Clinical Study on Atopic Dermatitis and Skin Itchiness Using Cosmetics Containing Palmitoyl Oligopeptide-1, a Skin Penetrating Peptide and Intercellular Lipids

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Abstract: ***The purpose of this study was to conduct a clinical trial to improve atopy dermatitis and skin itching caused by dryness using cosmetics containing ceramide precursor (palmitoyl oligopeptide-1), skin penetrating peptide (arginine oligomer peptide, R6) and intercellular lipids (ceramide, cholesterol, essential fatty acid). In this research, skin moisturization measurements (Corneometer), trans-epidermal water loss (TEWL) measurement (Vapometer), researcher visual evaluation (Scoring Atopic Dermatitis, SCORAD, index), visual analog scale (VAS) evaluation (subjective itchiness), and normal photo shoot (DSLR) were used. This study was conducted on 23 adult females with dry skin aged 19~59 years. Clinical results was summarized as followed; 1) skin moisturization value significantly increased 2 and 4 weeks after the products use ($p<0.05$); 2) TEWL value significantly decreased 2 and 4 weeks after ($p<0.05$); 3) there was no significant differences of skin pH value 2 and 4 weeks ($p<0.05$); 4) there was no significant differences of skin temperature value 2 and 4 weeks after ($p>0.05$); 5) SCORAD Index evaluation value significantly decreased 2 and 4 weeks after ($p<0.05$); 6) VAS value significantly decreased 2 and 4 weeks after ($p<0.05$); 7) there was no skin adverse event reported after using the products during the study period. Therefore, the test products (Smato Intensive Calming Cosmetics) containing palmitoyl oligopeptide-1, an epidermal penetrating peptide (R6) and intercellular lipids are considered to have beneficial effects on improvement of atopic dermatitis and skin itchiness caused by skin dryness of 4 weeks use.***

Index Terms: Atopy Dermatitis, Skin Itchiness, Palmitoyl Oligopeptide-1, Intercellular Lipids, Skin Penetrating Peptide

I. INTRODUCTION

Dry skin is characterized by the lack of moisture in the stratum corneum and is a result of decreased water, which leads to abnormal desquamation of corneocytes [1]. The first clinical sign of skin dryness is a dull gray-while color and increased topographical skin markings [2]. As the drying worsens, the loss of water causes a loss of cohesiveness between the corneocytes. It is reported that patients with dry skin have a perturbation in the normal bilayer structure of lipids which is associated with increased fatty acid and decreased ceramide levels [3]. It was also shown that desmosomes remain intact at higher levels of the stratum corneum and desmoglein I levels remain elevated in the superficial stratum corneum of individual with dry skin as compared to controls. This occurs because the enzymes necessary for desmosome digestion are impaired when the water level is insufficient, which leads to abnormal desquamation, resulting in visible clumps of keratinocytes that cause the skin to appear rough and dry [4].

Atopic dermatitis is a disorder characterized by dry skin. Many studies suggest that an insufficient of ceramides in the skin is a factor in this condition [5]. However, in a study that looked at patients with xerosis, the deficiency in water holing properties was not accompanied by an insufficiency of ceramides [6]. Researchers also found that sebum levels did not play a significant role in the etiology of xerosis. They hypothesized that xerosis could be due to an aberration of the lamellar structures of intracellular lipids in the stratum corneum. This lipid composed of 40% ceramides, 25% fatty acids and 20 % cholesterol [7] and alterations in any these three components can cause a disruption in barrier function. For example, feeding mice with essential fatty acid deficiency a diet deficient in linoleic acid induces barrier disruption, likely by lowering ceremide levels [8] so it is obvious that essential fatty acids play an integral role in dry skin conditions. Also, lovastatin, an inhibitor of cholesterol synthesis, slows barrier recovery [9] and leads to a defect in barrier function when applied topically [10]. It is believed that no single lipid alone mediates barrier function and that normal levels of ceramides, cholesterol, and fatty acids are necessary to achieve an intact barrier. Several studies support this idea. It was shown that after altering the barrier with acetone, reapplication of ceramides and fatty acids alone, or a combination of ceramides and fatty acids, further delayed barrier recovery [11]. Only the application of a combination of ceramides, fatty acids, and cholesterol resulted in normal barrier recovery. A study by L'Oreal researchers demonstrated that total ceramides levels are decreased in skin xerosis [12,19,20,21,22,23,24].

