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Equivalence evaluation of moisturizers in atopic dermatitis patients

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Synopsis

Skin care with moisturizers to compensate for dry skin and decreased barrier function, and to prevent recurrence of inflammation is thought to be very important for management of atopic dermatitis. However, many patients cannot continue the use of moisturizing medications because of unpleasantness. Cosmetics may be able to compensate for such deficiencies. To evaluate the usefulness of cosmetics in maintenance of the skin in remission, we conducted a clinical trial using moisturizing cosmetics of a phospholipid preparation that showed good moisture-retaining effect in dry skin. The utility of moisturizing cosmetics was evaluated by skin findings, subjective symptoms, adverse events, moisture content of the stratum corneum, transepidermal water loss (TEWL), and a questionnaire on feel of use in comparison with a heparinoid preparation as a control product. Degree of improvement in skin findings, dryness and desquamation score, pruritus score, TEWL, and moisture content were nearly the same as with the control product. The result indicated that the moisturizing cosmetic was of equivalent effect compared with the heparinoid control preparation.

INTRODUCTION

Atopic dermatitis (AD) is defined by the presence of pruritic eczema lesions with repeated remissions and exacerbations following a chronic course with diverse nonspecific stimulant reactions and specific allergic reactions due to physiological disorders of the skin, including skin dryness and barrier function abnormalities, arising from dysfunction of the stratum corneum.

Considering the pathophysiology of AD, skin care with moisturizers to compensate for dry skin and decreased barrier function and to prevent recurrence of inflammation is thought to be very important for addressing physiological abnormalities of the skin. The Guidelines for the Management of Atopic Dermatitis by the Japanese Dermatological Association also state the need for skin care with topical agents that do not include

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steroids or immunosuppressants (1). These topical agents include petroleum jelly, urea ointment, ointments containing heparinoid substances, zinc oxide ointment, and hydrophilic ointments. In 2007, Kawashima *et al.* (2) compared dermatitis relapse rates between a group of AD patients in remission who received a moisturizer (preparations containing heparinoid substances) and an untreated control group, showing that relapse of dermatitis could be prevented by topical application of the moisturizer.

Preparations containing heparinoid substances are widely used as a treatment for dryness in AD patients during remission, but many patients stop using these preparations for reasons such as unpleasantness of use, smell, or tactile feel of these moisturizing medications. As a result, inflammation recurs. Compliance with topical medications in remission periods is thus an issue in the treatment of AD. We therefore focused on how to continue the use of moisturizer in AD patients and thought that patient compliance could be improved using cosmetics that have moisture-retaining properties and are pleasant to use and offer a good tactile feel, and that this may lead to better quality of life (QOL) for patients by maintaining remission and controlling the skin condition. Cosmetics generally show moisture-retaining properties, and a variety of tactile feels suited to individual preferences can be obtained. Cosmetics with good texture also have the characteristic that they are more likely to be used over long term. Cosmetics may be able to compensate for the deficiencies of preparations with heparinoid substances, and are worth considering in the maintenance of remission phase of AD. Furthermore, the concept that skin care using moisturizer contributes to the prevention of not only AD but also other allergies, including food allergy or asthma, is widely accepted (3). Such moisturizing cosmetics as mentioned above are also suitable to use for allergy preventing skin care.

A test preparation was formulated from the perspective of pleasantness of use, tactile feel, easy to apply, and spreadability. Preparations with good moisture-retaining effects were also desired, so phospholipids were selected on the basis of the good moisture-retaining effects in dry skin diseases (4–6). We conducted a clinical evaluation of the efficacy of such a cosmetic with moisture-retaining effect in a randomized single-blind trial, and reported the results herein.

MATERIALS AND METHODS

This study was approved by the ethics committee at Keio University School of Medicine, Tokyo, Japan, on February 25, 2009, and was conducted from March 9, 2009 to April 19, 2010.

SUBJECTS

Subjects comprised AD patients examined in the Department of Dermatology at Keio University Hospital, who met the following inclusion criteria.

Inclusion criteria: subjects were taken from AD patients in remission (age, ≥20 to <65 years), in whom inflammation had subsided, in whom sites with main symptoms of dryness were present, and in whom the use of a moisture-retaining agent was considered appropriate.

Exclusion criteria: (i) patients with a history of frequent, severe skin symptoms with the use of cosmetics; (ii) patients with a history of hypersensitivity to preparations containing heparinoid substances; (iii) patients with hemorrhagic blood disease (hemophilia, thrombocytopenia, purpura, etc.); (iv) patients in whom serious consequences may occur with even minor bleeding; (v) patients receiving systemic treatment with oral corticosteroids or immunosuppressants for AD; and (vi) other patients judged by the physician as unsuitable subjects.

