Journal of Pakistan Association of Dermatologists. 2020; **30(1)**: 98-105.

Original Article

The role of ceramide, menthol and polidocanol on pruritus, skin barrier function, and disease severity of mild atopic dermatitis

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Abstract

Background Atopic Dermatitis (AD) relates with skin barrier defect. Unbearable itch leads to intense scratching, causing skin damage, and perpetuates the disease. The aim of this study is to investigate efficacy of topical ceramide, menthol, and polidocanol to decrease itch and AD severity, also improve skin barrier function.

Methods Total 30 subjects were included in this pre-experimental, before-after observational study. The subjects were children 8-18 years old with mild atopic dermatitis. We evaluated SCORAD index and daily patient-based Patient Eczema Scoring Time (PEST) for AD severity, transepidermal water loss (TEWL) using Tewameter to represent skin barrier function, and also visual analog scale (VAS) to observe itch. The preparation was applied twice daily for 4 weeks. The progression of AD after application, along with side effects, was evaluated on 5 minutes, week 1, 2, and 4.

Results SCORAD index started to decrease after 1-week application. PEST and itch VAS decreased as immediate as 5 minutes after application. Skin barrier function also improved represented by declining of TEWL values. The differences were statistically significant ($P < 0.05$).

Conclusion Combination of ceramide, menthol, and polidocanol suppress itchy and disease severity, also improve skin barrier function in AD patients.

Key words
Atopic dermatitis, pruritus, ceramide, skin barrier, moisturizer.

Introduction

Atopic dermatitis (AD) is the most common form of inflammatory skin diseases affecting up to 20% of children and could persist in adult.[1] Barrier disruption known as important component of AD pathophysiology and correlate with the disease severity.[1,2] Impaired barrier function increases vulnerability to environmental insults and increases transepidermal water loss (TEWL). Levels of TEWL correlate with AD severity.[2] Pruritus, which is defines as unpleasant sensation that evokes an urge to scratch, is the most dominant symptom and a hallmark of AD.[1,3,4] Pruritus has a negative impact on quality of life of AD patients, it often precipitates sleep disturbance, attention difficulties, and also social withdrawal.[5] It is important to notice that pruritus leads to an "itch-scratch" cycle that

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impaired epidermal barrier and enhancing inflammatory reaction that subsequently perpetuates the disease.[1] Itch-induced scratching seems to exacerbates lesions in clinical and experimental settings.[6]

Since itch is a prominent aspect of AD, the proper treatment of AD must be directed to evaluate and manage pruritus.[3] As stated in five pillars of AD management recommended by Asia Pacific consensus, medical treatment should be targeted to maintain skin barrier, suppress inflammation, and also control pruritus.[7] Moisturizing is considered as the first step in the treatment regimen in AD because it hydrates and restores epidermal barrier function. Furthermore, moisturizers may reduce itch, decrease the need for corticosteroids and prevent flares.[8] Ceramide, lipid molecules found naturally in high concentrations within cell membranes of stratum corneum, are already known as beneficial to repair skin barrier. Their major function is to keep skin barrier integrity that helps to prevent water loss.[9] Topical antiprurutic agents are known to be beneficial in itch management in AD patients. Menthol is a natural cyclic turpentine alcohol obtained from mint oils, or prepared synthetically. Applied topically, menthol dilates blood vessels, elicit cooling sensation, followed by an analgesic effect.[3,10] Menthol activates the Transient Receptor Potential cation channel subfamily M8 (TRPM8) receptor on C-fibers. When treating larger skin areas, polidocanol 2–10% in different galenic formulations can be used, frequently in combination with 3% urea.[3]

In this study, we evaluate the efficacy of topical combination of ceramide with menthol and polidocanol in controlling pruritus, improving skin barrier function, and decreasing disease severity in AD patients.

Methods

A pre-experimental, before-after observation study was carried out to investigate the efficacy of ceramide, menthol, and polidocanol combination in pruritus, skin barrier function, and disease severity of AD. Thirty AD patients were selected consecutively according to Hanifin & Rajka criteria in the outpatient department of Dermatology and Venereology of Dr. Soetomo Teaching Hospital, Surabaya, Indonesia. The study was carried out from May to September 2018. The study was reviewed and approved by Dr. Soetomo General Hospital Ethics Committee. An informed consent was obtained from each patient before the study.

