ORIGINAL ARTICLE

# Pseudoceramide for childhood eczema: does it work?

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**Objectives** Atopic eczema is a chronic relapsing skin disease associated with atopy, and characterised by reduced skin hydration, impaired skin integrity (transepidermal water loss), and poor quality of life. Proper emollient usage is an important facet of its management. This study aimed to establish an approach to evaluate the efficacy of using an emollient over a 4-week period.

**Design** Prospective observational study.

**Setting** A paediatric dermatology out-patient clinic of a university teaching hospital in Hong Kong.

**Patients** Consecutive new patients aged 5 to 18 years with atopic eczema diagnosed according to Hanifin and Rajka's criteria were recruited from March to August 2009. They or their parents were instructed to liberally apply the test emollient to the flexures and areas affected with eczema, twice daily. Outcome assessments were repeated 2 and 4 weeks later.

**Main outcome measures** Skin hydration and transepidermal water loss in the right forearm (2 cm below antecubital flexure), and disease severity (SCORing Atopic Dermatitis index) and Children's Dermatology Life Quality Index. At the end of the study period, a global assessment of treatment was recorded.

**Results** Thirty-three patients with atopic eczema were recruited and treated with applications of a pseudoceramide-containing cream (Curel, Kao, Japan). The mean age of the patients (16 males and 17 females) was 12 (standard deviation, 4) years. Four weeks following the use of the cream, skin hydration improved significantly and fewer patients were using topical corticosteroids. In these patients, there was no deterioration in transepidermal water loss, eczema severity, or quality of life.

**Conclusion** The pseudoceramide cream improved skin hydration but not severity or quality of life over a 4-week usage.

## Introduction

Atopic eczema (AE) is a chronic, relapsing, inflammatory skin disease commonly associated with atopy.[1-3] It typically presents in early childhood and is associated with dryness of skin, pruritus, and involvement of the skin flexures. In practice, there are two important facets to its management, namely, topical and systemic measures. Skin hydration (SH) and integrity are important parameters to objectively quantify AE. Many clinical scores, such as the SCORing Atopic Dermatitis (SCORAD), use crude clinical parameters (absent vs mild vs moderate vs severe dryness) and lack objectivity.[4-7] In recent years, SH and transepidermal water loss (TEWL) have been objectively measured in various sites including the antecubital fossae, forearm, face, abdomen, and the leg.[8-15] There is no unified opinion as to which site should be standardised for evaluation. We recently tested three popular sites in the anterior forearm and found that they were all convenient for standardised measurement of SH and TEWL. Moreover, these measurements correlated well with AE severity and may be used to evaluate therapeutic recommendations.[16,17]

It is debated whether eczema is a skin disease with systemic atopic associations or primarily a systemic disease with skin manifestations. In the brick-and-mortar hypothesis, the stratum corneum (the outermost layer of the epidermis) normally consists of fully differentiated corneocytes surrounded by a lipid-rich matrix containing cholesterol, free fatty acids, and ceramide; the structure of this matrix closely resembles that of bricks and mortar in a wall. In AE, lipid metabolism is abnormal, causing a deficiency of ceramide

**Key words**
Child; Dermatitis, atopic; Eczema; Emollients; Water loss, insensible

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that leads to TEWL.[3,18,19] The underlying genetic deficit might be due to a null mutation in the filaggrin gene.[20] In the management of AE, regular use of emollients is often recommended. Despite claims about their efficacy, little evidence has demonstrated their short- or long-term usefulness. In a previous study,[17] we demonstrated one emollient could improve SH but not TEWL or overall disease severity following its regular use for 2 weeks. The purpose of this study was to establish a research approach to test whether a 4-week use of a pseudoceramide-containing emollient was efficacious in improving the clinical and biophysiological properties of the skin in AE patients.


