Dry heel and Glycolic-Urea Cream
Proof of Concept

Prepared by: Neelam Muizzuddin, PhD
Skin Clinical Research Consultants, LLC
July 13, 2018

Objective:

To evaluate the effect of a Urea Glycolic acid cream formulation on improving skin dryness of the heels of the feet.

Summary

Dehydration and xerosis of the skin of heels of the feet present as cracking, scaling and/or redness of the heels. Clinical study was conducted to determine the effect of a Topiderm Urea Glycolic acid cream on smoothing and reducing the signs of dry cracked skin of the heels. The product was significantly effective in reducing the signs of dryness and cracking of the heels. All the subjects declared it was effective in smoothing and reducing the dryness and cracking the heels after just a few treatments.

Introduction

The human epidermis is the main barrier between the body and the external world with the outermost layer, the stratum corneum, playing a significant role in preventing water loss and limiting the ingress of toxic chemicals, allergens and potential pathogens. The stratum corneum behaves much like a brick wall with the bricks being the keratinocytes (made from a protein complex containing loricrin and involucrin) which are interlinked, giving a rigid envelope-like structure. The bricks are surrounded by the mortar – a complex of lipids rich in ceramides, cholesterol and free fatty acids which add the waterproofing layering to the epidermis.

These surface cells eventually desquamate but are constantly replenished with new keratinocytes ascending from the lower strata below namely the stratum basale, stratum spinosum and stratum granulosum respectively reaching the outermost layers of the corneum in around 28 days. During that migration, the keratinocytes undergo a range of complex changes that see them become cornified developing a protein rich envelope. , Keratohyalin granules develop within the stratum granulosum. These granules are rich in filaggrin, a histidine rich protein complex genetically coded which is subsequently degraded in the stratum corneum into shorter amino-acids which are vital for maintaining the barrier function within this outer layer (McGrath, 2012).

Dehydration and xerosis of the skin of heels of the feet present as cracking, scaling and/or redness of the heels. In severely neglected cases these fine cracks can become enlarged, painful, deep fissures, which in time may become infected with secondary bacteria. Xerosis may cause cutaneous discomfort and concerns about appearance that may warrant treatment. The goals of treatment include replacing water content and natural skin oils, maintaining skin hydration, providing a soothing protective film, controlling keratinization, and alleviating symptomatology.

Fissure formation often develops at sites where the epidermis is under direct physical stress, such as the heel margin. The heel pad plays an important role as a shock absorber by reducing and transmitting impact forces. These areas of high tissue stress are often associated with fissures, despite the apparent lack of direct pressure, particularly when combined with anhidrosis. Furthermore, impact forces increase tensile deformation of soft tissue and can create short-term vascular changes in the heel pad. All of which can result in tissue breakdown and fissuring (Longhurst and Steele, 2016)

Hashmi et al identified the mechanical properties of both dermal and epidermal cells on plantar skin and how they react to physical stress by generating inflammatory cytokines that cause incomplete cell differentiation. This leads to a clumping of corneocytes, which manifests as hyperkeratosis and, frequently, fissures (Hashmi et al, 2015).

Treatment of xerotoc hyperkeratosis of feet

Actives including Glycolic acid and Urea are widely used in topical applications to alleviate xerosis of skin. Glycolic acid has been reported to improve skin turnover and exfoliation (Perricone and DiNardo, 1996) while urea is known to be keratolytic and hydrating (Pan et al, 2013).

Urea

Urea (also known as carbamide) [(NH2)2CO] is a natural by-product created predominantly in the liver through the metabolism of protein in the urea or ornithine cycle. The chemical is a stable and of low toxicity and is a useful means of eliminating nitrogen safely from the body in urine. As a chemical it is highly water soluble, pH neutral and is produced by combining ammonia molecules (NH3) with carbon dioxide (CO2).

Although urea is considered to be a waste product it also occurs naturally within the epidermis as part of normal skin physiology. Keratinocytes in the lower epidermal layers express specific urea transporters and other channels known as aquaporins. Importing urea into the keratinocytes creates a humectant effect hydrating the cell and drawing in water through channels in the cell wall from the underlying dermis, maintaining cell turgidity and shape. Latterly, urea is also produced in the stratum corneum. A change from the neutral pH in the lower layers to a drier, acidic environment in the stratum corneum, promotes filaggrin breakdown into amino-acids and arginine. The latter being subsequently converted to ornithine, from which further urea is produced (McGrath, 2012).

