Update on the Use of Topical Agents in Neonates

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Topical agents include anything that touches the infant's skin. The skin is crucial to the way the infant perceives and responds to the care environment and, therefore, in neurodevelopment. Psychological stress negatively affects the barrier. The full-term infant has well-developed epidermal barrier despite spending 9 months being submerged in water. Vernix caseosa is a natural topical agent that facilitates stratum corneum barrier development through protective and adaptive mechanisms. Its properties include hydration, wound healing, antiinfection, and acid mantle development. The ontogeny of neonatal skin development and vernix biology provide the basis for assisting barrier maturation in premature infants, treating compromised skin and selecting topical agents. The published research on the effects of topical products on premature and damaged neonatal skin is very limited, especially for adequately sized randomized controlled clinical trials. Health care providers have keen interest and the skills to identify improved treatments through outcomes-based research.

Keywords: Skin barrier; Neonate, Topical agent; Stratum corneum; Compromised skin

Overview and Perspective

The article will review topical products in infants. Conceptually, we define topical products in the broadest sense to include anything that touches or interacts with infant skin. The skin is a primary care interface vitally important in any patient-caregiver interaction.[1] The most recent information about skin structure, development, and function will be discussed to generate the context of topical treatments and products.

Touch is the first sense to develop in the infant. As a result, the skin is an important element in the process of how the infant perceives and reacts to the environment of care and, therefore, in neonatal neurodevelopment. Examples of skin-based infant interactions include skin-to-skin contact (kangaroo care), infant massage, Newborn Individualized Developmental Care and Assessment (NIDCAP), and tactile stimulation. Skin-to-skin contact immediately after birth results in increased temperature and blood glucose levels compared with swaddling next to the mother.[2] Skin-to-skin contact for 1 hour shortly after birth impacted state organization and the time spent sleeping.[3] Premature infants cared for with NIDCAP methods had significantly better neurobehavioral function and more mature neuronal fiber structure.[4] In a longer-term study, infants receiving NIDCAP had significantly better mother-child interaction (cluster communication), better hearing/speech, and lower behavior symptom scores.[5] Tactile stimulation via repeated stroking increased circulating lactate levels by 200% in the neonatal rat model.[6] These findings demonstrate the critical role of simple infant-caregiver skin-based interactions on the cognitive development of the infant.

Specific skin receptors are sensitive to mechanical stimuli and are critical for survival. The signaling proteins involved in this transduction are being identified.[7] Psychological stress due to environmental overcrowding is associated with a delay in skin barrier recovery in mice, an effect attributed to increased production of glucocorticoids.[8] Psychological stress decreased epidermal cell proliferation, adversely effected differentiation, and decreased the size and density of corneodesmosomes, all of which negatively impact skin barrier function.[9] Stress decreased antimicrobial peptides in the epidermis (animal model), an effect that resulted in more severe skin infections.[10]

Skin Structure and Function

Human skin serves multiple functions including barrier (to water loss, irritant exposure, light, etc), immunosurveillance, infection control, sensation, structural support, and thermal regulation (Table 1). The major skin layers are the epidermis, dermis, and hypodermis (subcutaneous). Fig 1 shows a cross-section and the structures responsible for the functions. Two layers comprise the dermis. The upper is the papillary layer, contains capillary loops, and is loosely organized. The lower is the reticular dermis composed of tightly packed collagen and elastin with glycosaminoglycans, which provide mechanical properties and elasticity. The epidermis includes the stratum corneum (SC, outer) and the viable epidermis (Fig 2). An understanding of SC structure and function is essential for being

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Table 1. Skin Functions

Function	Skin Structure
Barrier	
Physical (irritants)	SC and epidermis
Light	Melanocytes of the epidermis
Immunologic	Langerhans cells of the epidermis
Resilient foundation	Dermis
Sensation	Sensory nerves in epidermis and dermis
Tactile discrimination	SC and sensory nerves
Thermal regulation	Eccrine sweat glands in dermis Blood supply in dermis Adipose fat in subcutaneous layer (hypodermis)

able to select topical products. The SC is the main barrier to water loss and penetration by outside agents. The viable epidermis has four layers (top to bottom): clear (stratum lucidum), granular (stratum granulosum), spinous (stratum spinosum, nucleated cells), and basal (stratum basale, nucleated cells). Two specialized dendritic cells are housed in the viable epidermis. Langerhans cells (antigen-presenting cells) are part of the immune system and serve as the line of defense if the SC barrier is breached (Fig 2). The melanocytes (pigment cells) reside in the basal layer and produce melanin, the pigment responsible in part for inherent skin color. When the skin is exposed to UV radiation, melanocytes are activated and transport melanin to the nuclei of the epidermal cells to shield them and protect the DNA. Skin tanning is the result of this process. The pigmentary system is influenced by irritation and inflammation and may respond by producing more pigment (hyperpigmentation) or by deactivation (resulting in hypopigmentation).

