Emollient Therapy for Premature and Full Term Infants – A Global Perspective

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May 2014
Objectives

1. Describe the effects of emollient therapy on premature and full term infants
2. Review global initiatives and potential implications for nurseries in the US, i.e., high technology institutions
3. Discuss knowledge gaps, remaining questions and future research needs
Significance

- Research on emollient therapy for newborn infants as a strategy to reduce mortality is a global priority
Goals

- Improve child health by reducing morbidity and mortality among newborn infants worldwide
- Review the current state of the science regarding progress against this goal via the use of emollient therapy
- Delineate a strategy to further improve the effectiveness of the therapy for implementation in other regions, e.g., Africa
Newborn Infants

- Studies covered range, most were on preterms
- Variable treatment duration, most 4-14 days with some to 30 – 60 days
- Generally 2x per day, variable dose
Premature SC Development

Premature SC Development

Full Term SC Development

Review of Published Studies

• “Emollient” considered to be any topical treatment: oils, creams, petrolatum based, films, humidity

• Search terms:
  – Infant skin and emollient
  – Premature infant skin and emollient
  – Premature infant skin and development
  – Newborn skin and oil
  – Neonatal skin and topical treatment
  – Neonatal skin and animal models

• Number of citations > 350
Review of Published Studies

- Studies on infants, $n = 29$
- Total number of infants = 2882
- Number of studies with measures of skin grades, TEWL, impact on infection/mortality, or skin effect = 17
Mustard Oil Massage: Rural Nepal

- Massage with mustard oil in 99.8% to
- Make baby’s body strong (69.6%) 
- Keep baby healthy (41.4%) 
- Keep baby warm (36.8%) 
- Make skin look good (23.7%)

<table>
<thead>
<tr>
<th>Frequency</th>
<th>N = 22871</th>
</tr>
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<tbody>
<tr>
<td>Daily</td>
<td>5.0 %</td>
</tr>
<tr>
<td>2-3 times daily</td>
<td>83.8 %</td>
</tr>
<tr>
<td>&gt; 3 times daily</td>
<td>9.5 %</td>
</tr>
<tr>
<td>Once per week</td>
<td>0.6 %</td>
</tr>
<tr>
<td>Twice per week</td>
<td>0.3 %</td>
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</table>

<table>
<thead>
<tr>
<th>First Massage</th>
<th>N = 22746</th>
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</thead>
<tbody>
<tr>
<td>Within 1st hour</td>
<td>49.3 %</td>
</tr>
<tr>
<td>1-6 hr after birth</td>
<td>41.6 %</td>
</tr>
<tr>
<td>6-24 hr after birth</td>
<td>6.8 %</td>
</tr>
<tr>
<td>24-48 hr after birth</td>
<td>1.4 %</td>
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<tr>
<td>After 48 hr</td>
<td>0.9 %</td>
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## Oils & Application Mode

<table>
<thead>
<tr>
<th>Emollient</th>
<th>Number of Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunflower, safflower</td>
<td>8</td>
</tr>
<tr>
<td>Petrolatum, Aquaphor, paraffin</td>
<td>11</td>
</tr>
<tr>
<td>Film</td>
<td>4</td>
</tr>
<tr>
<td>Humidity</td>
<td>1</td>
</tr>
<tr>
<td>Olive</td>
<td>2</td>
</tr>
<tr>
<td>Soybean</td>
<td>1</td>
</tr>
<tr>
<td>Coconut</td>
<td>2</td>
</tr>
<tr>
<td>Meadowfoam</td>
<td>1</td>
</tr>
<tr>
<td>Almond (differing compositions)</td>
<td>2</td>
</tr>
</tbody>
</table>
Emollient Treatment: Premature Skin

- Infants 29-36 wks GA (n=16)
- Eucerin 2x daily
- Grades lower days 7-11 (p < 0.05)
- No differences in TEWL
- Co-ag neg. Staph cultures same in both groups
- **NOTE: Skin damage increased for control**

*Lane et al., Pediatrics, 1993, 93(3):415-419*
Emollient #2: Premature Skin

- Infants 24-32 wks GA (n=60)
- Aquaphor 2x daily
- TEWL decreased for both groups, no significant differences.
- Grades significantly lower for Aquaphor
- Bacteria counts at axilla lower for Aquaphor

Emollient #3: Premature Skin

- Infants 26-30 wk GA (n=19)
- Aquaphor 2x daily
- Skin score significantly lower for Aquaphor
- Note increase in skin compromise over first 4 days for control
- 5 developed sepsis, 2 treatment and 3 control

Emollients #4: Premature Skin

**Multicenter Trial**

- Vermont Oxford Network, 54 NICUs
- 610 infants: Aquaphor 2x daily for 14 days
- 596 infants: Routine skin care
- Infants 500-1000g, mean GA = 26 weeks
- A significantly *higher* incidence of nosocomial sepsis occurred in smaller birth weight infants (501-750 g) with Aquaphor®
- Organism responsible for sepsis was coagulase negative staph.

