The Clinical Efficacy of a Multi-Lamellar Emulsion Containing Pseudoceramide in Childhood Atopic Dermatitis: An Open Crossover Study

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Background: **The abnormal barrier function in atopic dermatitis(AD) is caused by a reduction in the amounts of ceramides in the intercellular lipids in the stratum corneum(SC). Replenishing the SC via the topical application of ceramides and pseudoceramides leads to effective recovery of the barrier function of skin.**

Objectives: **An open clinical crossover evaluation was conducted to investigate the effects in AD of a multi-lamellar emulsion(MLE) that contained pseudoceramide(PC-9S)**

Methods: **The study group included 30 AD patients(average age: 4.4 yr, range: 1-8 yr), who applied MLE or a commercial moisturizing cream(CMC, 5% urea) alternately for four weeks each. We divided the subjects into two subgroups and started with different treatments in each subgroup. Treatment efficacy was evaluated using the average subjective satisfaction scores for each symptom and the global clinical response. In addition, the SCORAD(Scoring AD) index was adopted to evaluate the severity of AD as objectively as possible. The patients were evaluated using this index every other week.**

Results: **Although the SCORAD improved in both subgroups, the patients had better results ($p<0.05$) when applying MLE(31-35% decrease) than CMC(13% increase to 14% decrease). The subjective satisfaction scores of the symptoms and signs of patients, including itching, erythema, and dry skin, were higher in the MLE group than in the CMC group, and the global response to treatment was also better in the MLE group. During the follow-up period, AD improved in all patients. MLE was more effective than CMC in our patients.**

Conclusions: **The topical application of a multi-lamellar emulsion containing pseudoceramide is an effective regimen for improving symptoms of AD.**

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Key Words : Atopic dermatitis, Multi-lamellar emulsion containing pseudoceramide

The stratum corneum(SC) of the skin is one of the main barriers to harmful agents in the external environment[1]. The barrier function of skin results from a combination of corneocytes and intercellular lipids, which form multi-lamellar structures[2,3]. In atopic dermatitis(AD), abnormal barrier function results from disruption of the multi-lamellar structure due to a significant reduction in the amounts of ceramides of the intercellular lipids in the SC[4-6]. Replenishing the SC via the topical application of ceramides restores the barrier function, as shown by a significant reduction in the SCORAD scores and trans-epidermal water loss (TEWL) levels of

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AD patients[7,8]. Recently, a new multi-lamellar emulsion (MLE) containing pseudoceramide was developed, which has an ordered structure very similar to the multi-lamellar pattern of the intercellular lipids of the SC[9,10]. Moreover, it contributed to the recovery of the damaged skin barrier by restoring the SC intercellular lamellar structures better than placebo[11,12].

This study examined the clinical efficacy of this topical MLE containing pseudoceramide in childhood AD patients from 1 to 8 years of age. We designed an open crossover assessment comparing MLE containing PC-9S with a commercial moisturizing cream (CMC) containing 5% urea. The patients' clinical response to treatment was assessed subjectively, using a visual clinical examination, and objectively using the SCORAD index[13].

PATIENTS AND METHODS

Inclusion and exclusion of cases

Thirty patients with a diagnosis of AD, with intermittent or persistent symptoms for at least six months as determined by Hanifin's criteria[14], were studied. The following patients were excluded from the study: patients currently being treated with systemic glucocorticosteroids or cyclosporine, those treated with UV irradiation, and those unable to continue without minimal application of low-potency topical steroids to severe eczematous lesions. The male-female ratio was 1.5:1(Table 1). The patients averaged 4.4 years old, and ranged from 1 to 8 years.

Study design

After informed consent had been obtained, the patients were randomly assigned to one of two groups. The formulations applied topically were an MLE containing PC-9S(a trade name for the pseudoceramide with the INCI name myristyl/palmityl oxostearamide/arachamide MEA[9]; Neopharm Co., Ltd., Daejeon, Korea) and a commercial moisturizing cream(CMC, polidocanol and 5% urea Optiderm cream). In Group A, MLE was applied for four weeks, and this was followed by a crossover to CMC for four weeks after a short washout period (1-2 days). The schedule of topical application was reversed in Group B. All of the subjects applied MLE or CMC topically to the whole body twice per day, and were allowed to take antihistamines as needed.

