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ORIGINAL RESEARCH

Comparison of the Efficacy of Atopalm® Multi-Lamellar Emulsion Cream and Physiogel® Intensive Cream in Improving Epidermal Permeability Barrier in Sensitive Skin

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ABSTRACT

Introduction: The management of sensitive skin, which affects over 60% of the general population, has been a long-standing challenge for both patients and clinicians. Because defective epidermal permeability barrier is one of the clinical features of sensitive skin, barrier-enhancing products could be an optimal regimen for sensitive skin. In the present study, we evaluated the efficacy and safety of two barrier-enhancing products, i.e., Atopalm® Multi-Lamellar Emulsion (MLE) Cream and Physiogel® Intensive Cream for sensitive skin.

Methods: 60 patients with sensitive skin, aged 22–40 years old, were randomly assigned to one group treated with Atopalm MLE Cream, and another group treated with Physiogel Intensive Cream twice daily for 4 weeks. Lactic acid stinging test scores (LASTS), stratum hydration (SC) and transepidermal water loss (TEWL) were assessed before, 2 and 4 weeks after the treatment.

Results: Atopalm MLE Cream significantly lowered TEWL after 2 and 4 weeks of treatment ($p < 0.01$). In contrast, Physiogel Intensive Cream significantly increased TEWL after 2 weeks of treatment ($p < 0.05$) while TEWL significantly decreased after 4-week treatments. Moreover, both Atopalm MLE Cream and Physiogel Intensive Cream significantly increased SC hydration, and improved LASTS after 4 weeks of treatment.

Conclusion: Both barrier-enhancing products are effective and safe for improving epidermal functions, including permeability barrier, SC hydration and LASTS, in sensitive skin. These products could be a valuable alternative for management of sensitive skin.

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INTRODUCTION

Sensitive skin is a skin condition that is hypersensitive to various external stimuli. The prevalence of sensitive skin in the general population is over 60% in both males and females [1]. In the general population, over 50% have suffered sensitive skin for over 5 years, and more than 42% have over a 10-year history of sensitive skin [2]. In over 30% of this population their sensitive skin worsened [2]. The prevalence rate is higher in African-American than in Caucasians, particularly in the genital area [1, 3]. On the face and genital area, females have a higher prevalence than males [1]. Sensitive skin can be caused by a variety of external and internal factors, including sun exposure, psychological stress, wind and hot or cold weather conditions [1]. Among these factors, use of cosmetic products is the most common cause [4]. For example, use of inappropriate washing emulsion can elevate both skin surface pH and transepidermal water loss (TEWL) [5] which in turn can induce or exacerbate cutaneous inflammation [6–9]. Certain dermatoses, such as atopic dermatitis, are associated with sensitive skin [4].

The prevention and treatment of sensitive skin have been a challenge for both patients and clinicians due to its uncertain etiology and pathogenesis. However, sensitive skin features a number of abnormalities in its biophysical properties, including increased TEWL and skin erythema index, reduced stratum hydration (SC), and compromised SC integrity. Cho et al. did, however, show no difference in TEWL between sensitive skin and normal skin [10–13]. Moreover, a marked elevation in both skin surface pH and TEWL are observed in subjects with sensitive skin following topical application of lactic acid [14, 15]. Among these changes, increased TEWL, indicating a disrupted permeability barrier, has significant impact on cutaneous function. First, disruption of permeability barrier induces cutaneous inflammation via stimulation of proinflammatory cytokine release [16–20], inflammatory cell maturation and infiltration [9, 21–23] while inflammation is a pathophysiological feature of sensitive skin [24]. Second, barrier disruption increases the density of mast cell, a major source of histamine, in the dermis [7] whereas release of histamine can cause itching upon external stimuli [25]. The increased histamine could further disrupt epidermal permeability barrier via inhibition of keratinocyte differentiation and lipid production [26, 27]. Third, compromised permeability barrier increases cutaneous sensitivity to allergens through facilitation of allergen penetration [28] while increased transcutaneous penetration of substances is another feature of sensitive skin [29–31]. Taken together, compromised epidermal permeability barrier plays a crucial role in the pathogenesis of sensitive skin. Therefore, the strategies to enhance epidermal permeability barrier have been recommended by experts for the management of sensitive skin [32, 33]. However, the availability of barrier-enhancing products for sensitive skin is still limited. In the present study, we compared the efficacy of Physiogel® Intensive Cream (Stiefel Laboratories, Inc. Middlesex, UK) and Atopalm® Multi-Lamellar Emulsion (MLE) Cream (NeoPharm Co., Ltd, Daejeon, Korea) for improving epidermal permeability barrier in Chinese with sensitive skin.

