Original Article

The Comparative Efficacy Between Shea Butter-Ceramide Cream and 1% Hydrocortisone Cream in Childhood Atopic Dermatitis

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Background: Atopic dermatitis (AD) is the most common chronic eczema in children due to skin barrier dysfunction. Topical non-steroidal anti-inflammatory agents such as Butyrospermum parkii (shea butter) and ceramide are developed to target specific defects in skin barrier function in AD patients and to reduce the side effects of topical corticosteroids.

Objective: To compare the efficacy of the emollient containing shea butter and ceramide to 1% hydrocortisone in childhood AD.

Materials and Methods: The present study was a randomized, double-blind study in 26 children, aged 2 to 18 years, with mild to moderate AD. The patients were randomized to treat twice daily with shea butter and ceramide cream (SC) on one side of the body and 1% hydrocortisone on the other side. The treatment period was eight weeks, with follow-ups on the second, fourth, sixth, and eighth week. The shea butter and ceramide side were applied for eight weeks; while the 1% hydrocortisone side was applied for the first four weeks and changed to cream base for the latter four weeks. The clinical outcomes were evaluated by using SCORAD and POEM at baseline, and on every follow up week. Time to remission, time to relapse, and adverse events were evaluated.

Results: The result showed a significant improvement of SCORAD and POEM in both groups after eight weeks of treatment. When comparing the two groups, it was found that SCORAD and POEM were not different. Regarding the median time to remission and the median time to relapse, there was no statistical difference between the two groups of treatments. There were no related adverse events.

Conclusion: The emollient containing shea butter and ceramide is effective in the treatment and prevention of relapse in childhood mild to moderate atopic dermatitis.

Keywords: Ceramide; Butyrospermum parkii; shea butter; atopic dermatitis

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Atopic dermatitis (AD) is the most common eczema in children, with a prevalence of 15% to 20%[1]. The earliest clinical signs are skin dryness and roughness. The condition is progressively characterized by intense itching and recurrent eczematous lesions[2]. These manifestations can lead to sleep disturbance, low self-esteem, stress, and poor performance at school. AD can co-occur with other atopic diseases such as asthma and allergic rhinitis.

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The pathogenesis of AD is complex and multifactorial. There has been an "outside-inside-outside" theory suggesting that there is a skin barrier disruption in AD resulting from dysfunction of the metabolism of major lipids such as ceramides, cholesterol, and free fatty acids, due to genetic abnormalities[3]. This skin barrier disruption leads to immune system activation, which allows proinflammatory cytokines and chemokines to promote inflammation[4]. These proinflammatory cytokines then inhibit the ceramide synthesis resulting in more skin barrier disruption.

Topical corticosteroids (TCSs) are widely used as the first-line treatment of AD. However, improper use can cause local adverse effects such as skin atrophy, dyspigmentation, striae, telangiectasias, and acneiform eruption[5]. Systemic adverse effects from TCSs can also occur and include hypothalamic-pituitary-adrenal suppression and growth retardation. Thus, non-steroidal anti-inflammatory topical agents are developed to target specific defects in skin barrier

function in AD patients and to spare side effects of TCSs[6-10]. Butyrospermum parkii (shea butter) extract containing triterpene acetate and cinnamate esters can inhibit inflammation by suppressing proinflammatory cytokines via prostaglandin E2, cyclooxygenase-2, protein kinase C, and nuclear factor kB pathway[11-13]. Moreover, fatty acids in shea butter such linoleic acid has been reported to promote the epidermal permeability barrier[14]. The goal of the present study was to compare the efficacy of the emollient containing shea butter and ceramides (SC) to 1% hydrocortisone (HC) cream for the treatment and prevention of mild to moderate AD.