Table 1. Base demographic characteristics of study groups

Characteristics	Group A (n = 16)	Group B (n = 11)
Age in years(SD)	4.9 2.3	3.8 1.7
Maximum	8	8
Minimum	1	2
Sex		
Male	11	5
Female	5	6
Severity(SCORAD)	44.9 16.9	39.2 14.9
Maximum	74	79
Minimum	15	26

One physician observed and assessed the patients biweekly throughout the trial. First, the clinical response to treatment was assessed subjectively, using 10 visual scales in which the patients' parents scored the atopic symptoms and signs, including itching, erythema, and dry skin at home. In addition, the parents also determined the global response to treatment using the following five-item scale: 0 = aggravated, 1 = no change, 2 = mildly improved, 3 = moderately improved, 4 = marked improvement. To objectively assess the clinical response to treatment, the SCORAD index was adopted. The SCORAD index was calculated from the involved surface area, intensity, and subjective symptoms[9]. Moreover, the clinical response to treatment was reported as the efficacy of treatment determined by the formula:

Efficacy(%) = (1 - (SCORAD at present visit / SCORAD scores at previous visit)) × 100

Statistical methods

A paired t-test and analysis of variance (ANOVA) were used to verify the significance of the differences in scores or scales between Groups A and B during the follow-up period.

RESULTS

Thirty patients were enrolled in the study. During the follow-up period, one patient applying CMC withdrew after two weeks of treatment because of worsening skin lesions. Two patients applying CMC withdrew after four weeks for personal reasons. Consequently, data were recorded for 27 subjects (Table 1, 16 boys, 11 girls; mean age: 4.4 yr, range: 1-8 yr).

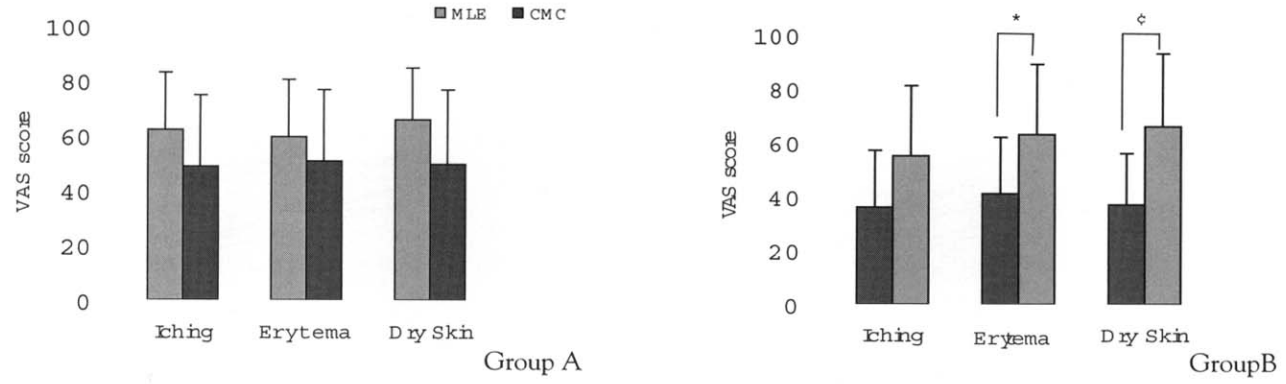

Fig. 1. The satisfaction scores(VAS scores) of the MLE versus CMC on clinical symptoms such as itching, erythematic change, and dry skin in Group A(upper panel) and B(lower panel). *p = 0.028, p = 0.007.