## 假性神經醯胺治療兒童濕疹是否可行？

**目的** 異位性濕疹是一種慢性復發性皮膚病，與特應原有關。患者會出現皮膚乾燥、皮膚屏障功能損失（經表皮水分丟失）及生活質素下降。適當使用潤膚膏是控制此病重要的一環。本研究評估連續4星期使用一種潤膚膏的效果。

**設計** 預後觀察性研究。

**安排** 香港一所大學教學醫院內的小兒皮膚門診部。

**患者** 根據Hanifin及Rajka對異位性濕疹的診斷作準則，從2009年3月至8月期間所有5至18歲被首次診斷異位性濕疹的兒童參與本研究。參與的兒童或其家長按指引在患處及交接部位塗上一種潤膚膏，每日兩次，然後分別在兩個及四個星期後進行結果評估。

**主要結果測量** 右前臂處（肘前窩下的2 cm）的皮膚水分及經表皮水分丟失的情況、疾病嚴重程度（異位性皮炎指數：SCORAD），以及兒童皮膚病生活質量指數。研究結束前會對治療方法進行整體性評估。

**結果** 參與研究的共有33名（16男，17女）異位性濕疹小兒患者，他們平均年齡12歲（標準差4歲）。患者使用一種假性神經醯胺（Curel）的潤膚膏，4星期後發現皮膚水分明顯有改善，只有少部分患者仍須外敷類固醇。經表皮水分丟失、濕疹嚴重程度及生活質素並沒有出現惡化的情況。

**結論** 使用假性神經醯胺潤膚膏4星期後，異位性濕疹患者皮膚水分有改善，但濕疹嚴重程度及生活質素則未見改變。


## Methods

Consecutive new patients aged 5 to 18 years with AE diagnosed according to Hanifin and Rajka's criteria[21] were recruited from the paediatric dermatology out-patient clinic of a university teaching hospital. Subjects were excluded if they had non-specific dermatitis.

We have previously described our method of standardising measurements of SH and TEWL.[16,17] After acclimatisation in the consultation room with the patient sitting comfortably in a chair for 20 to 30 minutes, SH (in arbitrary units) and TEWL (in $g/m^2/h$) were then measured according to manufacturer's instructions with the Mobile Skin Center MSC 100 equipped with a corneometer CM 825 (Courage & Khazaka electronic GmbH, Cologne, Germany), and a Tewameter TM 210 probe (Courage & Khazaka electronic GmbH). We documented that a site 2 cm distal to the right antecubital flexure was optimal for standardisation. Oozing and infected areas were avoided by moving the probe slightly sideways.[22] The clinical severity of AE was assessed with the SCORAD index[4,23-25] and quality of life with a validated Chinese version of the Children's Dermatology Life Quality Index (CDLQI).[5,26] Children were given a liberal supply of a pseudoceramide-containing emollient (Curel, Kao, Japan) that was pre-weighed.[27] The cream contained 8% synthetic pseudoceramide. The patients were instructed not to use any other topical treatment other than their usual corticosteroid on an as-necessary basis. They were encouraged to use the pseudoceramide cream twice daily on the flexures and areas with eczema. In case the emollient effect was not sufficient, they could use their usual emollient and medications but the frequency of such use was to be reported. The patients were reviewed at the end of 2 and 4 weeks, and the amount of pseudoceramide-containing emollient supplied and used was recorded by weighing the returned containers with the same electronic scale. Measurements of SCORAD, CDLQI, SH, and TEWL were repeated. Patient weight and height were determined for body surface area (BSA) computation. Acceptability of the emollient was rated as very good, good, fair, and poor. Data were expressed as means and standard deviations (SDs). Changes in clinical parameters (objective SCORAD, pruritus score, sleep loss score, CDLQI, SH, and TEWL) with the BSA-adjusted use of Kao cream were analysed by repeated measures analysis of variance (SPSS, Chicago, US). The correlations between SCORAD components, SH, and log-transformed TEWL were analysed by Pearson correlation coefficients: at baseline, and after treatment for 2 weeks and 4 weeks. Categorical data were compared using the $\chi^2$ test. All comparisons were two-tailed, and P values of less than 0.05 were considered significant. Informed written consent was obtained from parents before recruitment. Ethical approval was obtained from the Clinical Research Ethics Committee of the Chinese University of Hong Kong.