The trial was explained to the subjects in writing, and informed consent was obtained before enrollment. A total of 50 subjects were recruited in this study and assigned to two groups as described in TRIAL METHOD section.

TEST MEDICATIONS

The following two preparations were used in the trial. Moisturizing cosmetic: an oil-in-water (O/W)-type emulsion using a phospholipid emulsifier provided by KOSÉ Corporation (Tokyo, Japan). The main components of this moisturizing cosmetic other than phospholipid were glycerin, butylene glycol, squalane, cholesterol, and cetyl ethylhexanoate, which were listed in the Japanese Standards of Quasi-drug Ingredients. Control product: an O/W-type preparation (pharmaceutical product, Hirudoid® lotion; Maruho, Osaka, Japan) containing 3.0 mg/g of a heparinoid substance. The components other than heparinoid substance in the control product were glycerin, squalane, petrolatum, cetyl alcohol, carbomer, and so on.

TRIAL METHOD

Subjects were randomly assigned to a moisturizing cosmetic group and a control product group at a ratio of 1:1 and were asked to apply an appropriate amount of the respective preparation to the test site (forearm or abdomen) basically according to the finger-tip unit method (7) twice a day (morning and evening or after bathing) for 4 weeks. The subjects were observed at the start of the trial, after 2 weeks, and after 4 weeks (day of completion). When adverse reaction occurred, subjects were instructed to immediately discontinue the preparation and come to the hospital.

OBSERVATION ITEMS

Dryness and desquamation at subject sites were observed and evaluated using the criteria as: 0 (none), no dryness or desquamation; 1 (slight), very minor dryness or desquamation of the skin; 2 (mild), minor dryness or desquamation of the skin; 3 (moderate), obvious drying or desquamation of the skin; and 4 (severe), severe dryness or desquamation of the skin. Other findings were described on the observation form. Subjects were asked about itchiness at subject sites, and evaluations were made using the 5-point scale as: 0, almost no itchiness is felt; 1, sometimes feels a little itchy, but not enough to scratch; 2, sometimes reach and scratch lightly; 3, quite itchy and scratch even in front of other people; and 4, itches so much that one cannot remain still. The degree of improvement during

the trial period was determined according to the following criteria as: improved, obvious improvement is seen in skin findings including dryness, desquamation, and pruritus; somewhat improved, very slight to slight improvement is seen in skin findings including dryness, desquamation, and pruritus; unchanged, no change in skin findings including dryness, desquamation, and pruritus; and exacerbated, exacerbation of skin findings including dryness, desquamation, and pruritus.

Adverse reaction was observed and subjects were asked about subjective symptoms at 2 weeks from the start and at the completion of application. In cases of withdrawal, an evaluation was made at the time of discontinuation. The degree of safety was determined according to the following criteria as: safe, no side effects; almost safe, mild side effects, but use can be continued without treatment; some problem, side effects, but use can be continued with treatment; and problem, side effects requiring discontinuation.

Transepidermal water loss (TEWL) was measured using a VAPO SCAN AS-VT100RS® (Asahi Biomed, Tokyo, Japan), and skin surface conductance as an indicator of stratum corneum moisture content was measured using a Corneometer ASA-M2® (Asahi Biomed). Temperature and humidity at the measurement environment were 23.2° ± 1.0°C and 53.7 ± 5.1%, respectively.

A questionnaire on skin condition, feel of use with the test preparation, and QOL was administered to subjects on the day started (before application of preparation) and the day completed. The questionnaire was composed of multiple-choice and free-answer questions.

STATISTICAL ANALYSIS

Improvement and safety rates were calculated and a between-group comparison was performed using the Wilcoxon rank-sum test. Regarding skin finding (dryness and desquamation) score and pruritus score, a between-group comparison was made with the Wilcoxon rank-sum test for the change in scores between the start day and 2 and 4 weeks.

In measurements of TEWL and moisture content in the stratum corneum, the same measurement site was measured five times and outliers were excluded using the Smirnov test (significance level, 1%). The change of TEWL and moisture content before and after use was statistically evaluated using the Wilcoxon rank-sum test because of non-normal distribution. A between-group comparison of difference values (Δ) of TEWL and moisture content was carried out using Welch's *t*-test because of no equality of variance.

