The effectiveness of ceramide moisturizing cream in pruritic papular eruption treatment of HIV/AIDS patients

Ayu Wikan Sayekti, Ann Kautsaria Putri, Satiti Retno Pudjiati, Dwi Retno Adi Winarni

ABSTRACT

**Background:** Pruritic papular eruption (PPE) is one of the most common skin manifestations in HIV/AIDS patients. Pruritic papular eruptions are due to immune dysregulation, causing dominance of interleukin-4, which causes a decrease in ceramide synthesis (CER) and impaired skin barrier function. This study aimed to investigate the effectiveness of CER over non-CER moisturizing cream in HIV/AIDS patients with PPE.

**Methods:** Double-blind experimental design. The research subjects are PPE patients at Dr. Sardijto General Hospital. CER and non-CER moisturizing cream are applied for three weeks, respectively. Analysis of the trans-epidermal water loss (TEWL), skin hydration, and itching were analyzed using an unpaired T-test or the Mann-Whitney test with a significance of p<0.05.

**Results:** Ceramide synthesis moisturizing cream decreased the TEWL value by 3.56 ± 2.38 g/m²/hour; increased the value of skin hydration by 16.39±7.19 a.u.; decreased skin lesions by 0.79 ± 4.95; reduced itching by 1.54 ± 0.78 and without causing side effects. Non-CER moisturizing cream decreased the TEWL value by 1.57 ± 2.00 g/m²/hour; increased the value of skin hydration by 12.03 ± 6.88 a.u.; decreased skin lesions by 1.42 ± 3.00; reduced itching by 1.17 ± 0.70 and also without causing side effects.

**Conclusion:** Ceramide cream is more effective than non-CER moisturizing cream in reducing TEWL and increasing skin hydration. Ceramide and non-CER moisturizing creams have the same effectiveness in reducing the number of lesions and reducing itching. Ceramide and non-CER moisturizing creams do not cause side effects.

**Keywords:** ceramide moisturizer, pruritic papular eruption, skin hydration, TEWL

INTRODUCTION

Pruritic papular eruption (PPE) is one of the manifestations of skin disorders commonly found in patients with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), which is chronic and difficult to treat. This disorder is reported quite often in tropical and subtropical countries with a mean prevalence of 11-46%. The etiology and pathogenesis of PPE are not fully understood. Several factors considered to play a role in the etiology and pathogenesis of PPE are hypersensitivity to insect bites in HIV/AIDS patients, host cellular immune response to abnormal infection processes, drugs, skin autoimmune reactions, and direct effects of viruses through immune dysregulation and skin tissue. Pruritic papular eruptions are associated with an increased role of Th2 lymphocyte cytokines in the advanced stages of HIV/AIDS infection and result in impaired skin barrier function. Research in the United States (2010) which measured skin barrier function in HIV patients with xerotic dermatitis, without xerotic dermatitis, and healthy non-HIV controls showed a significant decrease in skin barrier function in HIV patients without xerotic dermatitis compared to healthy controls and impaired barrier function increasingly significant in patients with xerotic dermatitis through an “inside-to-outside” mechanism mediated by the dominant Th-2 lymphocyte cytokine in HIV/AIDS infection. The potential role of Th2 lymphocyte cytokines, especially the increase in IL-4, will suppress ceramide synthesis through interference with catalytic enzymes, thereby disrupting the skin barrier function. Increased IL-4 also induces vascular cell adhesion molecule (VCAM), which increases eosinophil and macrophage migration. Increased IL-4 is associated with reduced E-cadherin, inhibition of involucrin synthesis, desmosome maturation, and inhibition of profilaggrin synthesis into filaggrin, which is a natural moisturizing factor (NMF) precursor. These factors impair skin barrier function, increasing skin sensitivity and itching sensation.

The PPE therapy in people living with HIV/AIDS is still a challenge because various treatment modalities have not been able to solve the problems that patients complain about. Impaired skin barrier function, which results in dryness of the skin and the appearance of itching in dermatoses generally improves with the
application of moisturizers. Moisturizers are topical products designed to improve and maintain skin barrier function. The latest generation of moisturizers contains better ingredients than classic moisturizers. The latest generation of commonly used moisturizers are ceramides (CER), free fatty acids, and cholesterol, which help replace fat deficiency in several skin diseases with impaired skin barrier function. The skin barrier function can be assessed through non-invasive biotechnological methods based on the amount of water lost through the stratum corneum or transepidermal water loss (TEWL) and skin hydration level.