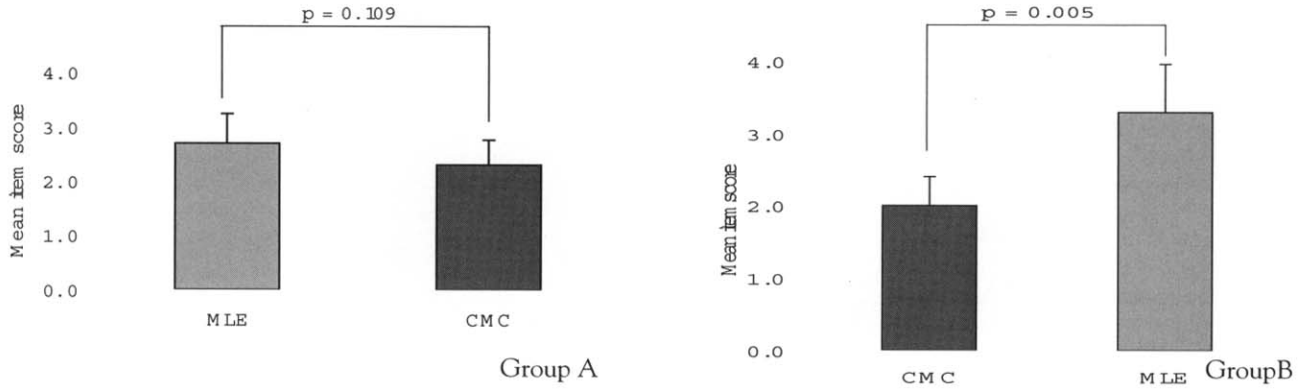

Fig. 2. Global response(mean items scores) to treatment in Group A(upper panel; p = 0.109) and B(lower panel; p = 0.005).

Subjective assessment

1. The satisfaction scores for clinical symptoms and signs

Twenty-seven patients finished the eight-week study. The satisfaction scores for the ability of MLE and CMC to resolve clinical symptoms, such as itching, erythema, and dry skin, are listed in Fig. 1. There was a significant difference in subjective scoring of the clinical response to MLE and CMC in the two groups. After eight weeks of treatment, the respective satisfaction scores for itching, erythematic change, and dry skin in Group A were 62, 59, and 66 points in the MLE subgroup, and 49, 51, and 50 points in the CMC subgroup. In Group B, the respective scores were 55, 63, and 66 points in the MLE subgroup and 36, 41, and 37 points in the CMC subgroup. The efficacy of MLE was superior to that of CMC in both groups, although the difference was significant only for erythematic change(p=0.028) and dry skin(p=0.005) in Group B.

2. Global response

The efficacy of MLE versus CMC with respect to the global response to treatment is compared in Fig. 2. After four and eight weeks, the global response to treatment in the patients that applied MLE was superior in Groups A(MLE: CMC=2.7: 2.3) and B(CMC: MLE=2.0:3.3), and the difference was statistically significant in Group B (p=0.005).

Objective assessment

After the clinical trial, the SCORAD scores decreased in most of the patients in Groups A(12/16patients) and B(11/11 patients)(Fig. 3). In Group A, after four weeks of treatment with MLE the decrease in the SCORAD scores(31%) from

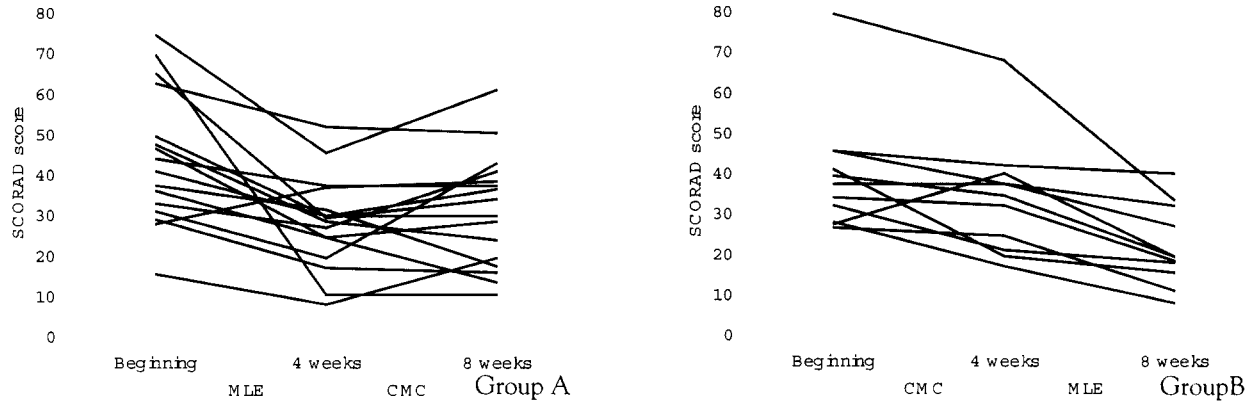

Fig. 3. Individual SCORAD scores before and after application in Group A(n=16) and B(n=11).