Materials and Methods

Study design

The present study was a randomized, intra-individual comparison (right/left), double-blinded, single-center study performed at Srinakharinwirot University in Thailand between April and June 2019. The study was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization and Good Clinical Practice Guidelines and was reviewed and approved by the Clinical Research Ethical Committee of Srinakharinwirot University, certificate No. SWUEC 443/61. Twenty-six children aged 2 to 18 years with mild to moderate AD were enrolled. The sample size was calculated by using PS: power and sample size calculation software, version 3.1.2 and the study from Abbasi et al[15]. The mean difference of SCORing Atopic Dermatitis (SCORAD) and standard deviation (SD) was 6.54 and 10.05, respectively. With 95% confidence, 80% power, and a dropout rate of 20%, twenty-six patients had to be recruited. Study visits were performed at screening, which was two weeks before baseline, at baseline (week 0), second visit (week 2), third visit (week 4), fourth visit (week 6), and fifth visit (week 8). At the screening visit, the subjects and their parents or legal guardians were informed about the study procedures and asked to provide their written informed consent for their child to be included in the trial. The demographic data were obtained, and the computerize randomization was performed to divide into two groups. The third person concealed the allocation to blind the results to participants and evaluators.

Inclusion criteria

Patients aged between 2 and 18 years, diagnosed with AD with SCORAD of 1 to 50[16], and eczematous lesions on both sides of the body were included in the study.

Exclusion criteria

AD patients who had other skin conditions that might interfere with AD evaluation, for example, scabies, active viral, bacterial, and fungal skin infections, were excluded. In addition, subjects who had been treated with topical corticosteroids and calcineurin inhibitors for their AD within two weeks before week 0 and throughout the entire study as well as patients who had been treated with systemic treatment, such as oral corticosteroids, NSAIDs, and other immunosuppressants within four weeks before week 0 were also excluded.

Treatment protocol

At the baseline visit (week 0), volunteers were randomized to treat twice daily with SC cream (Ceramol cream 311, Unifarco Biomedical®, Italy) on the one side of the body and 1% HC on the other side. The treatment period was eight weeks, with the follow up on the second, fourth, sixth, and eighth week. The SC side was applied for eight weeks while the HC side was applied for the first four weeks for treatment and changed to cream base for the latter four weeks for prevention as shown in Figure 1. In addition, the subjects were also given the same body cleanser. However, they were not allowed to use any other treatments, including topical medications, oral medications, and other moisturizers. The primary objective was to compare the efficacy of the emollient containing SC to HC for the treatment and prevention of mild to moderate AD. The secondary objective was time to remission and time to relapse after treatment, patient's satisfaction, and related adverse events.

Outcome evaluation

During the first four weeks of the present study, the authors compared the effectiveness between topical corticosteroids in HC cream and shea butter-ceramide in the SC cream. For the latter four weeks, the authors switched topical corticosteroids to cream base in the HC group. Therefore, the authors compared cream base in the HC cream to shea butter-ceramide in SC cream.

The clinical severity outcome was evaluated by using the SCORAD and the Patient-Oriented Eczema Measure (POEM) at baseline, and on every follow up week. The SCORAD was a clinical tool for assessing AD severity by combining signs such redness, swelling, oozing, scratch mark, dryness, lichenification, and excoriations, symptoms such as pruritus and sleep

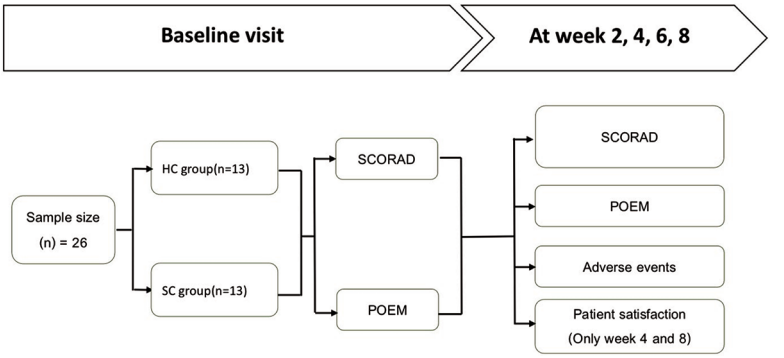

Figure 1. Timeline of a study protocol.

disturbance, and extents of the disease. The POEM was a validated, patient-assessed measure for monitoring AD severity by using seven questions.