A CER is a heterogeneous and complex sphingolipid group with the main structure containing sphingosine, phytosphingosine, or 6-hydroxy sphingosine, a C18-sphingoid base bound to an amide group by various non-hydroxy, α-hydroxy, or hydroxy acids. A CER is the stratum corneum's predominant lipid component, comprising 30–40% of stratum corneum lipids. It also plays an important role in the structure and maintenance of the skin's water-permeability barrier function. The skin barrier was interestingly investigated to determine whether a moisturizer containing CER is effective for the treatment of PPE in HIV/AIDS patients. To the best of the author's knowledge, no studies have measured the effectiveness of giving a moisturizing cream containing CER to patients with PPE. This study aimed to evaluate the moisturizing cream containing CER for treating PPE in HIV/AIDS patients in the context of TEWL, skin hydration, and itching.

**MATERIALS AND METHODS**

This study is an analytical study with a double-blind experimental design. The research was conducted at Dr. Sardjito General Hospital, Yogyakarta, Indonesia, and the Research Laboratory of the Department of Dermatology and Venereology, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada. Each subject received a ceramide moisturizing cream (CER) and non-CER, which was applied to the volar part of the forearm on different sides. The measurements taken were the rate of evaporation of water through the epidermis (TEWL) using a tewameter TM 300°, skin hydration using a corneometer CM 825°, the number of lesions, and itching with a VAS (visual analog scale) assessment as well as subjective side effects. Measurements were made in weeks 0 and 3.

The research population is HIV/AIDS sufferers with PPE who seek treatment at Dr. Sardjito General Hospital and meet the inclusion and exclusion criteria. Analysis of the results was done using an unpaired T-test or Mann-Whitney test. Multivariate analysis using MANOVA aims to determine what variables have changed after using ceramide moisturizing cream with a 95% confidence degree and declared significant if the p-value < 0.05.

**RESULTS**

**Characteristics of Research Subjects**

At the end of the study, the envelope was opened containing information on the contents of cream A and cream B. Cream A was a CER moisturizing cream (right arm), and cream B was a non-CER moisturizing cream (left arm). The characteristics of the research subjects are shown in Table 1.

Lesions on the upper extremities were found in all subjects (100%), followed by lesions on the lower extremities (67%), back (63%), chest (46%), and abdomen (33%). Efflorescence lesions in the form of hyperpigmented papules, excoriations, macules, and hyperpigmented patches were found in all subjects (100%) and followed by erythematous papules (96%). The normality test using the Saphiro-Wilk test showed that the data was normally distributed in addition to the variable number of lesions.

**Results of Bivariate Analysis**

The mean difference analysis in TEWL of CER and non-CER moisturizing cream using independent t-test. The average TEWL of week 0 of CER moisturizing cream was 13.19 ± 3.78, and the average TEWL of week 0 of non-CER moisturizing cream was 11.79 ± 3.69 (p=0.201). The average TEWL of the 3rd week of CER moisturizing cream was 9.63 ± 3.18, and the average TEWL of the third week of non-CER moisturizing cream was 10.23 ± 3.51 (p=0.543). The results of the mean difference delta in TEWL are shown in Figure 1.

The mean difference analysis in skin hydration of CER and non-CER moisturizing creams using independent t-test. The average skin hydration week 0 CER moisturizing cream was 34.94 ± 6.15, and the average skin hydration week 0 non-CER moisturizing cream was 34.63 ± 6.82 (p=0.807). The average skin hydration in the 3rd week of the CER moisturizing cream was 51.33 ± 8.35, and the average of the 3rd week of the non-CER moisturizing cream was 46.66 ± 9.31 (p=0.074). The results of the mean difference delta in the average skin hydration are shown in Figure 2.

The mean difference analysis in the mean number of CER and non-CER moisturizing cream lesions using the Mann-Whitney test. The average number of lesions in week 0 of CER moisturizing cream was 23.58 ± 1.39, and in week 0 of non-CER moisturizing cream was 17.38 ± 1.14 (p=0.043). The mean number of

**Table 1. Characteristics of research subjects**

<table>
<thead>
<tr>
<th>No.</th>
<th>Characteristics</th>
<th>n</th>
<th>%</th>
<th>Mean</th>
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<tbody>
<tr>
<td>1.</td>
<td>Age (years)</td>
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<td>32.67 ± 6.68</td>
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<td></td>
<td>Youngest</td>
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<td>-</td>
<td>32.67 ± 6.68</td>
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<td>Oldest</td>
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<td>-</td>
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</tr>
<tr>
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<td>95.83</td>
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</tr>
<tr>
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<td>Female</td>
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<tr>
<td>3.</td>
<td>Length of PPE (months)</td>
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<td>76.04 ± 7.92</td>
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<tr>
<td></td>
<td>Lowest</td>
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<td>12.6</td>
<td>10.46 ± 1.17</td>
</tr>
<tr>
<td></td>
<td>Longest</td>
<td>36</td>
<td>4.17</td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>Number of CD4 T lymphocyte cells (cell/mm³)</td>
<td>321</td>
<td>4.17</td>
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lesions in the 3rd week of CER moisturizing cream was 22.79 ± 1.31. This value was higher than the average of the 3rd week of non-CER moisturizing cream of 15.96 ± 0.97 (p=0.046). The results of the mean difference delta in the average number of lesions are shown in Figure 3.