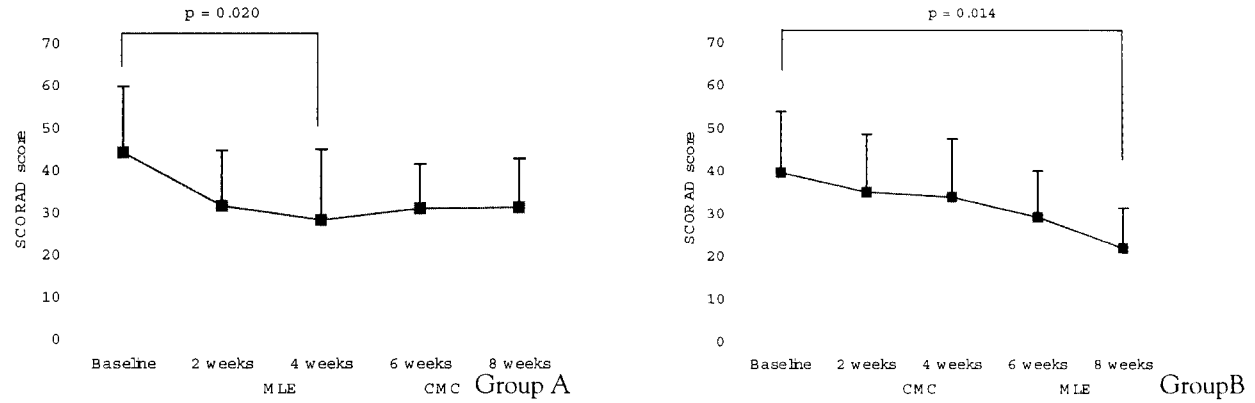

Fig. 4. Mean SD of SCORAD scores in both groups.

baseline was statistically significant(p=0.020), and the SCORAD scores increased slightly(13%) after switching to CMC. In Group B, the scores decreased from baseline with CMC(14%) after four weeks, and decreased further with MLE (35%), although after eight weeks only the effect of MLE was statistically significant(p=0.014). The efficacy of each of the treatments is summarized in Table 2; the difference in the efficacy of MLE and CMC was statistically significant in both groups(p=0.01 and p=0.05).

Table 2. Comparison between clinical efficacy of MLE and CMC subgroups

	Group A(n=16)		Group B(n=11)	
	MLE	CMC	CMC	MLE
Efficacy(%)	31	-13	14	35
P-value	0.01		0.05	

Adverse effects

Although two patients using CMC complained of a slight burning sensation during the first week of application, this was not considered an adverse effect, because they did not complain of this subsequently.

DISCUSSION

In this analysis of two independent eight-week studies with an open crossover design, AD patients applying MLE had better results in the objective assessment than those applying CMC. The subjective satisfaction scores for symptoms and signs, including itching, erythema, and dry skin, were also higher when applying MLE, and the global response to treatment was better with MLE. The application of MLE containing pseudoceramide significantly improved the clinical symptoms and

signs of atopic dermatitis.

Atopic dermatitis is a chronic relapsing eczematous dermatitis that is commonly associated with immunologic or barrier dysfunction[14,15],. Although topical corticosteroids and other immunosuppressive agents are the mainstays of AD therapy, prolonged use of these agents has potential risks in preadolescent children[15]. Therefore, useful, long-term therapy with safety is indispensable for the treatment of AD[15].

Moisturizing creams are used to increase skin hydration. Recent findings indicate that topical treatments with moisturizers prevent persistent dermatitis by reducing elevated TEWL[16,17]. Since normalization of TEWL is thought to mitigate the cytokine cascade, moisturizers have been described as steroid-sparing agents. Chamlin *et al*[8] recently reported that ceramide-dominant, barrier-repair lipids alleviate childhood atopic dermatitis, and attribute the improvement seen in their patients to a normalization of barrier function, which in turn dampened the cytokine cascade that initiates and sustains AD.

