (Table 1) (10), with a score of one denoting the best condition and a score of 4 the worst. Grading considered skin dryness, presence of erythema, and skin breakdown.

If a neonate in the control group required topical skin therapy as a consequence of dermatitis (skin condition grade 4), it contributed data to the analysis until this time point but not thereafter. An analogous procedure was chosen for infants who developed dermatitis (skin condition grade 4) under administration of topical skin therapy. One infant in the emollient cream group died. Another 25 infants (14.5%) were lost because of discharge or transfer to a different hospital (7 infants in the control group, 7 infants in the emollient cream group, and 11 infants in the olive oil group).

TABLE 1. *Skin Condition Grading Scale (Modification of the Score by Lane and Drost) (10)*

1	Normal, no sign of dry or irritated skin
2	Dry skin with few to moderate visible scales
3	Dry skin with darker scales, increased areas of mild erythema, skin has a rough texture with superficial fissures
4	Dry, crusted skin on erythematous base with dark scales and fissures

Furthermore, background and clinical information was collected, including sex, gestational age (full weeks of gestation), birthweight (grams), multiple pregnancy, and diagnosis at admission. For each week ongoing therapeutic procedures and modalities were documented—surfactant therapy (yes/no), antibiotic treatment (yes/no), phototherapy (yes/no), amount of parenteral feeding (percentage of total feeding), and air humidity in the incubator (percentage categories $<50\%$, 50–55%, 56–60%, 61–65%, 66–70%, 71–75%, 76–80%, and $>80\%$). Secondary sepsis was defined as any bacterial or fungal infection proved by positive blood or cerebrospinal fluid culture after day 2 of life (with associated symptoms and/or treatment with systemic antibiotics or antifungal agents). Grades of skin condition in the treatment and control groups were assessed at baseline and at weeks 1 to 4 and differences computed by means of general linear models. The Scheffe test was used for pairwise comparison. All p-values are two-sided. Computations were performed with the SPSS (version 12.0) statistical software.

RESULTS

In the current study a consecutive series of 173 preterm neonates were enrolled. A total of 115 (66.5%) were in the treatment groups—57 (32.9%) were treated with emollient cream and 58 (33.5%) with lanoline/olive oil cream. Another 58 (33.5%) served as untreated controls. Baseline characteristics of the three groups are depicted in Table 2. Mean gestational age of the neonates was 30.3 weeks in the Bepanthen group, 30.4 in the olive oil group, and 30.5 weeks in the control group. Mean birthweight was 1508 g in the Bepanthen group, 1581 g in the olive oil group, and 1556 g in the control group.

All infants were admitted with a diagnosis of prematurity, and 85% of infants had a diagnosis of respiratory distress. Eight infants (4.6%) developed blood-culture

TABLE 2. *Neonatal Characteristics in Control and Treatment Groups*

	Bepanthen group (n = 57)	Olive oil group (n = 58)	Control group (n = 58)
Male, % (n)	45.6 (26)	53.4 (31)	62.1 (36)
Multiple birth, % (n)	31.6 (18)	25.9 (15)	22.4 (13)
Birthweight, % (n)			
< 1000 g	39.1 (9)	21.7 (5)	39.1 (9)
1001–1500 g	33.8 (22)	29.2 (19)	36.9 (24)
> 1501 g	30.6 (26)	40.0 (34)	29.4 (25)
Gestational age, % (n)			
≤30 wks	33.3 (12)	27.8 (10)	38.9 (14)
30–32 wks	34.0 (18)	34.0 (18)	32.1 (17)
> 32 wks	32.1 (27)	35.7 (30)	32.1 (27)
Surfactant therapy, % (n)	24.5 (12)	32.7 (16)	42.9 (21)
Phototherapy, % (n)	37.9 (44)	33.6 (39)	28.4 (33)

positive sepsis. In six infants the causing organism was coagulase-negative *Staphylococcus*, in one patient *Staphylococcus aureus* and in one *Klebsiella* species. There was no significant difference in sepsis rate between controls (n = 3; 5.2%) and the two treatment groups (n = 4; 6.9% and n = 1; 1.8%), and sepsis rate in our NICU did not change during the study period.