The subjects were aged 8-18 years old with mild atopic dermatitis according to Scoring Atopic Dermatitis (SCORAD) index. They should not apply any moisturizer nor consume any systemic corticosteroid for 4 weeks before the study. Subjects had not suffered from immunosuppresive or other severe systemic diseases.

At baseline visit in outpatient clinic, ceramide dominant cream added with gel containing menthol and polidocanol were applied onto subjetcs' upper and lower extremities. Then subjects were ordered to do the same procedure at home regularly, twice daily after bath. Subjects were also provided with same body wash for twice daily bathing during the study.

Evaluation was conducted prior to the drug's application (baseline), at 5 minutes after first application (5 minute), at the end of weeks 1, 2 and 4 (1-week, 2-week, and 4-week respectively). The assessments were disease severity using SCORAD index and Patient Eczema Scoring Time (PEST), skin barrier function represent by transepidermal water loss (TEWL), and visual analog scale (VAS) for itch. Clinical assessment and instrumental measurement were performed on each

evaluation point. A dermatologist performed clinical examination of extent and intensity of erythema, papules, crust, excoriation, lichenification, and dryness that scored to determine SCORAD index. Disease severity also measured using simple patient-centric AD scoring system; Patient Eczema Scoring Time (PEST) was assessed subjectively by patients or care giver. PEST was recorded daily using a diary containing pictorials ranging from 'not at all unhappy' to 'extremely unhappy' and scoring 1–5. Subjects were also asked to point 0 - 10 in VAS chart to express their itchiness level, where 0 represented no itchy and 10 represented most itchy. The value of TEWL was analyzed using Tewameter TM300® (Courage + Khazaka electronic GmbH, Cologne, Germany). The measurement was done on the inner forearm following washing with normal saline and acclimation in a room at 20±1 °C and 40%±5% relative humidity for 15 minutes.

Data were analyzed descriptively and comparatively using One-Sample Kolmogorov-Smirnov test by Statistical Package for the Social Sciences (SPSS) version 23 (SPSS Inc., Chicago, IL, USA). Level of significance is $p< 0.05$.

Results

Thirty subjects, 14 females and 16 males, who met inclusion criteria were selected consecutively and enrolled to this study. Subjects were mostly children. When visit to outpatient clinic, subjects were diagnosed as mild AD, according to Hanifin & Rajka criteria and SCORAD index. All subjects and their parents were informed about the study protocol and signed consent to entry the study. For subject under 17 years olds, the consent was signed by their parent.

All subjects had mild AD according to SCORAD index on baseline, as observed in **Table 1**. Pruritus was observed in all subjects. Five subjects reported mild pruritus (VAS < 4), 17 subjects with moderate pruritus (4 ≤ VAS < 7), 7 subjects with severe pruritus (7 ≤ VAS < 9), and only 1 subject complained a very severe pruritus (VAS ≥9).[6] Skin TEWL was measured in special acclimation room. Baseline TEWL was 26.91±14.48 g/m^2/h (mean ± SD). The first evaluation was done on 5 minutes after application. Later evaluations were in the end of week 1, week 2 and week 4.

Pruritus as dominant symptom of AD was measured using VAS for itch. On the baseline the average itch level was moderate, while on week 4 the itch level was mild. Five minutes after drug application, the itch level was decreased significantly to the upper border of mild itch, as observed in Table 2. At other evaluation points, the VAS score was consistently decreased, reaching 0 score on week 2 and 4, as seen in **Figure 1**. The differences were statistically significant ($P < 0.05$). Skin barrier function represent by TEWL level, as presented in **Figure 1**, was significantly improved after the drugs application. Average TEWL level at the end of study was

Table 1 Baseline characteristic

Mean age (years ± SD[§])	10.9 ± 3.28
Male, n (%)	16 (53.3)
Female, n (%)	14 (46.7)
SCORAD*, mean±SD[§] (category)	19.04 ± 4.13 (mild)
Itchy VAS[‡]	
Mild, n (%)	5 (16.7)
Moderate, n (%)	17 (56.7)
Severe, n (%)	7 (23.3)
Very severe, n (%)	1 (3.3)
Mean ± SD§ (category)	5.20 ±1.60 (moderate)
TEWL[†], mean ± SD§(g/m^2/h)	26.91±14.48
PEST^, mean ± SD[§]	2,97± 0.85