Urea has been used topically for many years as a hydrating agent [Kuzmina et al 2002, Cork et al 2009]. Urea treatment has been shown to reduce skin trans-epidermal water loss, thus improving the skin barrier function possibly due to increased levels of filaggrin, involucrin and loricrin (Grether-Beck et al 2012). Studies by Grether-Beck et al (2012) have demonstrated that urea application stimulates expression of two anti-microbial peptides - cathelicidin (LL-37) and Beta-defensin 2. In addition, urea application upregulates the production of natural skin lipids after just 48 hours of exposure to the chemical increasing waterproofing in the outer layers of the epidermis (Grether-Beck et al 2012).

Urea is known to be a good humectant; it is able to attract and hold water within the epidermis giving it excellent emollient properties. Urea, as a small molecule that has the ability to cause conformational change in skin protein structures, effectively unfolding them making them more vulnerable to degradation and exfoliation. Clinically this is seen as an epidermal thinning effect (Fluhr et al, 2008) without affecting normal skin physiology and integrity. This particular function being evident in lower strength formulations (less than 20%). Above 25%, the action of urea is more keratolytic than hydrating (Vidal et al 2008).

Products containing urea are used for a wide range of skin diseases which have dry skin as part of their symptoms. Clinical conditions treated include icthyosis, atopic dermatitis and eczema, contact dermatitis, seborrheic dermatitis, psoriasis and onychomycosis (Pan et al, 2013). The positive benefits of urea based emollients on the diabetic foot have also been extensively studied (Bristow et al, 2013; Locke et al, 2012).

Glycolic acid

Glycolic acid is a member of the alpha hydroxy acid family, which occurs naturally in foods and has been used for centuries as a cutaneous rejuvenation treatment. In low concentration (2– 5%) glycolic acid facilitates progressive weakening of cohesion of the intercellular material of the stratum corneum, resulting in uniform exfoliation of its outermost layers (the stratum disjunctum) (Fartasch et al, 1997; Effendy, et al 1995). At high concentrations (~50%) glycolic acid peels are increasingly popular.

It has been suggested that glycolic acid causes acute activation of corneodesmosomes in the lower layer by acidification around pH 3 (Horikoshi et al, 2005). Electron microscopy has revealed enhanced desmosomal breakdown of the stratum corneum with glycolic acid, promoting loss of cohesion and desquamation. This breakdown is restricted to the stratum disjunctum while the desmosomes of the stratum compactum are unaffected (Fartasch et al, 1997). According to Horikoshi et al (2005) the corneodesmosomes in the upper layer are inactivated after treatment with glycolic acid. In addition, the long-term de novo corneodesmosomes production is enhanced in the few weeks following glycolic acid treatment (Horikoshi et al, 2005)

The barrier structures of the stratum corneum are not disrupted by topical treatment with glycolic acid (Fartasch et al, 1997, Kim et al, 2001).

Clinical study Q0216-B was conducted to study the effect of a lotion containing Urea-and Glycolic acid on improving dry heels. The study was sponsored by Topix Inc and conducted at Cantor Research Laboratories, Inc., Blauvelt, New York. The following test material was tested:

- Topiderm Glycolic Urea Cream #310

Procedure

This study was conducted in adherence with the principles of Good Clinical Practice as contained in the U.S. Code of Federal Regulations (CFR), Title 21, CFR, Parts 50 and 312 and International Conference of Harmonization (ICH) Guidelines for Good Clinical Practice: Consolidated Guidance (GCP E-6, April, 1996). Since the study was not invasive, it was not necessary to obtain the approval of an Institutional Board.

All subjects in this study were completely informed about the pertinent details and purpose of this study. Subjects were provided with a copy of the Informed Consent form and were given sufficient time to read the document. The study was explained to each subject and they were given the opportunity to ask questions prior to signing of the Informed Consent. Written Informed Consent was obtained from each subject prior to conducting any study procedures. Subjects also signed a Photography Release Form for the capture and use of digital images.

