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Are Ceramide Containing Creams A Safe And Effective Treatment For Patients With Atopic Dermatitis?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not ceramide containing creams are a safe and effective treatment for patients with atopic dermatitis.

STUDY DESIGN: Review of three randomized controlled studies published in English between 2009-2016.

DATA SOURCES: Three assessor blind randomized controlled trials found using PubMed and EbscoHOST databases.

OUTCOMES MEASURED: Each of the three trials assessed safety and efficacy of a ceramide containing cream compared with another method in the treatment of atopic dermatitis. Outcomes were measured by Eczema Severity Score (ESS), rating of skin dryness on a 0-4 scale, transepidermal water loss (TEWL) measurements, and Severity Scoring for Atopic Dermatitis (SCORAD) on a scale of 0-72.

RESULTS: The Marseglia et al[1] study showed that subjects using the ceramide containing cream had an 84% reduction in their Eczema Severity Score (ESS), compared to the subjects using the simple hydrating cream who had a 50% reduction in the ESS. This difference was statistically significant as $p=0.0001$. The Simpson et al[2] study showed statistically significant improvements in skin dryness, skin hydration and transepidermal water loss (TEWL) in the cream with a ceramide precursor as compared to no treatment. The Sugarman et al[3] study showed a 50.7% decrease ($p<0.001$) in Severity Scoring for Atopic Dermatitis (SCORAD) when using a ceramide formulation. Additionally, it showed no statistically significant difference between the SCORAD in the ceramide formulation and fluticasone propionate 0.05%. No serious adverse effects were noted in the three studies.

CONCLUSIONS: The results of the three randomized controlled studies show that the use of a ceramide containing cream is a safe and effective treatment for atopic dermatitis. Each study showed a statistically significant improvement of symptoms without any serious adverse effects.

KEY WORDS: Atopic dermatitis, eczema, ceramide

INTRODUCTION

Atopic dermatitis, or eczema, is a chronic pruritic inflammatory skin disease. It is characterized by epidermal changes including spongiosis, acanthosis, hyperkeratosis, and lymphhistiocytic infiltrate into the dermis.[4] Two cardinal symptoms of atopic dermatitis are pruritus and xerosis, but the presentation can vary depending on the patient and severity.[4] This paper evaluates three randomized controlled trials (RCTs) comparing the efficacy of a ceramide containing cream as the treatment for atopic dermatitis as compared with other treatment options.

Atopic dermatitis is relevant to the Physician Assistant due to the prevalence and cost of the disease. Atopic dermatitis effects on average 5% to 20% of children worldwide, and approximately 11% of children located in the U.S. Most cases of atopic dermatitis present prior to the age of five years old, and there is a female to male ratio of 1.3 to 1. The incidence of atopic dermatitis is increasing.[4] JAMA Dermatology estimated that adults with eczema had $371 to $489 higher out-of-pocket costs per person-year compared to those without eczema.[6] They paid $37 billion and $29 billion in out-of-pocket health care costs in 2010 and 2012, respectively.[6] Not only are monetary costs of the disease higher; but patients with atopic dermatitis are physically visiting their physician more often. In the 2010 National Health Interview Survey (NHIS), approximately three of four adults with eczema (six million) had seen a physician for their eczema in the previous 12 months.[6] In addition, adults with eczema had a weighted total of 9.7 million (for 2010) and 7.8 million (for 2012) visits to an urgent care center or emergency department in the previous 12 months.[6]

The etiology of atopic dermatitis is multifactorial including skin barrier abnormalities, defects in innate or adaptive immunity response, and altered skin resident microbial flora.[4] Impaired skin barrier function of intercellular junctions or the stratum corneum, such as

deficiency in stratum corneum lipids (ceramides), can lead to increased transepidermal water loss (TEWL).[4] Increase in TEWL can lead to dryness and severe pruritus, which are the cardinal symptoms of atopic dermatitis. Patient presentations of atopic dermatitis can vary based on how long symptoms have been present. Acute symptoms include pruritic erythematous papules and vesicles which may include crusting or weeping lesions. Chronic atopic dermatitis usually presents with scales, excoriation, fissuring, and lichenification of skin. [4] Atopic dermatitis is often associated with elevated serum level of IgE as well as a personal or family history of atopy (atopic dermatitis, asthma, and allergic rhinitis).[4]