*SCORAD: scoring atopic dermatitis; [‡]VAS: visual analog scale; [†]TEWL: transepidermal water loss; ^PEST: Patient eczema severity time; [§]SD: standard deviation

Table 2 Comparison of clinical evaluation before and after treatment

Clinical evaluation		*Mean ± SD[§](n = 30)*
SCORAD* index	Baseline	19,04 ± 4,13
	5-minute evaluation	19,04 ± 4,13
	1-week evaluation	12,93 ± 3,36
	2-week evaluation	9,41 ± 2,94
	4-week evaluation	6,12 ± 2,07
VAS for itch[‡]	Baseline (category)	5,20 ± 1,61 (moderate)
	5-minute evaluation (category)	3,97 ± 1,56 (mild)
	1-week evaluation (category)	2,73 ± 1,17 (mild)
	2-week evaluation (category)	1,23 ± 1,04 (mild)
	4-week evaluation (category)	0,30 ± 0,47 (mild)
TEWL† (g/m2/h)	Baseline	26,91 ± 14,48
	5-minute evaluation	16,86 ± 8,75
	1-week evaluation	18,31 ± 10,67
	2-week evaluation	14,97 ± 7,66
	4-week evaluation	9,48 ± 2,29
PEST^	Baseline	2,97 ± 0,85
	5-minute evaluation	2,30 ± 0,84
	1-week evaluation	1,77 ± 0,68
	2-week evaluation	0,90 ± 0,66
	4-week evaluation	0,30 ± 0,47

*SCORAD: scoring atopic dermatitis; [‡]VAS: visual analog scale; [†]TEWL: transepidermal water loss; ^PEST: Patient eczema severity time;[§]SD: standard deviation