Subject Panel

A total of 11 subjects were recruited for the study; they all completed the first part of the study and 5 subjects completed the extension of the study. The subjects were recruited from the local population. They were males and females between the ages of 18 and 65 years; of Fitzpatrick Skin Types I-IV with dry and cracked heels of the feet. The subjects were carefully examined to make sure they did not show signs of visible skin disease which might be confused with a skin reaction from the test procedure or material. They were of normal health with no evidence of acute or Chronic disease including dermatologic problems. The subjects expressed willingness to cooperate with the investigator and comply to study requirements; and clearly demonstrated the ability to understand the purpose of the study and what is required of him/her to bring it to a meaningful conclusion as well as risks associated with participation. They Demonstrated the ability to read and understand all the items in the informed consent document; and willingly signed it and the photo release form.

Subjects in ill health or under a doctor's care or taking medication(s) which could influence the outcome of the study were excluded from the study. They were also excluded if they exhibited sunburn, rashes, scratches, burn marks etc., which might interfere with evaluation of test results or systemic illness that could contra-indicate participation. Additionally, the subjects were examined and excluded if they showed dermatological disorders in the test areas including warts nevi, moles, sunburn, suntan, scars and active dermal lesions, infections, burns, cuts, tattoos, visible scars or acne or any form of suspicious lesion or skin cancer on the treatment area.

The female subjects were not pregnant, lactating or planning to get pregnant for the duration of the study. They were instructed not to participate in any cosmetic or other clinical trials involving the lip area. Subjects were instructed not to use any other topical agents in the test area, or receive any skin treatments and manicures, other than the products provided, for the duration of the study. Subjects were instructed to maintain their daily cleansing routine for the duration of the study.

After admission to the study, the subject could withdraw at any time for any reason. The Investigator was to attempt to determine the reason and report it fairly and accurately.

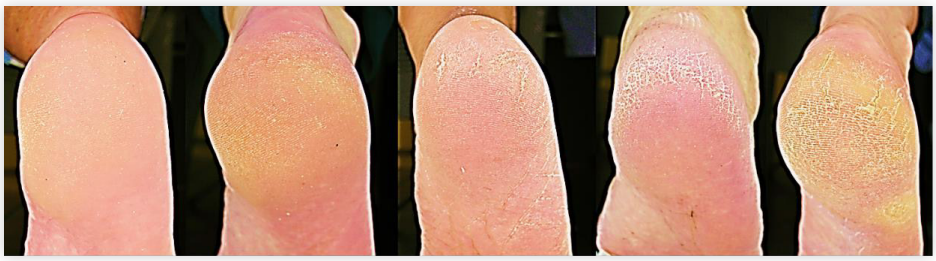
Clinical

The subjects reported to the testing lab with a clean foot devoid of any moisturizing treatment for the baseline measurements. Photographs were obtained using a steady lighting photobooth with a Nikon Coolpix 8400 Digital Camera. The subjects were provided with the test material to apply on their feet twice a day for 20 days. Product treatment was discontinued for 10 days and regression photographs were obtained.

The study protocol was extended with 5 subjects who were instructed to apply the product again for 20 days after which photographs were obtained again.

Data analysis

The photographs were graded for dryness/fissures using a 5 point photographic scale.



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An Excel analysis package was used to assess the statistical significance of the post-treatment data as compared to pre-treatment (baseline) by employing the two-sample paired student's t-test. This test for significance determines the probability that a given result could not have occurred by chance. The probability is called a p-value. Data was evaluated at a 95% ($p<0.05$) confidence level. In summary, the data is significant when the p-value is less than 0.05 and highly significant if the p-value is less than 0.001 (28-29).