Emollients #4: Premature Skin

*Possible Explanation:*

- Aquaphor® behaved as an occlusive film in the trial, delaying barrier development and facilitating growth of microorganisms.

Topical Oils: Hairless Mouse Model

- Adult hairless mice
- Tape stripped skin (simulate premature skin)
- Mustard oil, 2x daily
- TEWL of mustard oil significantly higher than control at 1 hr and days 2,3,5,7 (p < 0.05)

Topical Oils: Hairless Mouse Model

- Adult hairless mice
- Tape stripped skin
- Sunflower oil & Aquaphor increased skin barrier recovery 60-180 and 300-360 minutes later (p<0.05)
- Mustard oil delayed barrier recovery (p<0.05)

NOTE: single application

Topical Oils: Premature Skin

- Infants 27-33 wks GA (n=103) in hospital
- Sunflower seed oil, no treatment
- Skin score lower for SSO day 21 (p<0.05)
- Skin scores maybe higher for both groups at 28 days.
- Fewer infections in the SSO group (p<0.05)

Topical Oils: Premature Skin

- Infants < 33 wks GA, n=497
- Hospital setting, Bangladesh
- Parallel groups Sunflower oil, Aquaphor, no treatment
- 3x daily 14 days, 2x daily until 28 days
- Incidence of infections was reduced for sunflower oil (p<0.05) and directionally for Aquaphor (p=0.06).
- Incidence was lower for both for infants <1250 g and infants enrolled in first 24 hours.

Topical Oils: Premature Skin

- Infants < 33 wks GA, n=497
- Skin scores increased for all groups, likely reflecting skin dryness.
- Scores for Aquaphor and SSO lower than control on days 3-21 and 3-14 (p<0.05).
- SSO prevented infectious agents from entry into the blood.

Topical Oils: Premature Skin

- Same group of 457 infants ≤ 33 wks
- Nursery of Dhaka Shishu Hospital, Bangladesh
- Daily treatment with sunflower seed oil (n = 159) or Aquaphor (n = 157) versus no treatment (n = 181)
- Mortality rates were significantly reduced: 26% sunflower seed oil, 32% Aquaphor
- The results continue to support these treatments for use in developing countries.

Emollients #5: Premature Skin

- Infants 25–36 wks GA (n=173)
- 4 weeks Bepanthen emollient (dexpanthenol, phenoxyethanol)
  - Olive oil (fatty acid, linoleic) 30% and lanolin 70%
- Skin scores were lower for Bepanthen cream on days 14, 21 and 28 (p<0.05)
- Sepsis rates comparable

Summary of Key Findings

• Skin dryness increased in untreated controls for extremely and very premature groups
• In some, dryness appear to increase over time with emollient
• Petrolatum/aquaphor treatment reduced dryness
• TEWL does not appear to change over days 3-5 in extremely and very preterms
Summary of Key Findings

- TEWL decreased following application but then increased in some.
- TEWL decreased in one study of coconut oil.
- A high linoleic oil increased hydration and reduced dermatitis while almond oil did not impact skin condition. Saline massage increased dermatitis.
- Effects of emollient therapy on infection rate were mixed.
Some Considerations

• Fatty acids, particularly linoleic, activate factors that increase the rate of barrier formation.
• Linoleic acid has anti-inflammatory properties.
• Topical lipids penetrate to the granular layer, alter the structure of the lamellar bodies and, presumably, become SC lipids.
Some Considerations

• This approach may not work in systems, e.g., premature infants, if the processes of granule formation and lipid secretion are not yet developed.

• The question is whether the epidermis of a premature infant is sufficiently well developed to respond to the effects of topically applied agents.
Unanswered Questions

• How does emollient therapy reduce infection rates in premature infants?
• Do fatty acid based oils and petrolatum-based emollients achieve the benefits by the same mechanism?
• What is the influence of starting gestational age on outcome?
• How would emollient therapy impact infection rates in full term infants?
Key Gaps

• SC structure, composition, integrity, permeability, cohesiveness as a function of gestational age at birth, i.e., ontogeny
• When does the SC barrier become fully competent, i.e., comparable to full term healthy newborn at 1-3 months of life?
• Skin microflora vs. gestational age and environment
• How would variability due to gestational age influence treatment selection?
State of the Science: Premature Infant Skin

- Information on premature skin barrier maturation is limited.
- Data are largely descriptive, i.e., visual and instrumental quantitation of integrity, acidity, irritation, rash, etc. provide the
  - *What* but not the
  - *How*, i.e., the underlying physiology
- Interventions cannot readily be devised.
Global Initiative

Evaluation of emollient therapy in Africa
Collaboration: Johns Hopkins

- Impact of sunflower oil emollient therapy on neonatal skin barrier function, bacterial colonization and immune response
- Luke Mullany, JHU
- Sub-study of larger trial
- Parallel groups: mustard seed vs. sunflower
- Ontogeny over days 1, 3, 7, 14, 28
Study Design