## Results

The study was conducted from March to August 2009. A total of 33 eligible patients with AE (16 males and 17 females; mean age 12 years, SD 4 years) were consecutively recruited. Prior to recruitment, the patients had only been using topical emollients, and

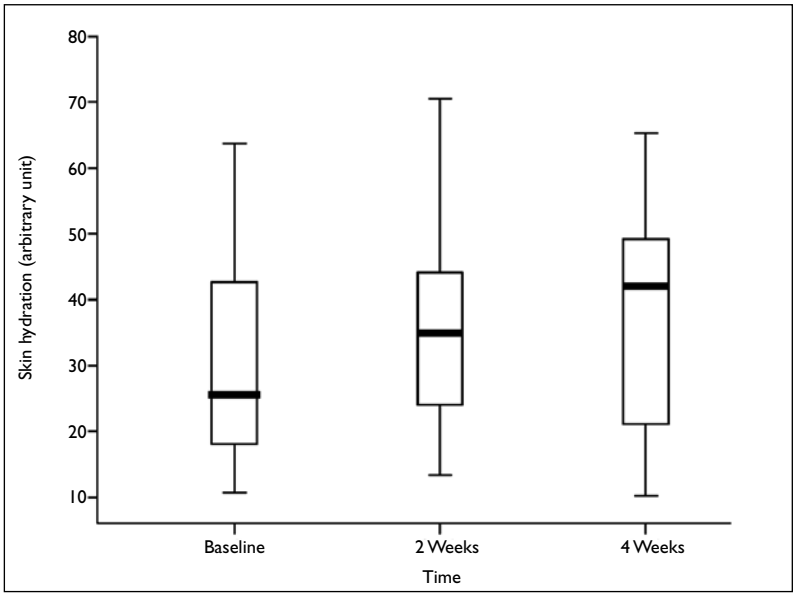


**FIG 1. Change of skin hydration compared with baseline (P=0.083 at 2 weeks and P=0.016 at 4 weeks)**

The horizontal lines within the boxes denote the medians, the lower and upper bounds of the boxes denote the 25th and 75th percentiles, and the I bars denote the 5th and 95th percentiles

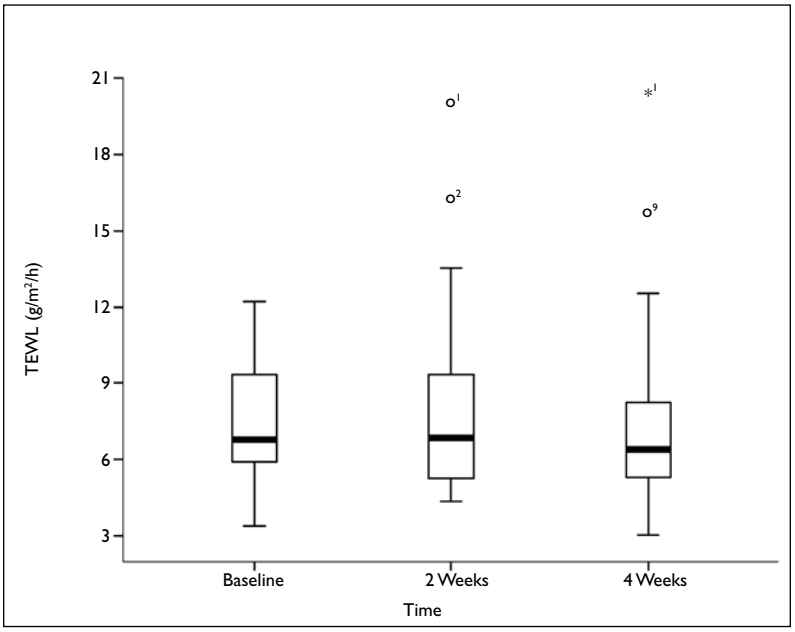


**FIG 2. Change of transepidermal water loss (TEWL) compared with baseline (P=0.029 at 2 weeks and P=0.808 at 4 weeks)**

Each open circle denotes an extreme value beyond 1 standard deviation (SD); the asterisk denotes an extreme value beyond 2 SDs. Medians and quartiles are calculated excluding the outliers. The number next to the circles and asterisk identifies the patients; cases coded 1, 2, and 9 show abnormal changes in TEWL. The horizontal lines within the boxes denote the medians, the lower and upper bounds of the boxes denote the 25th and 75th percentiles, and the I bars denote the 5th and 95th percentiles