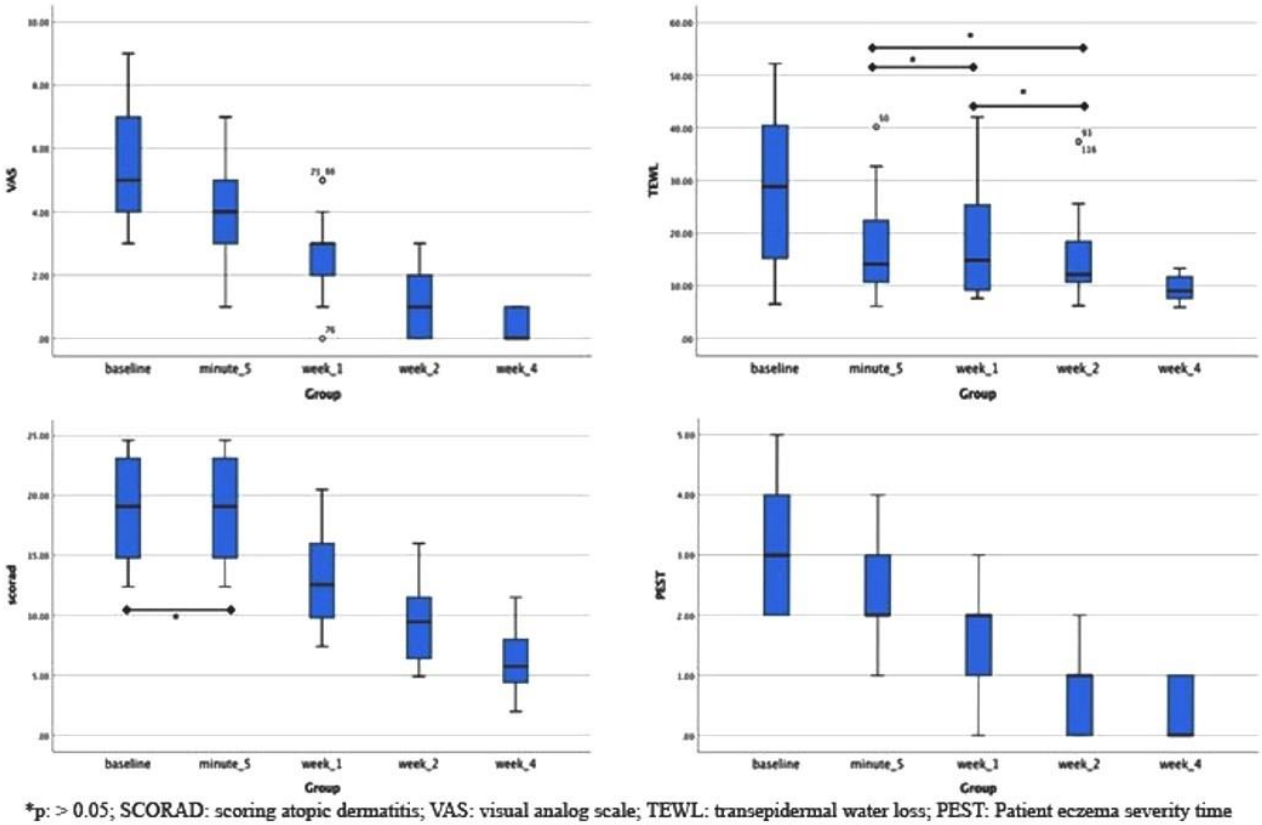

Figure 1 Diagram chart of clinical improvement before and after treatment

decreased from baseline. This significant decrease appears as soon as 5 minutes after drug application. However, it was not statistically significant between 5 minutes and week 1 evaluation **(Table 2)**.

The SCORAD score started to decrease at week 1 evaluation, and the trend was consistent among later evaluation point, week 2 and week 4 **(Figure 1)**. The differences between groups were statistically significant.

PEST is subjective assessment of disease severity, including itch sensation, relapse, and recovery according to patients' own perspective. At week 4 the average PEST score was significantly decreased and kept decreasing significantly ($P < 0.05$) **(Figure 1)**.

Discussion

Subjects in this study were 8-18 years old children, with mean age 10.9 years old. Gender proportion of the subjects was comparable. All subjects were diagnosed clinically as AD according to widely used criteria published by Hanifin and Rajka that composed of 4 Major and 23 Minor criteria. AD is established when 3 major and 3 minor criteria were met.[11,12] Even though categorized as having mild AD (SCORAD < 25), subjects were bothered by itching.

Atopic dermatitis requires holistic management. Integrated therapeutic recommendation "five pillars of AD management" introduced by Thiru Thirumoorthy which includes education, avoidance of triggers, rebuilding barrier function, clearance of inflammatory disorders, and control itch-scratch cycle has been adapted by Asian and Asia-Pacific guidelines and been practiced until now.[7,11] Combining two pillars, rebuilding barrier function and control itch-scratch cycle, in one step treatment seems to be promising and simplify AD patients' care.

Itching and skin xerosis are the hallmark of AD pointing out that skin barrier disruption is the background condition. In addition to filaggrin defect, which already known to have central role in skin natural moisturizing factor formation, ceramide-cholesterol ratio is also important to maintain the stratum corneum lipid bilayer structure. Abnormality in those two factors will provide skin barrier defect, that cause an increase in TEWL favouring dryness which initiate a kind vicious circle of itching and scratching.[14,15] Ceramide level in AD skin is lower than healthy skin. Ceramide containing moisturiser are thought to be beneficial for AD patients.[14]Transepidermal water loss is reflective of the skin barrier function and is associated with pruritus intensity in AD patients. TEWL has been shown to be lower at night. It explains the nocturnal exacerbation of atopic itch.[16]As revealed in this study, TEWL is significantly decreased immediately after ceramide combination application. Regular application for 4 weeks can maintain the low level of TEWL. The ceramide inside the preparation is thought to be responsible for this condition. However, a study in 2011 compared ceramide containing moisturizers with the other two different composition, revealed there is no significant difference in disease severity for mild to moderate AD.[14,17] Combination of ceramide moisturizer with menthol and polidocanol can restore skin barrier immediately, and the effect persist with regular application.