Atopic dermatitis and skin itchiness have been a disease characterized by dry skin and several studies [7-12, 19-23] have suggested a lack of ceramide in the skin of patients with atopic dermatitis. To solve this problem, existing atopic cosmetic products contain ceramide which is a main component of intercellular lipids in cosmetics, and artificially

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intend to increase the content of ceramide in intercellular lipids. However, this method has a limitation in increasing the amount of ceramide in the intercellular lipid, and thus the efficiency is not high.

On the other hand, a few researches have suggested that cell-penetrating peptides (CPPs) can improve the transdermal delivery of various biomaterials [13-15]. Short arginine oligomers facilitated transport across the stratum corneum as applied topically to either mouse or human skin [16] so it was suggested that short arginine oligomers have the potential for skin penetrating peptides.

It was reported by the present authors [17] that the topically applied precursor of ceramide, palmitoyl oligopeptide-1, was incorporated into ceramide biosynthetic pathways in the epidermis, increasing stratum corneum ceramide levels and thereby improving barrier integrity. Also, it was recently represented by the present author [18] that transdermal absorption was enhanced when palmitoyl oligopeptide-1 are contained with a short arginine oligomer, R6.

In this study, we investigated clinical evaluation on improvement of atopic dermatitis and skin itchiness caused by skin dryness using cosmetics containing palmitoyl oligopeptide-1 as ceramides precursor, arginine oligomer (R6) as a skin penetrating peptide and intercellular lipids such as ceramide, cholesterol and essential fatty acid.

II. MATERIAL AND METHODS

A. Test Formulations

The cosmetics used in this test are “Smato Intensive Calming Cosmetics” manufactured by Dermafirm Co., Ltd., which consist of 6 products (foam cleanser, mist, essence, lotion, eco stick and care Stick). The main ingredients contained 500 ppm (0.05%) palmitoyl tripeptide-1 as ceramides precursor, R6 as a skin penetrating peptide (arginine oligomer peptide) and 0.6% ceramide III, 0.2% cholesterol, 0.1% docosahexaenoic acid (DHA) as intercellular lipids. The other ingredients contained 99.04% of emulsifier, oil, humectants, fragrance and deionized water in 6 products.

Palmitoyl tripeptide-1 and R6 were manufactured from Dermafirm Co., Ltd., in Korea and have a purity of at least 99.0%, respectively. Ceramide III (purity, 99.0%) is made by Doosan Biotech Co., in Korea and cholesterol (purity 99.0%) and DHA (purity 98.0%) were purchased from Sigma-Aldrich Co. in Korea.

B. Skin efficacy evaluation items

This study was conducted body efficacy evaluation [24,25,26] according to the Helsinki Declaration based on the Ethical Regulations, Ministry of Food and Drug Safety, Drugs, the Regulations of Cosmetics and Medical devices agency, the Standards for the Management of Pharmaceutical Clinical Trial, the Guidelines for the Human Application, the Guideline of Effective test of Cosmetics, the Guideline for the Validation of Cosmetics Indication and Advertisements, and the Guideline of Bioethics and Safety Act by the Ministry of Health and Welfare via KC Skin Research Center. The study was approved by the Institutional Review Board of KC Skin Research Center Co., Ltd., in Korea (KC-IRB-015).

According to above criteria, 23 women aged 19-59 who were voluntarily participated, have no acute or chronic systemic disease including skin disease, and eligible for follow-up were selected. The test schedule was conducted from November 23 to December 22, 2017, and measured at 0, 2, 4 weeks of use of the product.

C. Evaluation method

1) Skin moisture content measurement

Skin moisture content was measured using Corneometer (Courage, German) before the test product, 2 weeks after using the product, and 4 weeks after using the product on the itchy area by dryness. The average value measured 3 times each was used as a test data for skin moisture content. The unit of the measured skin moisture content is the A.U(Arbitrary Unit) and the measured value is proportional to the skin moisture content.

2) Trans-epidermal water loss (TEWL) measurement

Trans-epidermal water loss (TEWL) was measured using Vapomete (Delfin Technologies Ltd, Finlan) before using the product, after 2 weeks of product use and 4 weeks of product use on the itchy area by dryness. Measurements were performed once per site and the unit of measurement was g/m2h. The measured value indicated the degree of TEWL which means that the lower the measured value, the better TEWL.