RESULTS

SUBJECTS

The age distribution of patients is shown in Table I. No differences were seen between groups in terms of age or sex of patients. No related complications were observed except for ichthyosis in one patient in the control product group. Levels of dryness/desquamation and pruritus at the start of the trial are shown in Tables II and III, respectively. No major differences were seen between both groups in the amount of variation and in the answer

Table I
Age Distribution of Subjects

	Number of subjects		
Age (years)	Overall	Moisturizing cosmetic group	Control product group
20–29	24	15	9
30–39	15	6	9
40–49	9	3	6
50–59	2	1	1
Mean age	32.3 ± 8.5	30.7 ± 8.2	33.9 ± 8.7

to the questionnaire before using the preparation. Of the 50 subjects, following four were excluded from statistical analysis: two stopped coming to the hospital (control product group), one used steroid on subject's own judgment to treat recurrence (control product group), and one discontinued use because of side effects, showing erythema and small papule in the test region 1 week after starting (moisturizing cosmetic group).

EVALUATION OF EFFICACY AND SAFETY

The usefulness of the test preparation was evaluated from the viewpoint of improvement, safety, dryness/desquamation, and pruritus. Results for improvement and safety are shown in Table IV. The number of subjects evaluated as "improved" or "somewhat improved" in both groups was almost the same. For safety, almost the same number of subjects evaluated as "safe" or "almost safe" was observed in both groups. No significant difference was seen between the groups in improvement or safety.

The results for dryness and desquamation are shown in Table II and trends during the trial are shown in Figure 1A. In both groups, the largest distribution range shifted from 2 points at the start of the trial to 0 points at the end of the trial (Table II). Significant improvements were seen in dryness and desquamation score compared with the score before use in both groups. Although no significant differences were seen between groups, no subjects showed 3 and 4 points in moisturizing cosmetic group.

Evaluation of pruritus is shown in Table III, and trends during the trial are shown in Figure 1B. In both groups, score was centered around 1–2 points before the start of the

Table II
Evaluation of Dryness and Desquamation

	Moisturizing cosmetic group		Control product group	
Score	Start of trial	End of trial	Start of trial	End of trial
0 (none)	0	15	0	11
1 (slight)	5	3	5	8
2 (mild)	15	6	14	2
3 (moderate)	5	0	4	1
4 (severe)	0	0	2	0

Values represent the number of subjects.

Table III
Evaluation of Pruritus

	Moisturizing cosmetic group		Control product group	
Score	Start of trial	End of trial	Start of trial	End of trial
0	2	15	2	12
1	11	4	10	8
2	12	5	11	2
3	0	0	2	0
4	0	0	0	0

Values represent the number of subjects.

trial, but the distribution shifted to 0 points by the end of the trial. Significant improvement was seen in both groups compared with the score before the start of the trial. No significant difference was seen between groups.

EVALUATION OF STRATUM CORNEUM FUNCTION

The TEWL value at the start of the trial in both groups showed the same distribution by Student's *t*-test. Change in TEWL values between before and after use was evaluated (Table V). In both groups, TEWL value decreased in three subjects and rose in more than half of the subjects. The mean value before and after use significantly changed in respective groups. Mean difference value (ΔTEWL) between both groups showed no significant difference.

The distribution equality of moisture content at the start of the trial between both groups was confirmed by Student's *t*-test. Change in moisture content before and after use was also compared (Table VI). An increase in moisture content was seen in nearly 60% of subjects in both groups. Comparison of mean values before and after use showed that the moisture content was significantly increased in respective groups. In a comparison of difference of values (Δ moisture content) before and after use, no significant difference was seen between groups.

Table IV
Evaluation of Improvement and Safety

Improvement			Safety		
	Moisturizing cosmetic group	Control product group		Moisturizing cosmetic group	Control product group
Improved	15	13	Safe	23	22
Somewhat improved	6	7	Almost safe	0	0
Unchanged	2	2	Some problem	1	0
Exacerbated	2	0	Problem	1	0
Significance test	Not significant		Significance test	Not significant	

Values represent the number of subjects.