The function of the viable epidermis is to continually build and replenish the SC. The cells "move up" from the basal layer and transition to SC cells through a programmed process. About 28 days is required for a cell to go from the basal layer and be lost from the outer SC. The SC is made up of about 16 layers of flattened cells (corneocytes) joined together by molecular "rivets" (aggregates of large molecules) called desmosomes (insert in Fig 2). The SC is about half of the thickness of a sheet of paper but incredibly strong. The process of going from nucleated cells to SC corneocytes begins in the upper spinous and granular cells with formation of the cross-linked cell envelope. Structures, called lamellar bodies, in the spinous layer store lipids. In the upper granular layer (below the SC), the lipids (cholesterol, fatty acids, ceramides) are secreted from the lamellar bodies into the intercellular spaces between the corneocytes to form a regular "brick (cells) and mortar (lipids)" structure. The lipids form a regular ordered bilayer structure, alternating with water, between the cells. By design, the SC structure is difficult to penetrate from the outside. It is the barrier to water loss but allows normal water vapor from respiration to be released. The integrity of the SC is measured in terms of the rate of transepidermal water loss (TEWL). Normal skin has TEWL values of approximately 6 to 8 grams per square meter per hour, and higher rates indicate a damaged barrier, poorly developed SC, or SC with fewer layers than normal. The important goal of topical skin treatments is to maintain or restore the SC barrier. A schematic of showing normal and compromised SC barriers is shown in Fig 3. Normal skin looses about one SC layer per day through the process of desquamation where the connections between SC cells degrade and release the cells to the environment. An appropriate level of hydration is required for proper desquamation. Stratum corneum that is too dry will not desquamate properly and results in large aggregates of cells, scales or dry skin flakes. The protein filaggrin in the SC corneocytes is converted to small water-binding amino acids called natural moisturizing factor (NMF). Natural moisturizing factor is in part responsible for maintaining the appropriate level of SC hydration, and loss of NMF or disruption of the NMF generation will result in low SC moisture. Excess hydration will also cause barrier damage as will be discussed later.

Neonatal Skin Development

Birth marks are a significant environmental change for the infant from a warm, sterile, and safe womb to a dry high-oxygen environment with multiple organisms (bacteria) and demands for self-sufficiency such as air breathing, enteral nutrition, waste elimination, and maintenance of water balance. Neonatal skin serves many functions at birth, including a barrier to water loss and chemicals, temperature regulation, tactile discrimination,

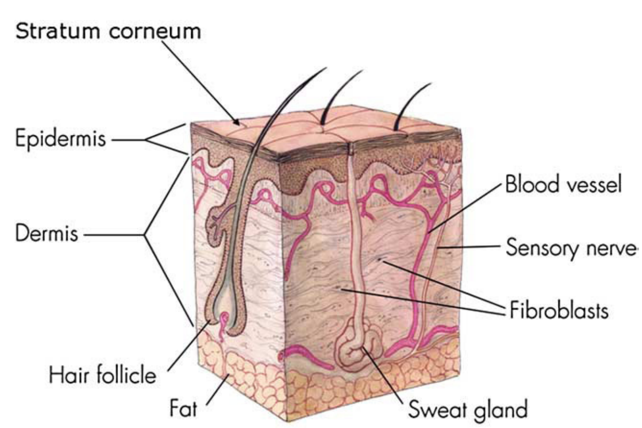

Fig 1. Skin structures. A cross-section of the skin shows the structures responsible for the functions. The major skin layers are the epidermis, dermis, and hypodermis (subcutaneous). The outermost layer, the SC, is directly exposed to the environment. The figure was provided by the National Institutes of Health for use by the public and can be found at http://media.nih.gov/imagebank/display_search.