The mean difference analysis in the average itching feeling of CER and non-CER moisturizing cream using independent t-test. The average itching week 0 of the CER moisturizing cream was 7.08 ± 1.06, and the average itching week 0 of the non-CER moisturizing cream was 6.96 ± 1.08 (p=0.675). The average itching at the 3rd week of CER moisturizing cream was 5.54 ± 0.83. This value was lower than the average itching in week 3 of non-CER moisturizing cream, which was 5.79 ± 0.93 (p=0.241). The results of the mean difference delta of itching are shown in Figure 4.

The CER and non-CER moisturizing creams showed no side effects in all subjects. Mild erythema that disappeared in the first three days of use was found in one subject (4.17%) on the arm using CER and non-CER moisturizing cream.

**Multivariate analysis**

The multivariate test in this study used the MANOVA (multivariate analysis of variance) test. The variables included in the multivariate analysis were p-value < 0.25 in the bivariate analysis, including changes in TEWL, skin hydration, and itching. The results of the multivariate test are shown in Table 2.

**DISCUSSION**

The youngest age of the subjects with PPE in this study was 24 years, and the oldest was 50 years, with a mean age of 32.67 ± 6.68 years. Most of the subjects were male (95.83%). A large proportion of people living with HIV/AIDS in this age group is associated with higher-risk sexual behavior and increased commercial sex services by men.10 Research by Afonso et al. (2012) in Brazil also reported that the mean age of PPE sufferers was 38.3 years, the age range was 28-61 years, and the predominance of male subjects (72.2%).11

This study showed that the mean number of CD4 T lymphocytes was 76.04 ± 7.92 cells/mm3, and most of the subjects had a CD4 T-lymphocyte count < 200 cells/mm3 (87.5%). Research by Wiraguna and Adam (2018) also reported that most of the CD4 T lymphocyte cells in PPE patients was < 200 cells/mm3 with a CD4/CD8 T lymphocyte ratio lower than normal.3

The pruritic papular eruption is a chronic itchy dermatosis in HIV/AIDS patients. Previous studies have shown that more than half of people with HIV/AIDS reported PPE as an early manifestation that appeared several months before the diagnosis was made.2,12

The results of this study indicate that the length of PPE suffers from 1 to 36 months, and the mean suffers from PPE is 10.46 ± 1.17 months.

Research by Chua et al. (2014) stated that lesions on the extremities (arms and legs) were found in most patients with PPE. These findings are consistent with the results of this study, namely lesions on the upper extremities were found in all subjects (100%), followed by lesions on the lower extremities (67%), back (63%), chest (46%) and abdomen (33%). This confirms the alleged role of insect bites in the etiopathogenesis of PPE due to the predilection for dominant lesions in exposed skin areas.13

Research by Arista and Murtiastutik (2015) showed that the main skin lesions of PPE were hyperpigmented papules (58.6%), followed by hyperpigmented...
Several studies have shown that CER is an important component of intercellular lipids needed to connect corneocytes to the skin barrier to protect the underlying skin tissue. The CER morphology holds corneocytes from adhering to the intercellular matrix, thereby maintaining skin integrity. The tightly packed lipid array forms a system to prevent the increase in TEWL and makes the stratum corneum impermeable/waterproof. A decrease in CER, especially CER 1 and 3, is associated with a significant increase in TEWL, the main factor affecting skin dryness. CER moisturizing cream (ceramide-3) can improve skin barrier function disorders (reduce TEWL) through a semi-occlusive moisturizing effect that limits water evaporation from the skin.

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Bivariate analysis (test of difference in mean change) of TEWL showed that the difference (decrease) in the mean TEWL of non-CER moisturizing cream was higher than the difference (decrease) in the mean TEWL between the arms using CER moisturizing cream and non-CER moisturizing creams. CER moisturizing cream, is more effective in reducing TEWL than non-CER moisturizing creams. The subjects’ mean at the beginning of the study was in good TEWL condition (11 – 14 g/m2/hour).