3) Skin pH measurement

The skin pH is divided into acidic, normal, and alkaline and varies with gender, age or environment. The indicators are as follows (Table 1).

Table 1. The range of skin pH according to gender

pH	<3.5	4.0	4.3	4.5	5.0	5.5	5.7	6.0	>6.5
Female	Acidic			Normal			Alkaline		
Male	Acidic			Normal			Alkaline		

Skin pH measurement were made using skin pH meter (Courage, German) before the test product, 2 weeks after using the product, and 4 weeks after using the product on itchy area by dryness. The average value measured 3 times each was used as the skin pH evaluation data. The unit of measured pH of the skin is A.U (Arbitrary Unit). The lower the measured value, the higher the acidity, and the higher the measured value, the more alkaline skin. The change of skin pH before and after using the product and whether it was within the normal range was evaluated.

4) Skin temperature measurement

The skin temperature was measured using the Thermometer (Courage, German) before using the product, 2 weeks after using the product, and 4 weeks after using the product on itchy area by dryness.

The average values measured 3 times each were used as skin temperature evaluation data. Itchy skin by dryness has higher skin temperature than normal skin because of heat loss due to damage of epidermal layer. The unit of measured skin temperature is °C and the measured value is proportional to skin temperature, so that the lower the value, the better the skin temperature.

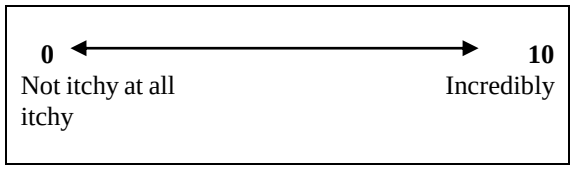
5) Visual assessment of researchers

The SCORAD Index (Scoring atopic dermatitis index) was evaluated before using the product, 2 weeks using the product, 4 weeks using the product, and used it as a material for assessing skin change. The subjects who were moderate or lower were selected as test subjects through the SOCRAD Index evaluation, and the smaller the values of the assessment, the better the skin.

6) Visual Analog Scale (VAS) evaluation (Analysis of improvement degree of skin irritation)

The Visual Analog Scale (VAS) evaluation directly assessed the degree of itching felt by the test subjects (Table 2). The subjects were asked to mark the degree of itchy skin by dryness between 0 and 10 before, after 2, 4 weeks of use and it was used as a numerical index for improving the assessment of skin itching.

Table 2. Visual Analog Scale (VAS) evaluation index



7) Evaluation of skin adverse reaction

If the test site shows any adverse reactions or other symptoms such as erythema, edema, stinging, burning, tightness, prickling, or irritability, it is stated on individual case report form (CRF) with degree of the symptom: mild, moderate, or severe.

D. Statistical Analysis Method

Statistical analysis of this study was performed using SPSS 23.0 for windows. Statistical significance was confirmed when $p < 0.05$ in 95% confidence interval.

1) Comparison before and after test product use (single measurement)

2) Paired samples T-test (parametric method) for the normality test and Wilcoxon signed ranks test (non-parametric method) for the non-compliance test were used.

III. Results and Discussion

A. Skin moisture content measurement

Changes in skin moisture content were assessed 3 times, including before using the test products (0 weeks), after 2 weeks (2), and after 4 weeks (4) of using the test products. Using the test products resulted in an increase of skin moisture content from 19.549 ± 4.736 before use, to 28.383 ± 7.927 after 2 weeks of use and to 32.793 ± 9.295 after four weeks (Table 3).

The degrees of skin moisture content in the second and fourth weeks were calculated as percentage to analyze improvement rate, by setting the skin moisture content after using test products as 100%. Skin moisture content increased by 46.456% after two weeks, while increased by 69.146% after four weeks (Table 3).

From these results, it was found that as results of measuring skin moisture content, the measurement value after 2 weeks and 4 weeks using this product were increased statistically (p<0.05) compared to before use (Table 3).