Results of the skin condition grading scores were summarized (Table 3). Baseline scores did not differ between controls and treatment groups. Significant treatment effects were visible after 1 to 2 weeks of treatment and most pronounced at weeks 3 and 4. Olive oil cream was superior to water-in-oil emollient cream. Figure 1 shows percentages of best skin condition (skin condition grading scale 1) for controls and treatment groups at weeks 1, 2, 3, and 4. Findings were similar in girls and boys and evident for all gestational ages. For example, at week 3 percentages of best outcome in control, emollient, and olive oil cream groups amounted to 8.7%, 29.6%, and 61.3% ($p < 0.001$, gestational age ≤30 weeks), 17.6%, 61.1%, and 94.1% ($p < 0.001$, gestational age 31/32 weeks), and 0%, 60%, and 90% ($p = 0.001$, gestational age > 32 weeks), respectively. In the control, emollient, and olive oil cream groups 31 (53.4%), 11 (19.3%), and 2 (3.4%) infants, respectively, were switched to a therapy regime with ultrasic/ultrabas because of skin condition grade 4 (2 infants after week 1, 10 after week 2, and 32 after week 3).

Application of olive oil cream was well tolerated by the infants. However, NICU nurses noted that adhesive probes did not attach well to the treatment group with lanoline/olive oil cream unless the site of attachment was first gently cleansed with soft gauze.

DISCUSSION

This study was designed to evaluate the effect of topical therapy on skin condition in preterm neonates. We evaluated the effect of a twice-daily therapy with Bepanthen, a water-in-oil emollient cream, and with olive oil cream.

Significantly less dermatitis was seen in all treated infants from day 7 to day 28 postnatal. In all assessments treated skin was graded better than was untreated skin, documenting improved skin appearance. This was especially true for the treatment with olive oil cream and pertained to infants of all gestational ages. Data from this study support the view that topical treatment effectively decreases the risk of dermatitis in premature neonates.

TABLE 3. *Skin Condition Grading in Treatment and Control Groups at Weeks 0–4**

	Day 0	Day 7	Day 14	Day 21	Day 28
Olive oil group	1.10 ± 0.31 (58)	1.09 ± 0.28 (58)	1.28 ± 0.56 (58)	1.40 ± 0.79 (58)	1.40 ± 0.81 (45)
Bepanthen group	1.07 ± 0.29 (57)	1.18 ± 0.43 (57)	1.67 ± 0.81 (57)	2.07 ± 1.15 (55)	2.00 ± 1.09 (38)
Control group	1.10 ± 0.31 (58)	1.33 ± 0.74 (58)	2.11 ± 1.04 (56)	3.00 ± 1.05 (48)	2.70 ± 1.03 (20)
p-Value unadjusted	N.S.	0.042	< 0.001	< 0.001	< 0.001
p-Value multivariable†	N.S.	0.094	< 0.001	< 0.001	< 0.001
p-Value multivariable‡	N.S.	0.093	< 0.001	< 0.001	< 0.001
Pairwise comparisons (Scheffe test)					
p-Value controls versus Bepanthen	N.S.	0.292	0.019	< 0.001	0.036
p-Value controls versus olive oil	N.S.	0.045	< 0.001	< 0.001	< 0.001
p-Value Bepanthen versus olive oil	N.S.	0.653	0.041	0.002	0.022

N.S., not significant.
*Values are mean ± SD of skin condition grade. The sample size (n) is given in parentheses.
†Multivariable comparisons were adjusted for gestational age, birthweight, sex, multiple pregnancy, surfactant therapy, phototherapy, and pretreatment skin condition.
‡Multivariable comparisons were adjusted for gestational age, birthweight, sex, multiple pregnancy, surfactant therapy, phototherapy, pretreatment skin condition, antibiotic treatment, humidity, and parenteral feeding.