The approach to interpreting the results of this study after giving moisturizing cream showed that in TEWL, there was an improvement in TEWL from good category (11 – 14 g/m2/hour) to very good (<11 g/m2/hour).

Increased skin hydration occurs through an increase in the expression of the FLG gene that encodes filaggrin, resulting in increased levels of natural moisturizing factor (NMF) to maintain skin hydration (46 – 52 a.u.). The approach to interpreting the results of this study after giving moisturizing cream showed an improvement in the dry skin hydration category (34 – 35 a.u.) to good hydration (46 – 52 a.u.).

Research by Spada (2018) reports that a moisturizer with CER-3 content is the latest generation of moisturizer that increases skin hydration because it resembles the skin’s natural moisturizing system. Increased skin hydration can reduce therapy duration and disease symptoms with impaired skin barrier function. Increased skin hydration occurs through an increase in the expression of the FLG gene that encodes filaggrin, resulting in increased levels of natural moisturizing factor (NMF) to maintain skin hydration (46 – 52 a.u.).
homeostasis of the stratum corneum. Low NMF levels are associated with mutations in the FLG gene, a major factor in skin barrier disruption.

The subjects in this study used the right arm as the dominant arm when working and doing daily activities. Research by Novak Bilic et al. (2018) showed that the dominant arm was more affected by exposure, thus allowing more skin lesions. This is similar to this study in that the dominant arm has more skin lesions.

This study showed that CER moisturizing cream was not more effective than non-CER moisturizing cream in reducing the number of lesions. Most of the subjects had a CD4 T lymphocyte count < 200 cells/mm³ (87.5%), so the more severe the disruption of skin barrier function occurred. This increases skin sensitization to exposure to antigens and environmental stimuli, including arthropod bites that can activate the inflammatory process. This causes new PPE lesions before the old ones disappear or exacerbate existing ones.

Research by Kubba et al. (2009) showed that post-inflammatory hyperpigmented lesions took 3 – 24 months to fade completely. Research by Udompataikul (2015) showed that CER has an anti-inflammatory effect both in vitro and in vivo. Still, the anti-inflammatory response, especially the parameters of edema and erythema, is slower and weaker than the corticosteroid response. Research by Kim et al. (2002) showed that CER can inhibit melanogenesis by activating extracellular-signal-regulated kinase (ERK), but CER cannot directly suppress tyrosinase. The number of lesions is greater in the dominant arm, the anti-inflammatory and depigmentation effects were weak, and due to the short observation time, it was possible that the changes in lesion reduction were not significant.

Scratching due to severe itching that lasts chronically (itch-scratch cycle) results in mechanical disruption of the skin barrier in the form of a decrease in the skin's natural moisturizing content. Topical ceramide administration aims to improve skin barrier function and reduce itching to break the chronic itching-scratch cycle.

The CER and non-CER moisturizing creams in this study showed no side effects in all subjects. Mild erythema in one subject that disappeared in the first three days could be due to preservatives in the content of the two creams. Preservatives are important components that inhibit the development of microorganisms, extend the shelf life of cosmetic products, and prevent oxidation of active ingredients. Still, they have been reported to cause skin irritation and are a common source of cosmetic allergies.

CER moisturizing cream is an emollient with a mechanism of action on fluidity and permeability of cell membranes to improve the skin barrier function. This is in accordance with the results of the multivariate analysis of this study, namely that CER moisturizing cream has an effect, especially on changes in TEWL, by 15.8%, followed by an effect on changes in TRL. Skin hydration by 7.1% compared to non-CER moisturizing creams.

CONCLUSION

The CER moisturizing cream is effective and more effective than the non-CER moisturizing cream in lowering TEWL. CER moisturizing cream is effective and more effective than non-CER moisturizing cream in increasing skin hydration. CER and non-CER moisturizing creams have the same effectiveness in reducing the number of lesions. CER and non-CER moisturizing creams have the same effectiveness in reducing itching. CER and non-CER moisturizing creams do not cause side effects.

CONFLICT OF INTEREST

There is nothing to declare.

ETHICS IN PUBLICATION

The research has obtained an ethical suitability letter on 26th June 2020 from the Medical and Health Research Ethics Committee (MHREC) Faculty of Medicine Public Health and Nursing Universitas Gadjah Mada - Dr. Sardijito General Hospital with reference number KE/FK/0622/EC/2020.

FUNDING DISCLOSURE

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AUTHORS CONTRIBUTION

Sayekti A.W. wrote the manuscript with support from Putri A.K. Both Pudjiastuti S.R. and Winarni D.R.A. supervised the project.

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