Table 3. Results of skin moisture measurement

Time	Average ± STD (A.U)	Improvement rate[a] (%)	Probability[b] (p value)
product use	19.549 ± 4.736	-	-
After 2 weeks	28.383 ± 7.927	46.456	0.000*
After 4 weeks	32.793 ± 9.295	69.146	0.000*

• Improvement rate[a] (%) = [(After product use –Before product use) / Before product use] x 100
• Probability[b] (p *value*) *: p<0.05 by Paired samples T-test

B. Trans-epidermal water loss (TEWL) measurement

The changes in Trans-epidermal water loss (TEWL) were measured 3 times, including before application (0 weeks), after 2 weeks, and after 4 weeks. Measurement of TEWL after use of the test products showed a decrease to 11.704 ± 5.734 after 2 weeks and 11.770 ± 6.817 after 4 weeks, from 14.170 ± 6.914 (Table 4).

In order to analyze the rates of improvements, when the degrees of change on the 2nd and 4th week were 100% based on the TEWL before the use of the products, the TEWL decreased by 16.247% after 2 weeks and 17.804% after 4 weeks (Table 4). Therefore, it was concluded that as results of measuring the TEWL, the measurement value after 2 weeks and 4 weeks using this product were decreased statistically (p <0.05) compared to before use.

Table 4. Results of trans-epidermal water loss measurement

Time	Average ± STD (g/m^2h)	Improvement rate[a] (%)	Probability[b] (p value)
roduct use	14.170 ± 6.914	-	-

After 2 weeks	11.704 ± 5.734	-16.247	0.000†
After 4 weeks	11.770 ± 6.817	-17.804	0.000†

• Improvement rate[a] (%) = [(After product use –Before product use) / Before product use] x 100
• Probability[b] (*p* value) † : $p<0.05$ by Wilcoxon signed ranks test

C. Skin pH measurement

As results of measuring skin pH, the measurement value after 2 weeks and 4 weeks using this product had no significant difference statistically ($p<0.05$) compared to before use (Table 5).

Table 5. Results of skin pH measurement

Time	Average ± STD	Improvement rate[a] (%)	Probability[b] (*p* value)
e product use	5.426 ± 0.492	-	-
After 2 weeks	5.393 ± 0.460	-0.308	0.696
After 4 weeks	5.429 ± 0.370	0.512	0.977

• Improvement rate[a] (%) = [(After product use –Before product use) / Before product use] x 100
• Probability[b] (*p value*) *: $p<0.05$ by Paired samples T-test

D. Skin temperature measurement

As results of measuring skin temperature, the measurement value after 2 weeks and 4 weeks using this product had no significant difference statistically ($p<0.05$) compared to before use (Table 6).

Table 6. Results of skin temperature measurement

Time	Average ± STD (° C)	Improvement rate[a] (%)	Probability[b] (*p* value)
luct use	29.907 ± 1.221	-	-
After 2 weeks	29.749 ± 1.409	-0.530	0.275
After 4 weeks	29.804 ± 1.284	-0.335	0.387

• Improvement rate[a] (%) = [(After product use –Before product use) / Before product use] x 100
• Probability[b] (*p value*) *: $p<0.05$ by Paired samples T-test

E. Visual assessment of researchers (SCORAD index)

The changes in the SCORAD index were measured 3 times, including before application (0 weeks), after changes in the SCORAD index were measured three times, before using the products (week 0), two weeks after using them (week 2), and four weeks after using them (week 4). The results showed that the SCORAD index decreased from 31.197 ± 6.455 to 16.736 ± 9.540 after 2 weeks and to 12.235 ± 10.949 after 4 weeks (Table 7, $p<0.05$).

Analysis of the rate of improvement in the SCORAD index revealed that the percentage of change between the 2nd and 4th weeks was 100% and the SCORAD index decreased by 48.498% after 2 weeks and 63.271% after 4 weeks (Table 7). Figure 1 shows clinical photographs of major subjects measured by SCORAD index (pictures taken by DSLR camera, DSR).

From these results, it was found that as results of visual assessment of researchers, the SCORAD index value after 2 weeks and 4 weeks using the products were decreased statistically ($p<0.05$) compared to before use (Table 7).

Table 7. Results of SCORAD index measurement

	Average ± STD (SI)	Improvement rate[a] (%)	Probability[b] (*p* value)
e product use	31.197 ± 6.455	-	-
After 2 weeks	16.736 ± 9.540	-48.498	0.000†
After 4 weeks	12.235 ± 10.949	-63.271	0.000†

• Improvement rate[a] (%) = [(After product use –Before product use) / Before product use] x 100
• Probability[b] (*p* value) †: $p<0.05$ by Wilcoxon signed ranks test

F. Skin itching improvement (the VAS value)

Changes in subjective assessment of improvement of itching were assessed 3 times, including before using the test products (0 weeks), after 2 weeks (2), and after 4 weeks (4) of using the test products.