Remission was defined as a reduction in disease activity assessed by SCORAD to 50% or less of the patient's baseline value. Relapse was defined as an increase in SCORAD to more than 50% of the patient's baseline value.

The patient's satisfaction to study's result was assessed by using a visual analog scale.

The adverse effects were recorded at each visit. The severity was assessed as mild, moderate, or severe by the investigator.

Statistical analysis

Baseline characteristics of patients were described. Categorical variables were analyzed and reported as frequency and percentage, while continuous variables were analyzed and reported as mean ± SDs.

For SCORAD and POEM, multi-level data analyses using a mixed linear model was used to compare the difference between the two groups and the difference between each visit. The data were considered as two-level data, subject, and time levels.

The Kaplan-Meier method was performed for calculating to estimate the median time and rate of remission and relapse.

Cox's proportion hazard model was used to estimate hazard ratio (HR) of remission and relapse. The statistical analysis was performed by using Stata, version 13 (StataCorp LP, College Station, TX, USA). A p-value considering statistical significance was less than 0.05. All patients were included in the analyses.

Results

Patients

Twenty-six patients with AD were included and completed the study without any protocol deviations.

Table 1. Demographic data

Demographic data	Number of subjects (n=26); n (%)
Sex	
Male	9 (34.6)
Female	17 (65.4)
Age; mean±SD	6.04±3.29
2 to 5 years	12 (46.2)
6 to 10 years	9 (34.6)
>10 years	5 (19.2)
Family history of atopy	
Yes	24 (92.3)
No	2 (7.7)
Medical treatment history of AD	
Yes	12 (46.2)
No	14 (53.8)

SD=standard deviation; AD=atopic dermatitis

Nine (34.6%) patients were male and seventeen (65.4%) were female. The mean age of all subjects was 6.04±3.29 years (range 2 to 14). Twenty-four (92.3%) patients had their family history of allergy. Twelve (46.2%) patients had been treated with either topical or oral medication (Table 1). The baseline of SCORAD and POEM of both groups were recorded. There were no statistically significant differences of baseline (D0) SCORAD and POEM between both groups.

Outcomes

During the treatment, the SCORAD of both groups progressively decreased in each follow up with statistical significance ($p<0.001$) as shown in Figure 2. The differences between the two study arms with respect to SCORAD reduction were not significant ($p=0.62$).

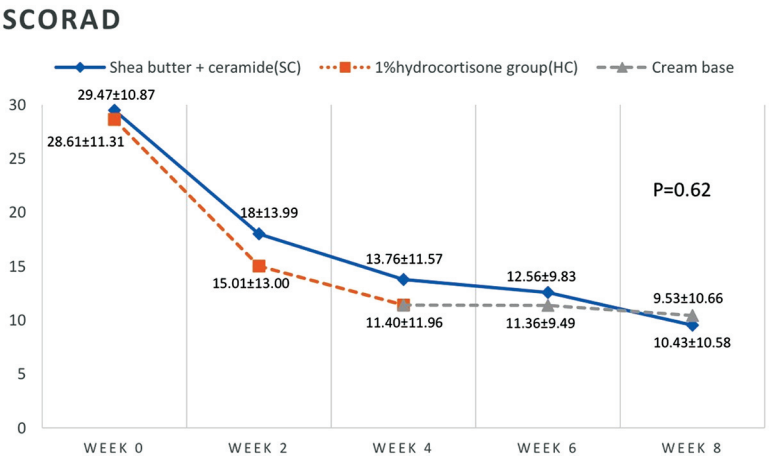

Figure 2. The SCORAD in the SC and the HC arm compared to baseline (week 0).