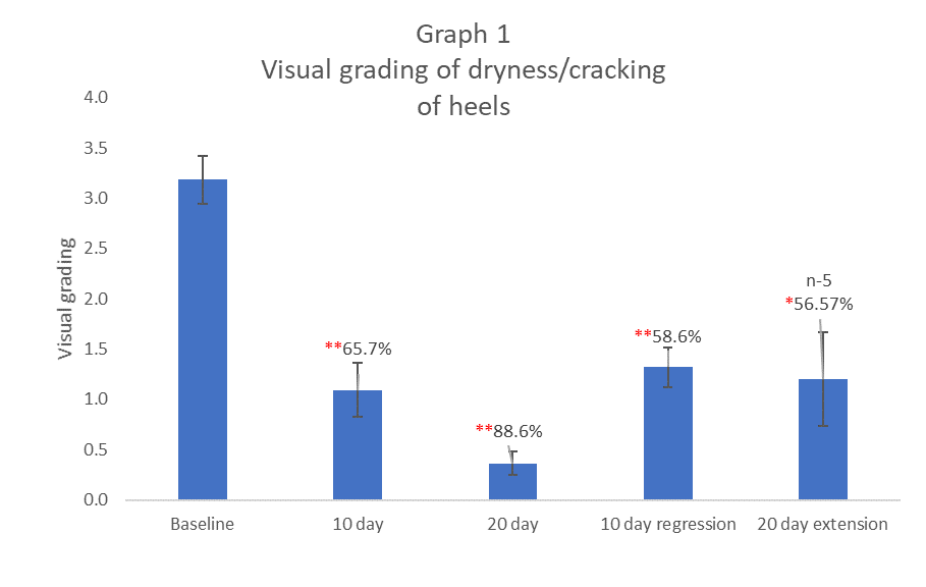
Subject self assessment

The subjects were provided with a questionnaire to determine their preference after using the product for 10 and 20 days.

Results and discussions

Visual grading of Heels

Graph 1 exhibits average of visual grade for dryness/fissures using a 5 point photographic scale. As observed in the graph, there was a highly significant ($p<0.001$) drop in drying and cracking of the heels of the subjects after only ten days of treatment. All eleven subjects exhibited a reduction in drying/cracking of heels at this time points; two subjects had zero grading of dryness at this time point.



After 20 days of treatment there was an average of 88.6% ($p<0.001$) reduction in dryness and cracking of the heels. At this time point five subjects had zero grading of dryness at this time point and four subjects had minimal grading of 0.5.

When treatment was stopped for ten days, all subjects exhibited signs of drying again, nevertheless, the heels were still a highly significantly ($p<0.001$) more moisturized than baseline (58.6%). Clearly some of the moisturizing effect of the product persisted for 10 days of regression.

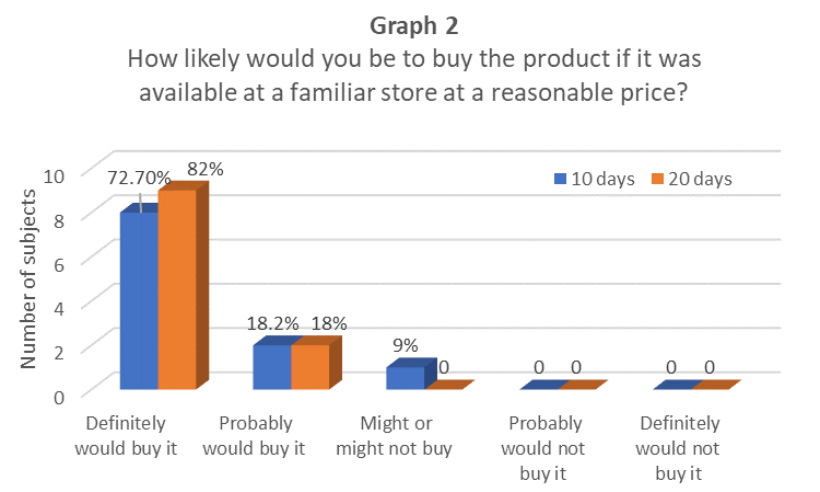
The study was extended for an additional 20 days use of the product. Only 5 subjects continued with the study extension. Since n was low, it appears like the heels did not improve much (56.57% compared to baseline) nevertheless the difference was statistically significant ($p<0.05$). Four out of five subjects showed improvement, one subject appeared to get worse, possibly because the subjects were reluctant to wear socks due to hot weather.