corticosteroids (n=20) on an as-need basis. They were all atopic with elevated immunoglobulin E levels and a personal or family history of atopy. At baseline, the level of SH was significantly correlated with the scores of the objective SCORAD ($r$= –0.545, P=0.001), but not those of CDLQI ($r$= –0.090, P=0.62), pruritus ($r$=0.173, P=0.334), or sleep loss ($r$=0.127, P=0.481). Similarly, TEWL was correlated with the scores of the objective SCORAD ($r$=0.503, P=0.003) but not those of CDLQI ($r$=0.092, P=0.609), pruritus ($r$=0.210, P=0.240), or sleep loss ($r$=0.180, P=0.316). Three patients reported that the cream caused local irritation, but still returned for regular assessments.

Clinically, SH and TEWL improved over the 4-week study period (Figs 1 and 2), but not the objective SCORAD, pruritus, sleep loss, or CDLQI scores (Table 1). The amount of Curel (Kao) emollient used/BSA for the whole 4 weeks was not significantly correlated with the baseline clinical parameters of the objective SCORAD ($r$=0.20, P=0.27), TEWL ($r$=0.07, P=0.69), and SH ($r$=0.22, P=0.22) scores.

The proportion of AE patients using topical corticosteroids was significantly lower at the end of the 4-week study period (n=20 vs 11, P=0.024). In terms of global acceptability of treatment (GAT), 14 (42%) AE patients rated the cream as good. More male than female patients (56% vs 29%) reported GAT as good, but this difference was not statistically significant (P=0.12) [Table 2]. There were no significant differences between males and females with respect to changes of clinical and biophysiological parameters over the 4-week study.

## Discussion

Eczema is associated with dry skin and SH correlates with disease severity. It is thus sensible to encourage patients to use emollients regularly.[28,29] The skin condition may improve significantly with the liberal usage of emollients, so that topical medications such as corticosteroids may be minimised. Son et al[15] demonstrated that the regular application of a moisturiser for 2 weeks improved SCORAD, SH, TEWL, and other cutaneous parameters. Chamlin et al[18] reported that a ceramide-dominant, barrier-repair emollient was efficacious for AE and argued that other non-ceramide–containing emollients could even be detrimental. We previously found that a popular non-ceramide emollient was efficacious in improving SH, and that the proportion of AE patients using topical corticosteroids was significantly reduced at the end of the 2-week study period.[17] In the present study, a 4-week course of a pseudo-ceramide–containing emollient was efficacious in improving SH. In both studies, however, we did not demonstrate any change in disease severity or quality of life in these AE patients. Eczema is a very common relapsing childhood disease that five subspecialties claim it to be within their scope, namely paediatrics, dermatology, allergy and immunology, family practice, and even psychiatry. It is also debated as

to whether eczema is a systemic atopic disease with skin manifestations or primarily a skin disorder with systemic associations. In our experience, topical treatment (emollients, steroids, and tacrolimus) is seldom sufficient to manage all but the mildest disease.