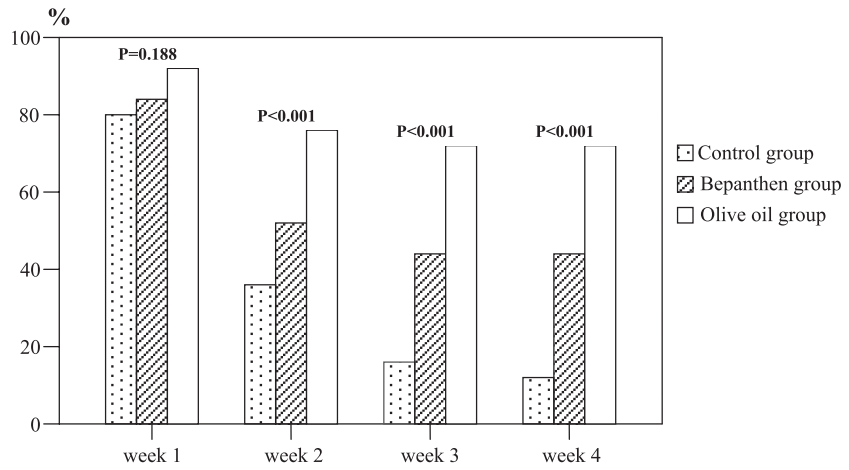

Figure 1. Percentage of infants with best skin condition (skin condition grading scale 1) in treatment and control groups after 1, 2, 3, and 4 weeks.

Our results are in accordance with those of four other previous, randomized, controlled trials showing improved skin condition in the case of daily prophylactic application of a topical emollient ointment (10–13). Duration of treatment in these studies ranged between 14 and 16 days. In two studies a water-in-oil emollient was used (10,12), while in the two other studies an anhydrous mixture was applied (11,13). The current study is unique for its treatment period of up to 4 weeks. Our results clearly indicate that therapy was of benefit over the whole period and the difference in skin grading was even most pronounced at weeks 3 and 4.

The skin of the preterm infant is an ineffective epidermal barrier. Topical ointment therapy may enhance epidermal barrier function by protecting the stratum corneum, leading to improved skin integrity. Epidermal keratinocytes can metabolize lipids derived from topically applied emollients because of a fatty acid transporter on their surface. The cells then use the lipids to form a functional epidermal barrier (14). Moreover, the dermis supplies the epidermis with moisture from the dermal capillary beds. If the stratum corneum barrier is injured, water escapes through the injured epidermis. Very preterm infants have high evaporative water losses from their skin during the first days after birth, and after 4 weeks the values are still higher than those in full-term infants (6,15). Daily application of a topical ointment was found to reduce transepidermal water loss (12,13,16,17). The Nopper study reported a reduction in transepidermal water loss after application of Vaseline-liquid paraffin in infants in the first 6 hours of life (12). Rutter and Hill demonstrated decreased transepidermal water loss after application of a paraffin mixture (80% soft, 20% hard paraffin) (17).

There has been concern that prophylactic application of topical ointment increases the risk of pathogen translocation and severe systemic infection. A Cochrane review concluded that prophylactic topical ointment therapy increases the risk of coagulase-negative staphylococcal infection and any nosocomial infection. It was therefore proposed that topical ointment not be routinely used in preterm infants (18). The current study, however, showed no significant difference in rate of infection due to bacterial pathogens including coagulase-negative *Staphylococcus* between the three groups. Overall, the risk of secondary sepsis was low and did not change during the study period. Of interest, Darmstadt et al even found skin application of sunflower seed oil to protect against nosocomial infections in preterm very low birthweight infants admitted to hospitals in developing countries (8,19,20). The discrepancy between all these studies is potentially explained by distinct types of topical therapy, regional differences in pathogen pattern, and infant care practices (19).

In conclusion, daily prophylactic application of a topical ointment in premature infants improves skin condition and lowers the risk of dermatitis. This was true for 4 weeks of topical skin therapy. Treatment with olive oil cream was superior to water-in-oil emollient cream. NICU that use topical skin care in infants are advised to carefully monitor the incidence of infections.