METHODS

Subjects

A randomized, double-blind controlled clinical trial was conducted in 60 Chinese females with sensitive skin in an outpatient clinic. The inclusion criteria included Chinese female, aged 20–40 years old, with sensitive skin, and Lactic Acid Sting Test (LAST) score $\geq$3 at 2.5 and 5 min. The exclusion criteria included pregnant women, nursing mothers, women planning to be pregnant in the next 3 months, receiving or going to receive any medications or any cosmetology treatments within the last 3 months and during the study period, direct facial exposure to sunlight or artificial UV irradiation without protection over the last 2 h, known allergic or sensitive to any ingredients in the test products and not using any other products during the study period (excluding lipstick, eyeliner or eye shadow). All subjects were non-atopic and with no skin disorders which are known to influence epidermal function. Informed consent was obtained from all individual participants in the study. Subjects were alternately assigned to group A or B after completion of consent form. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The protocol of this study was approved by human research committee of Peking University First Hospital, Beijing, China.

LAST

LAST was performed by applying 50 μl of 5% lactic acid solution with two layers of filter paper (diameter 0.5 cm) to the nasolabial folds. Skin stinging was evaluated by a 4-point scale (0, absence of stinging; 1, weak stinging; 2, moderate stinging; 3, strong stinging) 0, 2.5, 5 and 8 min after the application.

Materials and Treatments

30 subjects in group A were treated with Atopalm MLE Cream while 30 subjects in group B were treated with Physiogel Intensive Cream twice daily for 4 weeks. The major active ingredients in these two products are detailed in Table 1. Products were only applied to the face. This study was carried out at the Department of Dermatology and Venereology, Peking University First Hospital, Beijing, China, between April and August 2015.

Table 1 List of major active ingredients

Physiogel® intensive cream [34]	**Atopalm® MLE cream**[a]
Glycerin	Glycerin
Butyrospermum parkii	*Vitis vinifera* (Grape) seed oil
Squalane	*Simmondsia chinensis* (Jojoba) seed oil
Pentylene glycol	Olea europaea (Olive) fruit oil
Cocos nucifera oil	Portulaca oleracea extract
Ceramide 3	Phytosterols
	Sodium hyaluronate
	Arginine
	Tocopheryl acetate
	Myristoyl/palmitoyl oxostearamide/arachamide MEA

MLE multi-lamellar emulsion

[a] Information was provided by NeoPharm Co., Ltd., Daejeon, Korea

Assessment of Efficacy

TEWL, an indicator of epidermal permeability barrier function, was measured using a TewaMeter® TM210 (Courage + Khazaka electronic GmbH, Cologne, Germany) while SC capacitance, an indicator of SC hydration, was measured on the right zygomatic area using a Corneometer® CM 825 (Courage + Khazaka electronic GmbH, Cologne, Germany) before, 14 and 28 days after treatments. Meanwhile, the LAST was also performed on the nasolabial folds. All tests were carried out under controlled environmental conditions at the humidity of $40 \pm 10\%$ and temperature of 22 ± 2 °C. Subjects rested peacefully in such environment for at least 30 min before the tests.

Assessment of Adverse Event

Adverse events were assessed 2 and 4 weeks after treatments, using following numerical grading system: 0, no adverse event; 1, occasionally mild; 2, moderate, but endurable; 3, severe, with predominant symptoms. Subjects with adverse reaction ≥grade 2 were asked to discontinue the trial.

Statistical Analyses

Data are expressed as mean ± SEM except otherwise indicated in the text. Data were analyzed using GraphPad Prism 4 (GraphPad Software, Inc., La Jolla, CA, USA). Nonparametric two-tailed *T* test was used to determine significant differences between two groups.

RESULTS

Out of 60 subjects, one subject experienced facial redness after application of Atopalm MLE Cream. The subject refused to have a patch test.

Table 2 Demographic data of subjects

Group	Number	Age range (years)	Mean	SD
Group A	29	24–40	28	4.38
Group B	30	22–40	30.8	6.79

SD standard deviation

The lesion disappeared 1 day after discontinuation of using the cream. The remaining 59 subjects completed the trial with no sign of adverse reaction. The demographic data of these subjects were detailed in Table 2.

Both Products Improve Epidermal Permeability Barrier

Since Atopalm MLE Cream and Physiogel Intensive Cream contain stratum corneum lipids, which benefit the epidermal permeability barrier [35–37], we first assessed epidermal permeability barrier function after topical applications of these products. As shown in Fig. 1a, topical applications of Atopalm MLE Cream for 2 weeks induced an over 20% reduction in TEWL. In contrast, Physiogel Intensive Cream caused an 11% increase in TEWL after 2 weeks of treatment. After 4 weeks of treatments, both Atopalm MLE Cream and Physiogel Intensive Cream benefited the epidermal permeability barrier while the reduction in TEWL was more dramatic in Atopalm MLE Cream-treated than in Physiogel Intensive Cream-treated subjects.