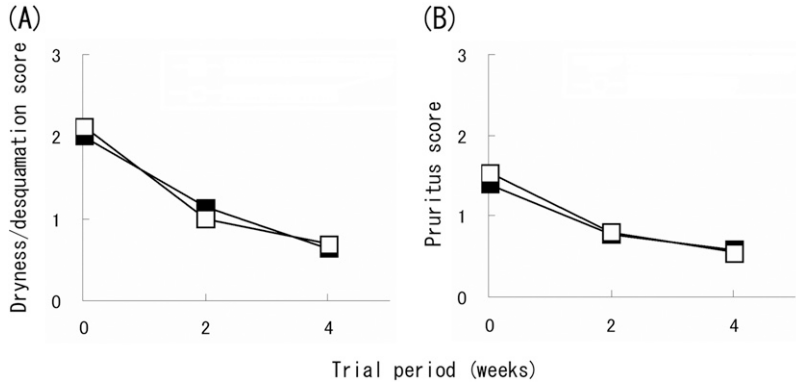

Figure 1. Trends in dryness/desquamation and pruritus during the trial. (A) dryness/desquamation, (B) pruritus. Closed and open squares indicate moisturizing cosmetic group and control product group, respectively.

SUBJECT QUESTIONNAIRE

For questionnaire items regarding feel of use, some differences were seen between groups, although there was no major difference. "Spreadability" was more highly evaluated in the moisturizing cosmetic group, whereas the control group got a little higher score in "stickiness" and "tightness." With regard to the skin condition after use for 1 month, the proportion of subjects who responded "improved" or "a little improved" was higher in the moisturizing cosmetic group than in the control product group. From a questionnaire regarding further use of the respective preparations, subjects who would like to continue use tended to feel improvements in moisture and dryness and to report good pleasantness of use of the preparation.

In free answers before use, many subjects provided favorable responses to the use of cosmetics as one part of treatment, stating that this would help to maintain the condition of their skin. On the other hand, negative opinions were also seen, such as the idea that medications are more reliable.

In the evaluation of QOL, an upward tendency was seen in several categories, including "evaluation of sleep," especially in moisturizing cosmetic group.

DISCUSSION

In this study, we thought that use of a moisturizing cosmetic with superior moisture-retaining properties for dryness symptoms of AD patients in remission together with pleasantness of use and good tactile feel would promote continuation of use and give a

Table V
Change in TEWL Values before and after Use

	Improved	Unchanged	Exacerbated	Total number of analysis subjects
Moisturizing cosmetic group	3 (13%)	7 (29%)	14 (58%)	24
Control product group	3 (14%)	7 (32%)	12 (54%)	22

The subject with a change of less than 1 of TEWL value was defined as "unchanged."

Table VI
Comparison of Number of Subjects with Moisture Content Improvement after Use

	Improved	Unchanged	Exacerbated	Total number of analysis subjects
Moisturizing cosmetic group	14 (58%)	6 (25%)	4 (17%)	24
Control product group	13 (59%)	3 (14%)	6 (27%)	22

The subject with a change of less than 1 of moisture content was defined as "unchanged."

greater degree of freedom in the selection of a moisturizing agent. Such results would lead to maintenance of remission and better QOL in AD patients. We thus conducted a 4-week continuous application trial with a moisturizing cosmetic and compared the results with a widely used moisturizing medication as a control.

This study showed that no apparent significant differences in both groups were observed in improvement, moisture content, safety, and questionnaire, indicating the equivalence of two test samples. Because control product was a pharmaceutical product, this study indicates the possibility of usefulness of moisturizing cosmetics in support for AD treatment. This is an important finding to give a clue to a novel role of cosmetics.

In the questionnaire at the completion of the trial, many subjects thought that the moisturizing cosmetic was good in the feel of use and that QOL was improved. Moisturizing cosmetics may thus help to maintain the skin condition of AD patients in remission and contribute to emotional recovery. However, subjects in the moisturizing cosmetic group felt that the sample had a "sticky" feel. These results indicated that there was room for improvement in product development.

The beneficial effects of moisturizing cosmetics in AD patients have been demonstrated so far (8,9). The significance of this study is to demonstrate the usefulness of moisturizing cosmetics for the maintenance of remission phase of AD by comparison study with a heparinoid pharmaceutical preparation as a control. Given these findings, the moisturizing cosmetic in this study displayed no special problems in terms of efficacy and safety in comparison with existing Hirudoid® lotion. This study focusing on how to continue the use of moisturizer may provide a new option for AD patients as a topical agent with which better compliance can be expected. Regarding allergy prevention by skin care, some reports have been published, but there are little reports of suitable cosmetics with appropriate moisturizing effect and safety (10,11). Our moisturizing cosmetics showed both moisturizing effect and safety in comparison with medical moisturizers. For allergy prevention purpose, cosmetics are more preferable than medicines because moisturizers are applied to normal skin but not affected skin in many cases. This study gives a clue to a novel role of cosmetics with taking advantage of their characteristics.

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