Treatment of atopic dermatitis includes a multipronged approach including elimination of exacerbating factors, restoration of skin barrier function, hydration of the skin, and pharmacologic treatment of skin inflammation.[5] Many patients with atopic dermatitis have a deficiency in stratum corneum lipids (ceramides), so maintaining skin hydration with thick cream, ointment, or moisturizers containing stratum corneum lipids is a key component.[5] Lotions that have a high water and low oil content can worsen xerosis, where thicker creams (such as Eucerin, Cetaphil, Nutraderm) and ointments (such as petroleum jelly, Vaseline, Aquaphor) have lower to no water content and can better protect against xerosis.[5] Symptoms of pruritus can be treated and controlled with antihistamines. Other pharmacologic treatments include topical corticosteroids. Typically, low potency for mild symptoms and medium to high potency for moderate to severe symptoms. Acute exacerbations may even require a short course of systemic glucocorticoids. [5]

The goal of the proposed treatment method is to have a safe and effective role in treating atopic dermatitis and reduce the severity of symptoms. This review compares a ceramide containing cream with three different treatment options: no treatment, a non-ceramide containing

cream, and a topical corticosteroid. The goal of using a ceramide containing cream is to replace the deficiency of stratum corneum lipids and potentially reduce or eliminate the need for topical or systemic corticosteroid use. The use of ceramide cream has been shown to be a safe and effective treatment of atopic dermatitis in those six months to 65 years old.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not ceramide containing creams are a safe and effective treatment for patients with atopic dermatitis.

METHODS

The three studies in this review were randomized controlled trials that met the following criteria: the population studied were men and women ages six months to 65 years with atopic dermatitis. Interventions included a ceramide containing cream, a moisturizer with ceramide precursor, and a ceramide-dominant triple-lipid barrier repair formulation. Comparisons were made to a non-ceramide simple hydrating cream, no intervention, and a steroid containing cream (fluticasone propionate 0.05% cream). The outcomes measured were decrease in atopic dermatitis severity (measured by Eczema Severity Scoring and Severity Scoring for Atopic Dermatitis), reduction in skin dryness, and improvement in skin barrier function via reduction in trans epidermal water loss (TEWL). [1,2,3]

Keywords used to search for articles consisted of: ceramide, atopic dermatitis, and eczema. All articles were published in English in peer-reviewed journals. Articles were researched by the author via PubMed and EbscoHOST and selected based on relevance to the clinical question that included patient oriented outcomes (POEMs). Inclusion criteria included

RCTs published after 2000, men and women aged six months to 65 years with atopic dermatitis, and patient oriented evidence that matters (POEMs). Exclusion criteria included articles published prior to 2000 and studies focused on disease oriented evidence (DOEs). Statistics reported and used include: p-value, relative benefit increase (RBI), absolute benefit increase (ABI), control event rate (CER), experimental event rate (EER) and numbers needed to treat (NNT). Table 1 displays demographics and characteristics of included studies.

OUTCOMES MEASURED

All outcomes measured included patient oriented outcomes in the reduction of atopic dermatitis symptom severity. The Marseglia et al[1] study examined the reduction in eczema severity using the Eczema Severity Score (ESS) by blind evaluators clinical observations of erythema, induration, edema and lichenification on a 0-3 scale. The Simpson et al[2] study examined a reduction in skin dryness and improvement in skin barrier function using blind evaluators to rate skin dryness on a 0-4 scale and take TEWL measurements at baseline and day 28. The Sugarman et al[3] study examined a decrease in eczema severity using the Severity Scoring for Atopic Dermatitis (SCORAD) on a scale of 0-72.

Table 1. Demographics and characteristics of included studies

Study	Type	#of Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Marseglia, 2014 [1]	Assessor blind RCT	107	6 months to 14 years	Children aged 6 months to 14 years with facial atopic eczema	Severe recent atopic eczema (<4 weeks), and treatment with systemic or topical steroids or calcineurin inhibitors, and presence of active cutaneous bacterial, viral, or fungal infections in target areas	0	A ceramide containing cream (Nutratopic Pro-AMP cream), which also contains 2.5% rhamnosoft and 2% L-isoleucine (ILE)
Simpson, 2013 [2]	Blind evaluator RCT	20	18 years to 65 years	Men and women ages 18-65 with controlled atopic dermatitis, patients also have clinical xerotic skin, corresponding to a score of at least 1 on a dryness scale	Pregnant or breast feeding women	0	Moisturizer with ceramide precursor (Cetaphil Restoraderm Body Moisturizer) applied twice daily on one leg for 27 days
Sugarman, 2009 [3]	Investigator blind comparison controlled RCT	121	6 months to 18 years	Male and female patients ages 6 months to 18 years old with moderate-to-severe atopic dermatitis	None listed	5 (4%)	Ceramide-dominant, triple-lipid, barrier-repair formulation (EpiCream Skin Barrier Emulsion)

RESULTS

All three articles studied the use of a ceramide containing cream as a safe and effective treatment for atopic dermatitis. The Marseglia et al[1] study compared a ceramide containing cream to no intervention, the Simpson et al[2] study compared to a non-ceramide containing cream, and the Sugarman et al[3] study compared with a topical corticosteroid.