Our prior studies have demonstrated that topical stratum corneum lipids or their containing product improve stratum corneum hydration [38–40], which is reduced in sensitive skin [10]. We next determined whether topical treatments with these products also improve stratum corneum hydration in sensitive skin. Indeed, both products significantly increased stratum corneum hydration after 4 weeks of treatment although the improvement of

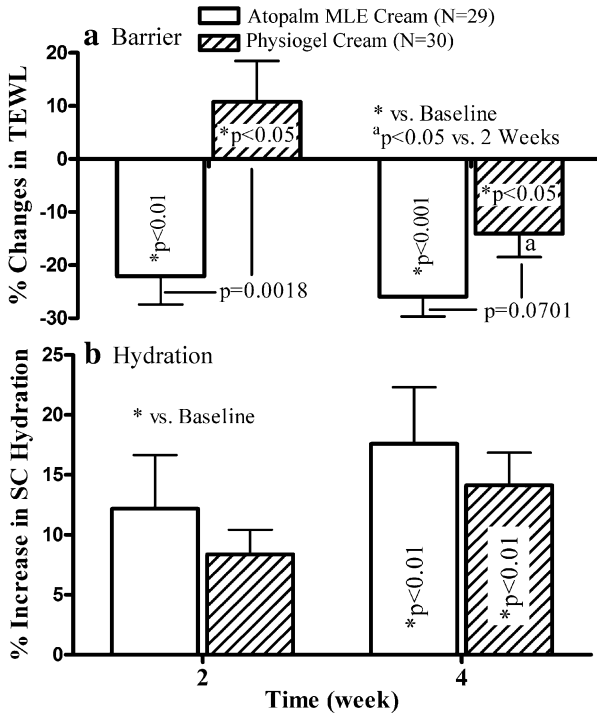

Fig. 1 The effects of barrier-enhancing products on the epidermal permeability barrier in subjects with sensitive skin. Subjects' faces with sensitive skin were treated with either Atopalm® MLE Cream or Physiogel® Intensive Cream twice daily for 4 weeks. TEWL and stratum corneum hydration were measured before, 2 and 4 weeks after treatments as described in "Methods". **a** Depicts the influences of topical products on TEWL after 2 and 4 weeks of treatments. **b** Displays the effects of topical products on stratum corneum hydration after 2 and 4 weeks of treatments. For both TEWL and stratum corneum hydration, the data were expressed as % changes from baseline. Significances and number of subjects are indicated in the figures. *MLE* multi-lamellar emulsion, *SC* stratum hydration, *TEWL* transepidermal water loss

stratum corneum hydration was not dramatic after 2 weeks of treatment (Fig. 1b). The improvement in stratum corneum hydration was no different between these two products after 2 or 4 weeks of treatment. Taken together, these results demonstrated that topical applications of either product improves epidermal permeability barrier and stratum corneum hydration in subjects with sensitive skin.

Both Products Improve LASTS

Sensitive skin is characterized by an enhanced response to LAST [30, 31], which is likely due to poor permeability barrier that facilitates the penetration of lactic acid into skin [28, 29]. Since both Atopalm MLE Cream and Physiogel Intensive Cream improved epidermal permeability barrier, we next assessed whether these two products also improve LAST scores. As seen in Fig. 2, after 2 weeks of treatments with these products, LAST scores were reduced by 14%. Further reductions in LAST scores were observed after 4 weeks of treatment (27.3 ± 7.2% for Atopalm MLE Cream and 34.1 ± 8% for Physiogel Intensive Cream, no significant difference was observed between these two products). These results demonstrate that Atopalm MLE Cream- and Physiogel Intensive Cream-induced improvement of permeability barrier is paralleled by a reduction in LAST scores.

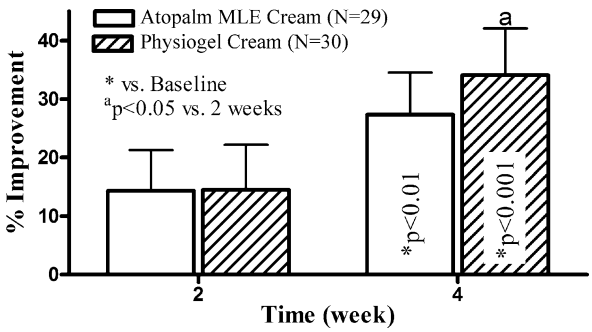

Fig. 2 The effects of barrier-enhancing products on LASTS in subjects with sensitive skin. Subjects' faces with sensitive skin were treated with either Atopalm® MLE Cream or Physiogel® Intensive Cream twice daily for 4 weeks. LASTS was performed before, 2 and 4 weeks after treatments as described in "Methods". Skin stinging was evaluated by a 4-point scale. The data were expressed as % improvement from baseline. Significances and number of subjects are indicated in the figures. *LASTS* lactic acid sting test scores, *MLE* Multi-Lamellar Emulsion