The natural moisturizing factors, urea and glycerine, can be severely depleted in patients with fissuring of the heels thus maintaining hydration is of importance in this population. A lower concentration of urea (5%) is an effective keratolytic agent for heels (Longhurst

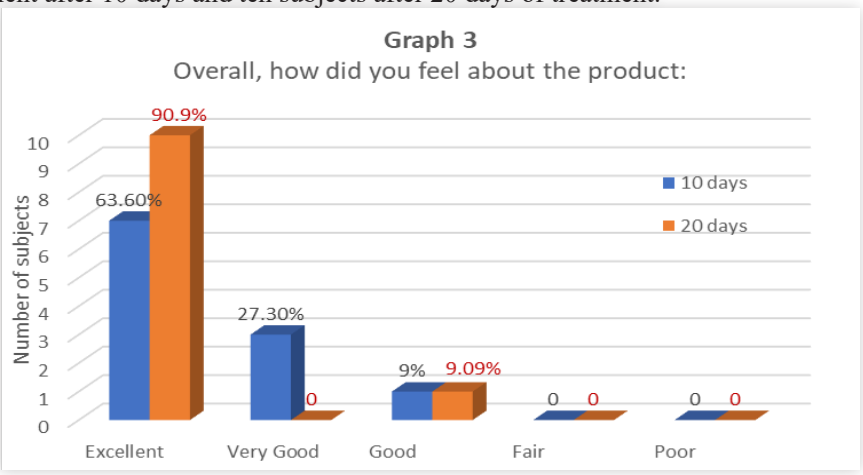
and Steele, 2016). Regular application of humectant based emollients improves elasticity, hydration and desquamation rates of the stratum corneum, thereby reducing risk of ulceration, and urea-based moisturisers appear to be particularly suitable for the removal and prevention of callus and fissures (Pavicic and Korting, 2006).

Subject self assessment

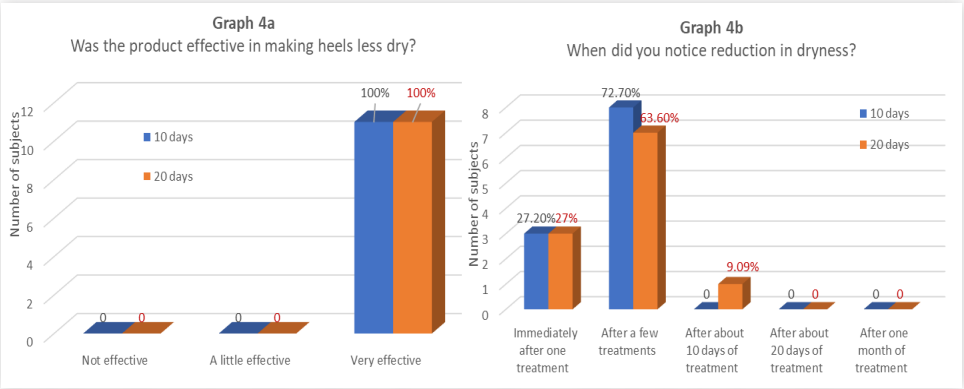
The subjects answered a questionnaire to determine their self-assessment of the product. When asked if they would purchase this product (Graph 2) Eight subjects out of eleven definitely wanted to purchase it after 10 days and nine subjects after 20 days of treatment. Two subjects declared they would probably purchase it. One subject declared she might or might not purchase the product after 10 days but was no longer unsure after 20 days of use. Clearly the product was very well approved by the panel.



The subjects were asked what they felt about the product, seven subjects graded it excellent after 10 days and ten subjects after 20 days of treatment.