The Marseglia et al[1] study examined 107 children aged six months to 14 years with facial atopic eczema and excluded children with severe recent atopic eczema, treatment with systemic or topical corticosteroids, and presence of active cutaneous infections at target lesions. Subjects were randomly assigned to one of two groups, and either applied a ceramide containing cream (Nutratopic Pro-AMP cream) or a simple hydrating cream (15% glycerol-based cream containing Vaseline 8% and liquid paraffin 2%). Subjects applied the topical treatments to the face two times a day for six weeks. Blind evaluators determined subject's Eczema Severity Score (ESS) at baseline, three weeks, and then six weeks. ESS is calculated based on clinical observation of erythema, induration, edema, and lichenification of skin. Table 2 displays the ESS at baseline, week three and week six. The baseline ESS score for the ceramide containing cream, mean +/- standard deviation (SD), was 6.1 +/- 2.5 versus 5.3 +/- 3.0 for the comparison group. At week 6 the ESS for the ceramide containing cream was 1.0 +/- 1.5, demonstrating an 84% reduction, p=0.0001. The comparison group ESS at week 6 was 2.6 +/- 2.0, showing a 50% reduction. The ESS mean change from baseline at week 6 was -5.0 points and -2.7 points for the treatment group and comparison group respectively. The ESS in the treatment group at week 6 was significantly lower than the comparison group (1.0 vs 2.6, CI 95%).[1]

Table 2. Change in ESS for Marseglia et al[1] study

Treatment	**Baseline ESS (Mean +/- SD)**	**Week 3 ESS Mean +/- SD % reduction**	**Week 6 ESS Mean +/- SD % reduction**	**Absolute reduction (CI 95%)**
Ceramide containing cream	6.1 +/- 2.5	2.5 +/- 2.0 59% reduction	1.0 +/- 1.5 84% reduction	5.0 points (CI: 5.5 to 4.5)
Simple hydrating cream	5.3 +/- 3.0	3 $\pm$ 2.0 42% reduction	2.6 +/- 2.0 50% reduction	2.7 points (CI: 3.6 to 1.4)

The Simpson et al[2] study examined 20 men and women (excluding pregnant or breastfeeding subjects) ages 18-65 with controlled atopic dermatitis and clinical xerotic skin. Subjects were given a moisturizer with a ceramide precursor (Cetaphil Restoraderm Body Moisturizer, or CRM) and applied it daily on one leg for 28 days. Each subject was also their own control, as no treatment was done to the other leg. Blind evaluators assessed level of skin dryness on a 0-4 scale, level of skin hydration, and TEWL measurements at baseline and 28 days later. Table 3 displays the results. Percentage change in skin dryness from baseline is -55.54% and -22.17% for treated area versus non-treated area, p-value <0.001. Percentage change in skin hydration from baseline was +117.53% and +25.42% for treated area versus non-treated area respectively, p-value <0.001. Percentage change in TEWL from baseline was -30.01% and -4.28% for treated area versus non-treated area, p-value = 0.002.[2]

Table 3. Results for Simpson et al[2] study

Treatment	**% change in skin dryness from baseline**	**% change in skin hydration from baseline**	**% change in TEWL from baseline**
Moisturizer with ceramide precursor	-55.54%	+117.53%	-30.01%
No treatment	-22.17%	+25.42%	-4.28%
p-value	p<0.001	p<0.001	p=0.002

The Sugarman et al[3] study examined 121 male and female patients ages six months to 18 years with moderate to severe atopic dermatitis. Subjects were randomly placed into two treatment groups. One group was treated with a ceramide-dominant, triple-lipid, barrier-repair

formulation (EpiCream Skin Barrier Emulsion), and the other group was treated with Fluticasone proprionate 0.05% cream. Subjects applied the cream to affected areas at approximately the same time every day for 28 days. Blind evaluators assessed atopic dermatitis severity using the Severity Scoring for Atopic Dermatitis (SCORAD) on a scale of 0-72 at baseline, day 14, and day 28. Table 4 displays the percent change from baseline in SCORAD on day 14 and day 28 as well as an analysis of variance (ANOVA) comparison. SCORAD mean change from baseline at 14 days was -36.6% and -50.7% for the ceramide barrier cream and the fluticasone cream groups respectively. SCORAD mean change from baseline at 28 days was -50.7% and -66.7% for ceramide barrier cream and the fluticasone cream groups respectively. When comparing the change in baseline from the ceramide group to the fluticasone group, the ANOVA p-value was 0.134. This reveals there is not a statistically significant difference in the outcome between the two treatment groups, suggesting the ceramide containing cream would be a safe and effective treatment option that could replace fluticasone cream use. When looking solely at the ceramide group change from baseline, the -50.7% change is statistically significant as $p<0.001$.[3]