ACKNOWLEDGMENT

Many thanks to the NICU nursing staff of Innsbruck Medical University for their support during the study.

REFERENCES

1. Saijo S, Tagami H. Dry skin of newborn infants: functional analysis of the stratum corneum. Pediatr Dermatol 1991;8:55–159.

2. Mize MM, Vila-Cora AA, Prager TC. The relationship between postnatal skin maturation and electrical skin impedance. Arch Dermatol 1989;125:647–650.
3. Holbrook KA. Structure and function of the developing human skin. In: Goldsmith LA, ed. Physiology, biochemistry and molecular biology of the skin, 2nd ed. New York: Oxford University Press, 1991:63–110.
4. Harpin VA, Rutter N. Barrier properties of the newborn infant's skin. J Pediatr 1983;102:419–425.
5. Evans NJ, Rutter N. Development of the epidermis in the newborn. Biol Neonate 1986;49:74–80.
6. Kalia YN, Nonato LB, Lund CH et al. Development of skin barrier function in premature infants. J Invest Dermatol 1998;111:320–326.
7. Lund C, Kuller J, Lane A et al. Neonatal skin care: the scientific basis for practice. J Obstet Gynecol Neonatal Nurs 1999;28:241–254.
8. Darmstadt G, Mao-Qiang M, Chi E et al. Impact of topical oils on the skin barrier: possible implications for neonatal health in developing countries. Acta Paediatr 2002;91:546–554.
9. Friedman Z, Shochat SJ, Maisels MJ et al. Correction of essential fatty acid deficiency in newborn infants by cutaneous application of sunflower-seed oil. Pediatrics 1976;58:650–654.
10. Lane AT, Drost SS. Effects of repeated application of emollient cream to premature neonates' skin. Pediatrics 1993;92:415–419.
11. Edwards WH, Conner JM, Soll RF. The effect of prophylactic ointment therapy on nosocomial sepsis rates and skin integrity in infants with birth weights of 501 to 1000 g. Pediatrics 2004;113:1195–1203.
12. Nopper AJ, Horii KA, Sookdeo-Drost S et al. Topical ointment therapy benefits premature infants. J Pediatr 1996;128:660–669.
13. Pabst RC, Starr KP, Qaiyumi S et al. The effect of application of aquaphor on skin condition, fluid requirements, and bacterial colonization in very low birth weight infants. J Perinatol 1999;19:278–283.
14. Schurer N, Schliep V, Williams ML. Differential utilization of linoleic and arachidonic acid by cultured human keratinocytes. Skin Pharmacol 1995;8:30–40.
15. Hammarlund K, Sedin G, Strömberg B. Transepidermal water loss in newborn infants. VII. Relation to post-natal age in very pre-term and full-term appropriate for gestational age infants. Acta Paediatr 1982;71:369–374.
16. Wanakukul S, Praisuwanna P, Kesorncam K. Effects of clear topical ointment on transepidermal water loss in jaundiced preterm infants receiving phototherapy. J Med Assoc Thai 2001;84:837–841.
17. Rutter N, Hull D. Reduction of skin water loss in the newborn. I. Effect of applying topical agents. Arch Dis Child 1981;56:669–672.
18. Conner JM, Soll RF, Edwards WH. Topical ointment for preventing infection in preterm infants. Cochrane Database Syst Rev 2003;4:CD 001150 DOI: 10.1002/14651858.CD001150.pub2.
19. Darmstadt GL, Badrawi N, Law PA et al. Topically applied sunflower seed oil prevents invasive bacterial infections in preterm infants in Egypt. Pediatr Infect Dis J 2004;23:719–725.
20. Darmstadt GL, Saha SK, Ahmed ASMNU et al. Effect of topical treatment with skin barrier-enhancing emollients on nosocomial infections in preterm infants in Bangladesh: a randomised controlled trial. Lancet 2005;365:1039–1045.