- Parallel groups: mustard seed vs. sunflower
- Randomized prenatally
- Apply oil per custom
- Visit days 1, 3, 7, 14, 28
- Skin grading
- TEWL
- pH
- Tape collection
Skin Surface Sampling for Biomarkers

- Skin surface cells are collected with plastic adhesive tapes, called d-squames®.
- Adhesive and procedure is well-tolerated by neonates.
- Samples are stored at -80°C until analysis.
Biomarkers: Cytokines

- Pro-inflammatory IL6, IL8, IL1β and MCP1 were higher in prematures than full terms.
- IL6 increased after barrier damage and treatment with IL6 enhanced repair.
- Higher levels of IL8, IL6 and MCP1 were higher in cord blood of premature infants vs. adults

Biomarkers: IL1α

- IL1α was higher in both infant groups compared to adults.
- IL1α was higher in
  - neonatal mice kept at low humidity
  - the neonatal rat at birth
- Treatment of explants with cytokines increased the rate of barrier maturation.

• Keratin 1,10,11 lower in infants than adults and reduction is associated with dryness.
• Involucrin higher in: premature versus full term, both versus adults.
• Early involucrin expression is associated with barrier damage.

Albumin

- Albumin, synthesized in the epidermis, was inversely related to gestational age.

Take a motorbike to the villages......
with Amiee Summers....grad student
White papules and some pustules
Papules and pustules

Other lesions or ruptured pustules
Papules and pustules
Predominant white papules

Yellow, fluid filled area is likely an infection, e.g., impetigo
Pustules
They tend to be larger and at no particularly “regular” interval. Their shape can be irregular.

This may be a white papule
The Skin – Brain Connection

• Skin and brain are both derived from ectoderm during gestation
• Evidence for a brain-skin axis
  1. Mast cells, substance P, nerve growth factor
  2. An “HPA” axis within the skin that makes:
     • CRH, ACTH, Cortisol
• A. Slominski: “The skin runs the brain.”

Thesis

- The skin is a key neuro-regulatory agent in how the infant perceives and ultimately handles the environment of care (sound, lights, heat, cold) and caregiver activities.
- Therefore, the skin is a crucial interface for neonatal neurodevelopment.
Infant Skin Interactions

- Touch is the first sense to develop.
- Touch is a central component of the infant-mother co-regulatory system.
- Touch is found in all cultures.

Infant Skin Interactions

**Specific Modalities:**
- Tactile Stimulation
- Kangaroo Care
- Newborn Individualized Developmental Care and Assessment
- Infant Massage
Types of Cutaneous Nerve Endings

- Innervated Hair Follicle
- Meissner’s Corpuscle (Tactile)
- Free nerve endings (pain)
- Merkel disks (touch)
- Krause end bulbs (cold)

Sensory Receptors in Human Skin

- Signaling Proteins
- Epidermis
- Dermis
Tactile Stimulation on Serum Lactate in the Newborn Rat

- Lactate is the chief end product of epidermal metabolism (Int J Biochem 23:1175-1183, 1991)
- In the fetus, lactate is produced by the placenta (J Clin Invest 70:179-192, 1982)
- The brain of the early suckling rat utilizes lactate in preference to other fuels such as glucose and 3-hydroxybutyrate (Neurochem Res 14:667-675, 1989)

Tactile Stimulation on Serum Lactate in the Newborn Rat

- Pups receiving TS were stroked on the dorsal surface in a rostral to caudal direction with a soft camel hair brush
- Pups were stroked at a rate of one stroke/sec for 30 s followed by a 30 s rest period q min x 10 min
- Lactate measured in serum

Tactile stimulation resulted in significantly higher serum lactate levels and the effect was maintained over time.

Tactile Stimulation

- Neonatal Animals: licking/grooming led to greater learning, better memory, suggesting increased hippocampal connections.
- Neonatal Animals: maternal behavior in infancy influenced formation of receptors for neurotransmitters (amygdala, hippocampus, prefrontal cortex).
Kangaroo Care

One hour of KC, 15-20 minutes after birth.

- KC infants slept longer, generally in quiet state, more flexor movements & postures, less extensor movements.
- KC impacted state organization.
- KC assists in appropriate timing of stimulation to help infant integrate subsystems.
- Continuation may effect mother-infant interaction, temperament and attention skills.

Kangaroo Care

• State Regulation/Organization: KC infants had a significantly higher % of time in quiet sleep and alert wakefulness than non KC controls.

• Mother-Infant Interaction: Significantly higher for positive affect, touch and visual regard in mother. Infants were more alert with lower gaze aversion.

• Mental Development Index: Significantly higher at 6, 12, and 24 months for KC infants.

Cortisol

- The higher cortisol in premature infants suggests an increase stress response.

Big Questions????

• Why does newborn infant skin develop rash in Nepal and, perhaps, elsewhere?
• What are the potential effects of the massage itself on skin barrier development, skin barrier integrity and susceptibility to infection?