Table 4. Results for Sugarman et al[3] study

Treatment	**% change in SCORAD from baseline at day 14**	**% change in SCORAD from baseline at day 28**
Ceramide formulation	-36.6%	-50.7%
Fluticasone proprionate 0.05%	-57.6%	-66.7%
ANOVA p-value	p=0.021	p=0.134

Sugarman et al[3] data was converted to dichotomous; see Tables 5 and 6. Subjects who had >75% improvement in SCORAD where considered to have "excellent responses." At day 14 the ceramide barrier cream group had five subjects and the fluticasone cream group had 21 subjects with "excellent responses". At day 28 the ceramide barrier cream group had 21 subjects with "excellent responses" and the fluticasone cream group had 27 subjects. Table 6 shows calculations for RBI, ABI, EER, CER, and NNT. NNT was determined to be -14. This means for

every 14 people treated with the ceramide cream, one less subject will obtain an "excellent response" compared to the fluticasone cream.[3]

Table 5. Dichotomous data for Sugarman et al[3] study

Treatment	**# people with >75% improvement in SCORAD on day 14**	**# people with >75% improvement in SCORAD on day 28**
Ceramide formulation	5	21
Fluticasone proprionate 0.05%	21	27

Table 6. Values for dichotomous data for Sugarman et al[3] study

CER	**EER**	**RBI**	**ABI**	**NNT**
0.46	0.39	1.84	-0.07	-14

DISCUSSION

Ceramides are stratum corneum lipids that aid in maintaining skin hydration.[5] There are no contraindications or black box warnings for the use of ceramides.[9] The Cosmetic Ingredient Review (CIR) Expert Panel[8] reviewed the safety of 23 forms of ceramides and concluded that, "the following ceramide ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment."[8] An article in the Journal of Food and Chemical Toxicology further expanded on the CIR Expert Panel conclusions and discovered, "there may be sufficient margin of safety for systemic toxicity to humans if ceramide 3 is used less than 1% as an ingredient for cosmetic products."[7]

The Marseglia et al[1] and Simpson et al[2] studies did not display any adverse effects from the use of ceramide cream. In the Sugarman et al[3] study, while there were no serious adverse events attributed to the agents studied, there were four subjects in the ceramide formulation group who initially worsened and required "rescue therapy" with fluticasone use. The adverse effects mimicked the subject's original disease (atopic dermatitis), so the authors did not attribute

the initial increase in severity of symptoms as directly caused by the ceramide formulation, but rather as "disease flares".[3]

Limitations to the Marseglia et al[1] study and the Simpson et al[2] study include that it was not double blinded. The subjects in the Marseglia et al[1] study could tell which cream (ceramide containing or basic glycerol based) they were using. The subjects in the Simpson et al[2] study where their own control as they applied cream to one leg and not the other. In both studies this was corrected for by having blind assessors evaluate the patients. Limitations to the Sugarman et al[3] study include that the subjects were not blinded, there was no placebo group, hydrocortisone was substituted for some subjects, and five patients dropped out of the study. The subjects could not be blinded as many had used fluticasone cream 0.05% before and knew the consistency. There was no placebo group because the investigators deemed it unethical not to treat pediatric patients with moderate to severe atopic dermatitis, so no subjects were left without treatment. The investigators also substituted hydrocortisone cream 2.5% for the fluticasone cream 0.05% if patients needed to use it on their face or intertriginous areas. Lastly, five patients either dropped out of the study or were lost to follow up.

CONCLUSION

The results of the three randomized controlled trials in this selective EBM review conclude that ceramide containing creams are a safe and effective treatment for atopic dermatitis. All three studies showed a statistically significant reduction in atopic dermatitis symptoms after the use of a ceramide containing cream. Additionally, the Sugarman et al[3] study showed there is no statistical difference between the ceramide dominant barrier cream and the fluticasone formula after 28 days of treatment of moderate-to-severe atopic dermatitis. This is advantageous

for pediatric patients who should not use steroid creams long term on their face. The ceramide cream can decrease the need for topical steroids. Future studies should examine combination therapy of a ceramide cream with a steroid cream. This type of research could also analyze the efficacy of ceramide creams being used for a longer duration as a maintenance or preventive therapy. In conclusion, this systematic review shows that ceramide containing creams are a safe and effective treatment for symptoms of atopic dermatitis.

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