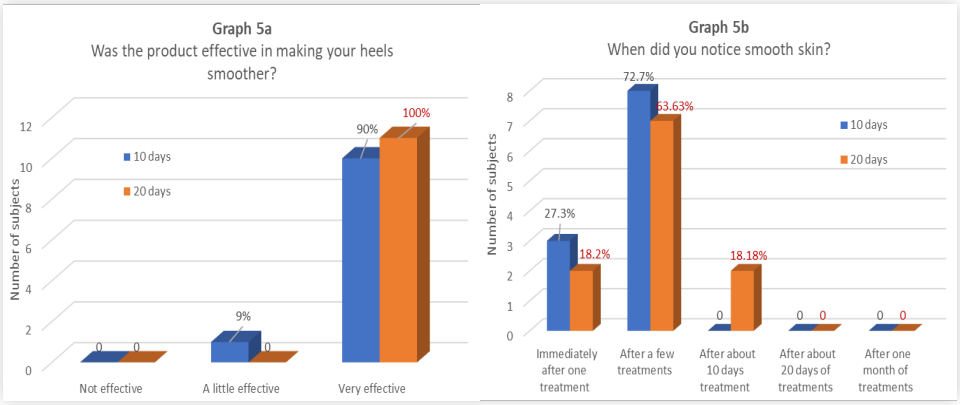


After 10 days of use three subjects graded it as very good and one as good. After 20 days one subject graded it as good. Clearly the subjects liked the product.
Graph 4 a and b address product effect in reducing the dryness and cracking of the heels. As observed in Graph 4a, all the subjects agreed that the product was very effective in making their heels less dry, after 10 and 20 days of use.
Three subjects declared that the product was effective immediately after one use. At the 10 day time point, eight subjects declared it was effective after a few treatment. At the 20 day time point, seven subjects stipulated that it was effective after a few days or use while one subject saw a difference after ten days of treatment.



Graph 5 a and b questioned the subjects about smoothness of the heels. As observed in Graph 4a, ten out of eleven the subjects agreed that the product was very effective in making their heels smooth, after 10 days and all the subjects agreed after 20 days of use.

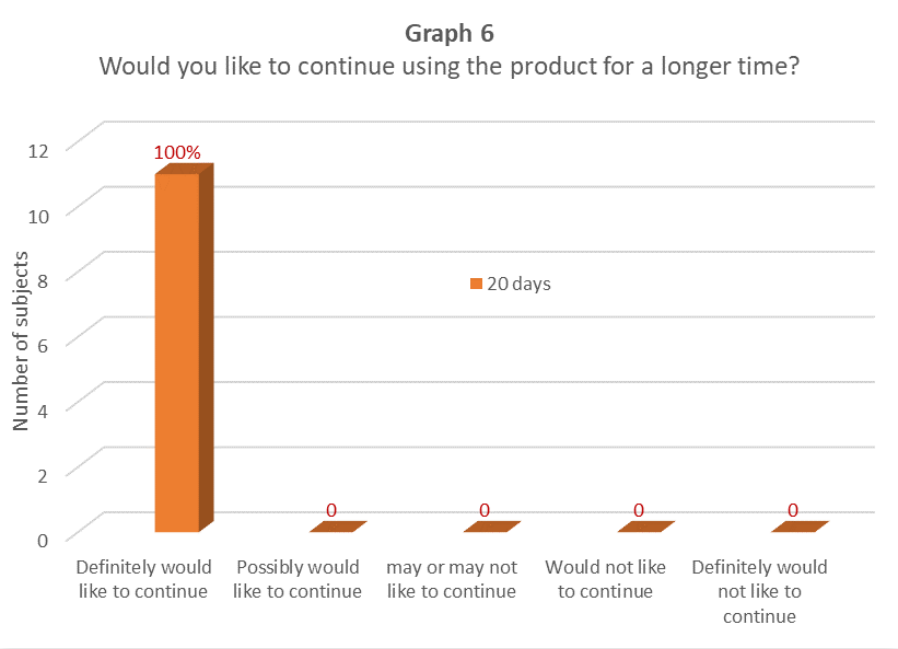
Three subjects declared that the product was effective immediately after one use. At the 10 day time point, eight subjects declared it was effective after a few treatment. At the 20 day time point, seven subjects stipulated that it was effective after a few days or use while one subject saw a difference after ten days of treatment.



Graph 5b shows that after ten days of use three subjects noticed a smoothness immediately after treatment, eight after a few treatments. After 20 days of use, two subjects declared they saw an improvement immediately after use, seven after a few treatments and two after 10 days of treatments.

The product is clearly quick acting since it was effective in smoothing and reducing skin dryness after just a few treatments.

At the 20 day time points the subjects were asked if they would like to continue using the product and all eleven subjects concurred.



Conclusion

Based on the confines and conditions of this study:

- Glycolic Urea Cream #310 was significantly effective in improving the dryness and cracked fissures of the heels of the feet after 10 days.
- After 20 days most subjects exhibited minimal or no dryness of the heels.
- 10 day regression resulted in reverting to some dryness, but it was still significantly better than baseline indicating that some of the moisturizing effect of the product persisted for 10 days of regression.
- Extending product use further improved the skin.