Using the test products resulted in a decrease of the VAS value from 6.643 ± 2.127 before use, to 3.317 ± 2.393 after 2 weeks of use and to 1.665 ± 1.721 after four weeks (Table 8).

To analyze the rates of improvements, when the degrees of change on the 2nd and 4th week were 100% based on the VAS value before the use of the products, the VAS value decreased by 48.778% after 2 weeks and 73.938% after 4 weeks (Table 8). Therefore, it was concluded that as results of subjective assessment of improvement of itching after use of the test product, the VAS value after 2 weeks and 4 weeks using this product were decreased statistically ($p<0.05$) compared to before use (Table 8).

(a) Before product use (b) After 2 weeks (c) After 4 weeks

Figure 1. Clinical pictures of SCORAD index using DSLR

Table 8. Results of skin itching improvement

Time	Average ± STD (Grade)	Improvement rate[a] (%)	Probability[b] (*p* value)
product use	6.643 ± 2.127	-	-
After 2 weeks	3.317 ± 2.393	-48.778	0.000*
After 4 weeks	1.665 ± 1.721	-73.938	

• Improvement rate[a] (%) = [(After product use –Before product use) / Before product use] x 100

• Probability[b] (*p value*) *: $p<0.05$ by Paired samples T-test

G. Result of skin adverse reactions

In the test subjects, the presence of adverse skin reactions such as erythema, edema, scaling, itching, stinging, burning, tightness, ting (rickets, swelling, scurvy, itching, aching, burning, stiffness, tingling) among others was investigated every time subject presented themselves for analysis. No specific skin adverse events were observed in all subjects participating that participated in the present study (Table 9).

Table 9. Assessing skin adverse events

Time	Erythema	Edema	Scaling	Itching
After 2 weeks	-	-	-	-
After 4 weeks	-	-	-	-

Time	Stinging	Burning	Tightness	Prickling
After 2 weeks	-	-	-	-
After 4 weeks	-	-	-	-

Step=1: Weak, 2: Medium, 3: Severe

IV. CONCLUSIONS

This study focused on a clinical evaluation of improvement on atopy dermatitis and skin itching caused by dryness using cosmetics containing palmitoyl oligopeptide-1 for increase of ceramide levels in the stratum corneum, arginine oligomer peptide (R6) and intercellular lipids (ceramide, cholesterol and essential fatty acids). This study was performed on 23 adult females with dry skin aged 19~59 years for 2 and 4 weeks in dry skin area. Subjects were asked to wash with their skin the same cleanser and after 30 minutes of stabilization in an indoor environment maintained at constant temperature and humidity. In this study, skin moisturization measurements (Corneometer), trans-epidermal water loss (TEWL) measurement (Vapometer), researcher visual evaluation (SCORAD index), visual analog scale (VAS) evaluation (subjective itchiness of subjects), and normal photo shoot (DSLR) were used.

Clinical results can be summarized as follows: 1) as the results of skin moisturization after the products use, skin moisturization value significantly increased 2 weeks and 4 weeks after the products use ($p<0.05$); 2) as the results of TEWL after the products use, TEWL value significantly decreased 2 weeks and 4 weeks after the products use ($p<0.05$); 3) as the results of skin pH after the products use, there was no significant differences of skin pH value 2 weeks and 4 weeks after the products use ($p<0.05$); 4) as the results of skin temperature after the products use, there was no significant differences of skin temperature value 2 weeks and 4 weeks after the products use($p<0.05$); 5) as the results of researcher's visual evaluation after the products use, SCORAD index evaluation value significantly decreased 2 weeks and 4 weeks after the products use ($p<0.05$); 6) as the results of subjective evaluation of subjects for improvement of skin itchiness after the products use, VAS value significantly decreased 2 weeks and 4 weeks after the products use ($p<0.05$); 7) there was no skin adverse event reported after using the products during the study period.

Therefore, the test products containing ceramides precursor (palmitoyl oligopeptide-1), an epidermal penetrating peptide (R6) and intercellular lipids (ceramide, cholesterol and DHA) are considered to have beneficial effects on improvement of atopic dermatitis and skin itchiness caused by skin dryness of 4 weeks use.

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