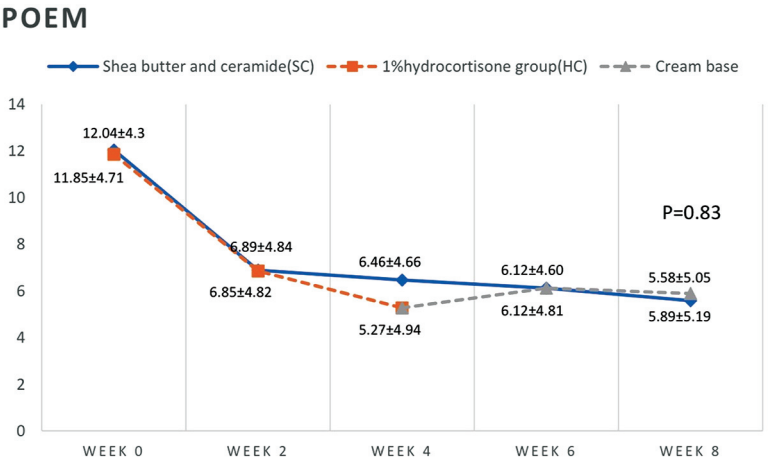

Figure 3. The POEM in the SC as well as HC arm compared to baseline (week 0).

The results showed similar pattern with respect to POEM score, both treatments significantly decreased POEM score at two, four, six and eight weeks compared with baseline ($p<0.001$) as shown in Figure 3. However, there was one increasing POEM score in the HC/cream group from week 4 to 6 after the change from HC to cream base. When comparing between the two arms, there were also no differences of POEM score reduction between the two study arms ($p=0.83$).

The median time to remission of both groups was not significantly different. The remission time of the SC and the HC group was 3.29 and 3 weeks, respectively. The cumulative incidence of remission for both arms is shown in Figure 4.

Throughout the study, there were five (19.23%) and seven (26.92%) relapsing patients in the SC and HC group, respectively (Table 2). The relapse time of the SC cream and the cream base was 6.54 and 6.90, respectively, as shown in Figure 5. When comparing a hazard ratio of the SC to the HC group, patients in the first group had a chance of getting relapse less than the latter group at 30.1%. However, there was no significant differences ($p=0.45$).

Regarding the patient's satisfaction score, it was seen that the score in the SC group was non-significantly higher than the HC group in the first four weeks. After changing HC to cream base in the last four weeks, it was found that the score in the HC group was non-significantly higher than the SC group. There was no related adverse event.

Discussion

In the present study, the authors found a

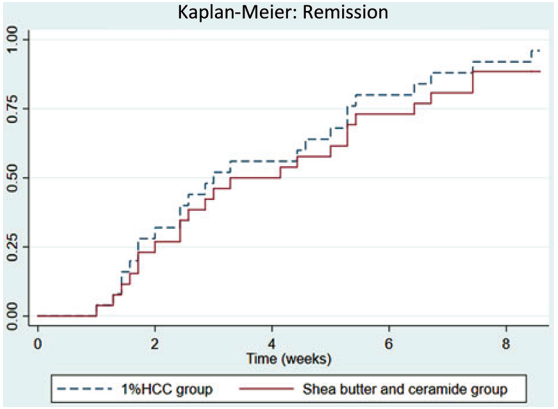

Figure 4. Median time to remission of SC and HC by Kaplan-Meier analysis.

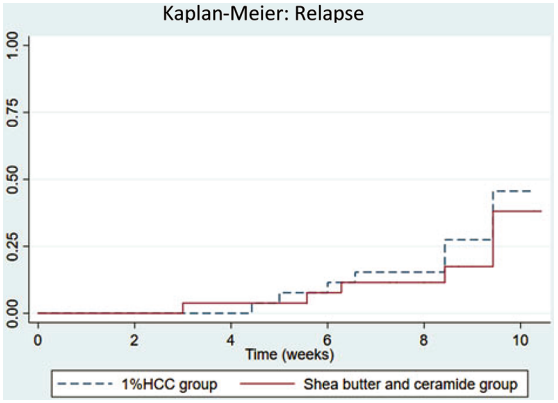

Figure 5. Median time to relapse of SC and HC by Kaplan-Meier analysis.