In a previous 2-week study, an adequate supply of emollient improved SH but not disease severity or quality of life. Our present study involving a longer duration (4 weeks with a pseudoceramide-containing emollient) confirmed that SH could be improved but that disease severity and quality of life remained unchanged. Nevertheless, fewer patients used topical corticosteroids. In both studies (collective total n=81), in the majority of patients we did not observe any significant change in severity grade, namely from severe to moderate or from moderate to mild. In recalcitrant cases, even the use of very potent topical corticosteroids in addition to topical emollients did not alleviate the skin disease, but the risk of systemic side-effects was possibly increased. Conversely, the systemic approach involving the use of an immunomodulating agent (eg azathioprine or cyclosporine) can significantly alleviate the problems and reduce topical corticosteroid usage.[30] Furthermore, a brief course of oral corticosteroid during an acute exacerbation can improve the skin dramatically and relieve the childhood misery, without having to escalate the topical treatment. In these two circumstances, systemic corticosteroids or immunomodulating agents alleviate disease manifestations, without altering the fundamental genetic deficit of filaggrin pathophysiology or ceramide metabolism. Also, the theory of "atopic march" proposes that many children with AE go on to develop asthma and allergic rhinitis, as their eczema improves with time. These observations all point to eczema being more like a systemic disease (atopy) with skin manifestations (dermatitis) than a skin disease with systemic associations. It follows that treating eczema as a dermatological disease with only a topical armamentarium, without considering a systemic, holistic approach for this complicated disorder is bound to be suboptimal.

The main limitations of this study were its short duration and lack of details about the exact amounts of topical steroid used. The 2-week research duration was considered a potential advantage for enhancing patient compliance to treatment, which was augmented by encouragement and positive reinforcement by the investigators. This duration was also used in previous studies on topical therapy.[15,17] In the present study, we assessed the effects at 2 and 4 weeks of therapy. It was probably unnecessary to prolong the study beyond 4 weeks, as it is unlikely that the enthusiasm associated with introduction of a new topical emollient would endure.

TABLE 1. Changes in the objective SCORAD, pruritus, sleep loss, and CDLQI, SH and TEWL scores with the body surface area–adjusted use of Kao cream over 4 weeks*

| Outcome measure† | Mean (standard deviation) | | | P value |
|---|---|---|---|---|
| | Baseline | 2 weeks | 4 weeks | |
| Objective SCORAD | 26 (16) | 26 (16) | 27 (17) | 0.175 |
| Pruritus | 5 (2) | 5 (2) | 5 (2) | 0.652 |
| Sleep loss | 4 (3) | 4 (3) | 4 (3) | 0.916 |
| CDLQI | 8 (5) | 8 (4) | 7 (5) | 0.292 |
| SH | 30 (15) | 36 (15) | 38 (15) | 0.039 |
| TEWL | 8 (2) | 8 (3) | 7 (4) | 0.049 |

* Of the 33 patients, 20 reported using topical corticosteroid on an as-need basis at baseline, and only 11 patients reported topical corticosteroid usage at completion of study (P=0.024)

† SCORAD denotes SCORing Atopic Dermatitis, CDLQI Children's Dermatology Life Quality Index, SH skin hydration, and TEWL transepidermal water loss

TABLE 2. Global acceptability of treatment (GAT)*

| GAT | Males (n=16) | Females (n=17) |
|---|---|---|
| Very good | 0 | 0 |
| Good | 9 (56%) | 5 (29%) |
| Fair | 6 (38%) | 11 (65%) |
| Poor | 1 (6%) | 1 (6%) |

* P=0.12 between the genders

Of the 33 patients, 20 reported as-needed usage of topical steroid prior to starting this study. Accordingly, they were instructed not to use such topical therapy during the study. At the end of the study, however, 11 patients continued to use usual amounts of topical steroid. Studies about the efficacy of emollients in moderate-to-severe AE are often confounded by co-existing treatment medications. Evidently, nine of the study patients were spared of the use of topical steroids, without any increase in disease severity as measured with the SCORAD.

Together with our previous study, we have confirmed that emollient usage does have a topical steroid–sparing effect. In terms of the GAT, 42% of AE patients rated the cream as being good. The choice of various products must be individualised and tailored to the patient's preference.[29]

In conclusion, we established a methodology for evaluating the clinical (severity and quality of life) and biophysiological effects (based on SH and TEWL) for any topical agent that might be important for the management of this very complicated disease.

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