Pruritus is dominant symptom of AD, even in mild disease. Atopic pruritus seems to be the result of epidermal hyper innervation that is mainly caused by imbalance between nerve elongation factors (nerve growth factor [NGF]) and nerve repulsion factors (semaphorin 3A [Sema 3A]) produced by keratinocytes.[18]

Controlling pruritus means preventing exacerbation, suppressing disease severity, and upgrading patients' life quality. Assessing itch is still challenging. The most commonly used method is using subjective VAS scored 0-10. VAS was originally build to assess pain intensity, but it was adopted for pruritus evaluation.[6] In this study, subjects were bothered by moderate pruritus on the baseline visit. After drug application, the itch was decreased within 5 minutes after. Menthol and polidocanol, topical neuromodulators, are assumed to be responsible component for controlling pruritus.

Polidocanol is a non-ionic surfactant belonging to topical anesthetics groups, which shown to have antipruritic effect and has been proven to relieve itch in several condition.[4] Antipruritic effect of Polidocanol has been proven to significantly reduce non-histamine-induced itch.[19] Beside antipruritic properties, polidocanol also has moisturizing effects. In an open multicenter drug surveillance in 1997, 1611 patients with AD, dry eczema, psoriasis, and pruritus treated with preparation containing of 5% urea and 3% polidocanol. Four weeks application has shown that pruritus was greatly reduced, almost half of patients (48.9%) were free of itch at the end of observational period. The effect was observed as soon as 2 weeks of daily application, the first study evaluation point. Mild adverse effects like burning sensation, itching, and irritation happened only in 2.8 % patients.[20]

Menthol is monoterpene in the essential oils isolated from menthe species e.g. Menthe piperita and Mentha arvesis, has been known for its antipruritic and analgesic effect since ancient times. When applied to skin, it provokes a cool sensation by achieving a temperature-sensitive receptor, member of melastatin transient receptor potential subfamily (TRPM8), expressed on cutaneous sensory fibers. Antipruritic properties of menthol also seem to be promoted from selective activation of κ-opioid receptors, which.[21] The κ-opioid receptor agonist can reduce itch, while μ-opioid receptor agonist will induce it. Serum β-endorphin, a μ-opioid receptor agonist, in AD patients is increase compared with control.[16] Menthol at concentration of 1%-3% will reduce itchy, but greater concentration such as 10% can lead to irritation.[22] A study discovered that subjective cooling sensation following menthol topical application last up to 32 minutes.[23] Patients who reported decrease pruritus by cold sensation will benefit from menthol containing topical preparation.[18]

Suppression of disease severity in this study was shown by reduction of SCORAD index with regular application of moisturizer preparation. The use of moisturizer cream alone has shown to have beneficial effect to improve clinical evolution in mild to moderate AD. Six previous studies comparing moisturizers alone and no treatment control group showed clinical evolution favouring treatment group after one to six months treatment.[24] A recent study about application of ceramide dominant moisturizer therapy for children under 6 years old reported the improvement of disease severity in all subjects, preventing relapse in 45%, result in 58% subject satisfaction.[25] Additional anti inflammatory and anti pruritus properties provide statistical superior effect on reduction of Eczema Area Severity Index (EASI) compare with control groups treated with simple moisturizer cream.[15] In this study, combination of topical ceramide with menthol and polidocanol can reduce SCORAD index after one-week application. Continuing regular daily application until 4 weeks maintains the effect.

To improve sensitivity of detecting changes in disease severity, this study also used PEST score. The PEST score records AD severity,

relapse and recovery as experienced by patient or caregiver.[25] PEST correlated well with SCORAD index, and can improve sensitivity in severity change of AD.[25] In this study, PEST score in the 5 minutes evaluation was significantly decreased compare with baseline **(Table 2).** This is in line with the result of a study comparing PEST and SCORAD in children in various AD severities treated with ceramide dominant moisturizers by Koh et al. In that study, PEST demonstrated greater responsiveness to AD severity change compared to SCORAD. PEST could be more sensitive to measure AD severity because of its patient-friendly scale range and daily measurement characteristic.[25]

Daily use of this combination for at least one week leads to decreased disease severity clinically and subjectively. Controlling itch-scratch cycle along with improving skin barrier function is important to suppress AD severity.

Conclusion

Combination of ceramide, menthol, and polidocanol improve skin barrier function, relieving pruritus, and result in decreasing AD severity.

Acknowledgement

The authors have no conflict of interest in this study. Authors would like to thank the hospital staff to help during data collection and patients enrolled in the study

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