DISCUSSION

Sensitive skin is a common skin disorder. The preventive and therapeutic regimens are limited although moisturizers are available [41–43]. In the present study, we showed that topical applications of these two products improved LAST scores, likely resulting from enhanced epidermal permeability barrier function in subjects with sensitive skin. Although both products contain stratum corneum lipids, which are known to improve epidermal permeability barrier in both normal and diseased skin [36, 37, 44], topical Atopalm MLE Cream induced a rapid improvement in epidermal permeability barrier after 2 weeks of treatment. In contrast, Physiogel Intensive Cream increased TEWL after 2 weeks of treatment. The mechanisms underlying the difference in the efficacy between the two products are unclear. However, several potential variations in the formulations could affect the efficacy. First, the effects of stratum corneum lipid mixture on epidermal permeability barrier are largely determined by the molar ratio of these lipids [36]. The molar ratio of these lipids could be different between these two products. Second, the composition of the lipid mixture can also affect the efficacy of the products. For example, linoleic acid is not only the structural requirement for barrier formation, but also activates peroxisome proliferator-activated receptor γ (PPAR γ) [45]. Activation of PPARγ stimulates epidermal lipid production and differentiation, both of which benefit epidermal permeability barrier [46]. The content of linoleic acid in cocos nucifera oil and butyrospermum parkii, sources of linoleic acid in Physiogel Intensive Cream, ranges 3–11% [47, 48] while olea europaea (Olive) fruit oil and vitis vinifera seed oil, ingredients in Atopalm MLE Cream, are enriched in linoleic acid (as high as over 70%) [49]. Third, both antioxidant (tocopheryl acetate) and hyaluronate, ingredients in Atopalm MLE Cream, benefit the epidermal permeability barrier [50–52]. Moreover, myristoyl/palmitoyl oxostearamide/arachamide MEA upregulates epidermal PPARα expression [53]. The latter is crucial for maintenance of epidermal permeability barrier function [54]. Moreover, activation of either PPARα or PPARγ inhibits cutaneous inflammation, which is a feature of sensitive skin [46, 55]. Thus, the different efficacy of these two products could be attributed to their compositional differences.

Although there were no untreated controls in the present study, the reduced TEWL value unlikely reflected spontaneous remission of disease due to the changes in humidity and/or environmental temperature. The study was carried from April (low humidity, spring) to August (high humidity, summer) during which environmental humidity and temperature gradually increased. Previous studies have shown that TEWL levels are lower in low humidity than in high humidity in both mice and humans [56, 57]. TEWL levels in humans are higher in summer than in winter [58]. However, our results show that TEWL levels were reduced after treatment. Thus, the reduction in TEWL is likely attributable to the products.

Previous studies have shown that disruption of the epidermal permeability barrier enhances percutaneous penetration of a substance [59, 60], and that enhancement of the epidermal permeability barrier can decrease cutaneous response to irritants [61] and improve inflammation [44]. In addition to facilitating percutaneous penetration of substances, a compromised permeability barrier alone can also provoke inflammation in sensitive skin. Thus, improved barrier function induced by

these two products may not only alleviate inflammation, but may also prevent substances from penetrating the skin, suggesting potential utilization of these products for the prevention and treatment of sensitive skin. The present study also showed that both products increased stratum corneum hydration, which is low in sensitive skin. Previous studies have demonstrated that moisturizers improve sensitive skin. Hence, the beneficial effect of these two products on stratum corneum hydration provides another rationale for their usage in treating sensitive skin. However, whether other products, such as diaper cream, cis-Urocanic Acid emulsion cream and Canoderm that improves epidermal permeability barrier in humans [62–64], also benefits sensitive skin, remains to be determined. Moreover, further clinical studies are required to validate the efficacy and safety of these products before they are widely recommended to patients with sensitive skin.

CONCLUSION

Barrier-enhancing products such as Atopalm MLE Cream and Physiogel Intensive Cream are effective for improving the epidermal permeability barrier, stratum corneum hydration and LAST scores. The benefits of barrier-enhancing products means that barrier-enhancing strategies could be a valuable approach for preventing and treating sensitive skin.

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Compliance with ethics guidelines. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The protocol of this study was approved by human research committee of Peking University First Hospital, Beijing, China. Informed consent was obtained from all individual participants in the study.

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