In this study, we compared the clinical efficacy of MLE containing pseudoceramide with CMC containing 5% urea. Urea is a humectant that increases skin hydration by attracting water. Loden *et al*[18] reported that a urea-containing moisturizer improved skin barrier function in atopic dermatitis and reduced skin susceptibility to irritants. However, they were unable to demonstrate the precise mechanism of this improvement. Unlike urea, MLE is potentially incorporated into the damaged lamellar structure and restores the skin barrier in AD[11]. In a previous study, MLE containing pseudoceramide was reported to produce faster recovery of the damaged skin barrier by effectively restoring the SC intercellular lamellar structures relative to placebo, which suggested the potential clinical use of MLE cream in chronic barrier abnormalities, such as AD and psoriasis[11]. Furthermore, MLE application significantly decreased the TEWL and skin pH after four weeks of application[12]. These results demonstrate the potential efficacy of a newly developed multi-lamellar emulsion (MLE) containing pseudoceramide in childhood AD. In this study, we demonstrated that topical MLE resulted in better improvement than topical CMC in childhood AD patients.

REFERENCES

1. Leung DYM, Rhodes AR, Geha RS, Schneider L et al. Atopic dermatitis. In: Fitzpatrick TB, Eisen AZ, Wolff K, Freedberg IM, Austen KF eds. Dermatology in general medicine, 4th ed. New York : McGraw-Hill, 1993; 1543-1564.
2. PM Elias. Lipid and the epidermal permeability barrier. Arch Dermatol Res 1981; 27: 95-117.
3. PM Elias. Epidermal lipids, membranes, and keratinization, Int J Dermatol 1981; 20: 1-19.
4. Williams HC: Is the prevalence of AD increasing? Clin Exp Dermatol 1992; 17: 385.
5. Ogawa H, Yoshiike T. a speculative view of AD: barrier dysfunction in pathogenesis. J Dermatol Sci 1993; 5: 197-204.
6. Imokawa G, Abe A, Jin K, Higaki Y et al. Decreased level of ceramides in stratum corneum of AD: an etiologic factor in atopic dry skin? J Invest Dermatol 1991; 96: 523-526.
7. Tatsuya H. An open clinical trial of glycoceramide-containing cream and lotion on dry skin of atopic dermatitis. Skin Research 1998; 40: 415-419.
8. Chamlin SL, Frieden IJ, Fowler A, Williams M et al. Ceramide-dominant, barrier-repair lipids improve childhood atopic dermatitis. Arch Dermatol 2001; 137: 1110-1112.
9. Park BD, Lee M, Kim Y, Youm JK. Synthesis of N-ethanol-2-(myristyl/palmityl)-3-oxo(stearamide/arachidamide) and its physical properties for a cosmetic raw materials. J Cosmet Sci 2000; 51: 253-262.
10. T Suzuki, J Fukasawa, H Iwai, Surgai et al. Multilamellar emulsion of stratum corneum lipid formation mechanism and its skin care effects. IFSCC Yokohama 1992; 13-28.
11. Park BD, Youm JK, Jeong SK, Choi EH et al. The Effectiveness of multi-lamellar emulsion(MLE) on damaged skin. Conference Proceedings of PCIA 2001; 125-134.
12. Park BD, Youm JK, Lee SH. The clinical efficacy of multi-lamellar emulsion(MLE) contained pseudoceramide(PC-9S) on atopic dermatitis. The JSBR 2001; 3: 81-89.
13. European task force on atopic dermatitis. Severity scoring of atopic dermatitis: the SCORAD index. Consensus report of the European task force on atopic dermatitis. Dermatology 1993; 186: 23-31.
14. Hanifin JM, Rajka RG. Diagnostic features of atopic dermatitis. Acta Derm Venereol 1980; 92: 44-47.

15. Cooper KD. Atopic dermatitis: recent trends in pathogenesis and therapy. J Invest Dermatol 1994; 102: 128-137.
16. PM Elias, LC Wood, KR Feingold. Epidermal pathogenesis of inflammatory dermatoses. Am J Contact Derm 1999; 10: 119-126.
17. M Loden, AC Andersson. Effect of topically applied lipids on surface-irritated skin. Br J Dermatol 1996; 134: 215-220.
18. M Loden, AC Andersson, M Lindberg. Improvement in skin barrier function in patients with atopic dermatitis after treatment with a moisturizing cream(Canoderm). Br J of Dermatol 1999; 140; 264-267.