Table 2. Percentages of disease relapse during the 4th to 8th week

	SC; n (%)	1% HC switched to cream base; n (%)
4th week	2 (7.69)	2 (7.69)
6th week	1 (3.85)	2 (7.69)
8th week	2 (7.69)	3 (11.54)

SC=shea butter and ceramide; HC=hydrocortisone

significant improvement of SCORAD and POEM in both HC and SC groups after eight weeks of treatment.

The better outcomes in the HC group could be explained by the anti-inflammatory effect as topical corticosteroids inhibit cytokines and tumor necrosis factor release[17]. While the better outcomes in the SC group could be explained by two major substances in the cream, which were ceramide and shea butter. Topical ceramide filled the gaps between desquamating corneocytes promoting permeability barrier function and hydration[18-20].

Consequently, correction of the stratum corneum could result in decreased inflammation. Triterpene acetate and cinnamate esters found in shea butter were shown to suppress proinflammatory cytokines via prostaglandin E2, cyclooxygenase-2, protein kinase C, and nuclear factor kB pathway[11]. Moreover, linoleic, stearic, and oleic acids in shea butter were reported to promote the epidermal permeability barrier[14]. Apart from these, linoleic acid in shea butter could reduce the inflammation by inhibiting prostaglandin E2 formation[21].

Topical corticosteroids had been the mainstay of AD treatment for many years[17]. However, when comparing the outcomes between the HC and the SC group at the fourth week, there were no significant differences of SCORAD reduction, POEM reduction, and time to remission. This was because subjects in the present study were in the mild to moderate level of AD. Thus, the anti-inflammatory properties in ceramide and shea butter were high enough to suppress inflammatory cytokines. This led to the answer why the results between two arms were not significantly different.

When looking into the earlier studies, there were no study that compared both ceramide and shea butter with topical corticosteroids. There was only one study that compared either ceramide alone or shea butter with other components to topical corticosteroids. There was a previous study in 2009 from Sugarman et al[22] that conducted a randomized trial on 121 patients with AD for 28 days comparing ceramide-dominant, triple-lipid barrier repair formulation (EpiCeram) to fluticasone cream. At the end of the study, SCORAD of both groups were not significantly different. Due to a similarity of SCORAD decreasing in both groups, it was concluded that emollient containing ceramide could be used for AD treatment when steroid-sparing effect is needed. Another study from Jirabundansuk et al[23] conducted a randomized trial on 29 patients with AD for 28 days, comparing spent grain wax, shea butter, and Argania Spinosa kernel oil to 1% HC cream. The result of the study showed that there were no statistically significant differences in the decrease of SCORAD between both arms. These two previous published research papers showed the same result as the present study, that both shea butter and ceramide could reduce the inflammation in mild to moderate AD, therefore, shea butter and ceramide could be used as a treatment of mild to moderate AD.

Regarding the limitation of the present study, which was a split-side study, there could possibly be

a contamination bias between the two groups.

Conclusion

In conclusion, emollient containing ceramide and shea butter could be used for treatment in acute and maintenance phase in childhood mild-to-moderate AD.

What is already known on this topic?

Non-steroidal anti-inflammatory topical agents were developed to spare side effects from long-term corticosteroids use in the treatment of AD. Ceramide and shea butter were used in many topical agents, however, both substances were never combined as the major ingredient in the treatment of AD.

What this study adds?

In this study, there is a significant improvement of the outcome in the ceramide and shea butter group. When comparing the result of this group with the topical corticosteroid group, there is no significant difference.

Authors' contributions

Sivapiromrat P and Udompataikul M have given substantial contributions to the conception or the design of the manuscript. Kamanamool N have given substantial contributions to acquisition, analysis, and interpretation of the data. All authors have participated to drafting the manuscript, and Udompataikul M revised it critically.

All authors contributed equally to the manuscript and read and approved the final version of the manuscript.

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Conflicts of interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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