Efficacy of a Moisturizer for Pruritus Accompanied With Asteatosis in Dialysis Patients: An Open-Label, Randomized, Exploratory Study

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Background: In dialysis patients, skin disorders (dryness and itching) are frequently observed and treated with a moisturizer, in the absence of clear evidence of efficacy.

Study Design: An open-label, randomized, before/after, parallel-group, comparative/exploratory study.

Setting & Participants: 12 Japanese patients with chronic kidney failure undergoing maintenance hemodialysis who presented with dry skin and itching.

Intervention: Patients received a topical heparinoid moisturizer as the study drug for 2 weeks from the first day of the study treatment, followed by either a 2-week washout (group A: 6 participants) or further 2-week treatment (group B: 6 participants).

Outcomes: The primary end point was change in water content in the stratum corneum in the hypochondrium. Secondary end points included change in visual analogue scale itching score and subjective evaluations of symptoms. To evaluate safety, adverse events were also investigated.

Measurements: Water content of the stratum corneum, dryness/itching improvement rating, itching visual analogue scale/duration of itching, photographic evaluation of skin symptoms, principal investigator's overall assessment of study drug, and adverse events.

Results: Mean water content of the stratum corneum in the combined groups significantly increased at week 2 (51.2 arbitrary units [AU] vs treatment start day, 31.6 AU; $P<0.001$), but significantly decreased at week 4 in group A, in which patients discontinued treatment with the study drug (39.4 AU; $P = 0.005$). Other efficacy end points, including the visual analogue scale itching score, were also improved by treatment with the study drug, but such improvement was not sustained after discontinuation of treatment. There were no adverse events related to the study treatment.

Limitations: Only Japanese patients were included in the study, with a small sample size.

Conclusions: Continuous application of the topical heparinoid moisturizer increased water content in the stratum corneum and lessened itching in dialysis patients.

Funding: Maruho Co, Ltd.

Trial Registration: Registered at the University Hospital Medical Information Network Clinical Trials Registry with study number UMIN000017016.

Complete author and article information provided before references.

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Kidney Med. 1(4): 191-199. Published online June 27, 2019.

doi: 10.1016/j.xkme.2019.04.008

Dialysis patients frequently experience skin disorders, with moderate to severe dryness experienced by ~75% of patients,[1] and itching, by ~40%.[2] It has been reported that more intense itching in particular tends to lower patients' quality of life[3] and that patients more bothered by itching have more disturbed sleep, resulting in increased risk for mortality.[4,5] These findings suggest that the treatment of patients' skin disorders is an important challenge. Such treatment may improve not only quality of life, but also patients' prognosis.

Water content of the stratum corneum, which is the outermost layer of the skin, is often used in dermatology as a marker to indicate the level of dryness of the skin. Its use for evaluating not only dry skin conditions in nonpatients[6] but also for those with a number of diseases, including atopic dermatitis[7] and psoriasis,[8] has been reported. A study that measured the water content of the stratum corneum of dialysis patients and healthy volunteers using a high-frequency conductance meter has demonstrated significantly lower water content in dialysis patients.[9] In addition, structural disturbance and lower glycerol content in the stratum corneum have been reported in the forearms of dialysis patients.[10] Because these physiologic characteristics of dialysis patients are similar to those of asteatosis, treatment with a moisturizer is considered logical.[11]

However, the pathogenesis of itch in dialysis patients mostly remains obscure, although stimulation by parathormone and histamine are considered to be main contributing factors,[12] and pharmacotherapy for itching itself is sometimes not sufficiently effective. Partly because itching sometimes accompanies dry skin, some argue that application of a moisturizer is effective for dialysis patients reporting skin disorders.

In Japan, topical heparinoids are widely used as ethically approved drugs for the treatment of asteatosis. Heparinoids absorb and retain water and are known to increase the water content of the stratum corneum when applied to the skin.[13] Topical heparinoid drugs are sold worldwide for the treatment of superficial thrombophlebitis, among other conditions, but are indicated for asteatosis only in Japan.

Although a topical heparinoid moisturizer is also sometimes used for dry skin in dialysis patients, evidence of its usefulness is lacking.

We therefore evaluated the usefulness of a moisturizer for the treatment of skin disorders in dialysis patients, using a heparinoid-containing preparation. End points included the effects of the study drug on the water content of the stratum corneum and itching, which were evaluated in an exploratory manner.

METHODS

Setting and Population

The study was conducted at the Kidney Disease Clinic of Nippon Medical School, during the period from May 2015 to January 2016. The study population consisted of 12 patients with chronic kidney failure undergoing hemodialysis, aged between 20 and 80 years, who presented with dry skin and itching. Patients considered ineligible for the study by the investigators were excluded, including those who had used heparinoid or urea drugs within 2 weeks before the day of informed consent and those who had a history of allergy to any heparinoid drugs.

Study Design

This was an open-label, randomized, before/after, parallel-group, comparison study. The study timeline is shown in Figure 1. After the observation period, when patients were treated with only base therapy (oral drugs, injections, and/or topical agents that they were receiving on the day of informed consent; base therapy includes but is not limited to petrolatum and oral antihistamines), all patients were treated with the study drug in combination with base therapy during treatment period I, from the treatment start day to 2 weeks afterward (week 2).

Next, patients were randomly assigned to either group A, which received base therapy alone, or group B, which continued the moisturizer in combination with base therapy, during treatment period II, from week 2 to week 4. Randomization was performed at the start of the study with allocation to groups in a ratio of 1:1. Evaluation was performed on day 1 (treatment start day) and weeks 1, 2, 3, and 4.

Hirudoid lotion 0.3% (Maruho) containing heparinoid as the active ingredient was used. Application sites were dry and itching areas of the skin and always included the hypochondriac region. Participants were asked to apply the study drug twice daily, in the morning and after taking a bath in the evening (or at bedtime if not taking a bath). The standard application dose was 0.5 g, which was applied to an area twice that of the palm. Participants were instructed to watch a video to learn the external application method and amount of the study drug to be applied.

During the period from the observation start day to week 4 or the day of discontinuation, the use of urea preparations and heparinoid drugs other than the study drug was prohibited. In addition, changes in the dosing regimen of topical agents (eg, petrolatum and topical steroids), oral drugs (eg, oral antihistamines and oral antiallergic drugs) and injections, and changes in the conditions of dialysis therapy (type and treatment frequency) were prohibited.

Outcome Measures

At screening, the following items were recorded: sex, date of birth, height, weight, duration of kidney failure, duration of dialysis, and the proportion of skin area with dryness and/or itching to the total body surface area. The proportion of skin area with dryness and/or itching was visually determined by the investigators, based on the fact that the area of the entire hand is equal to ~1% of the body surface area.[14]

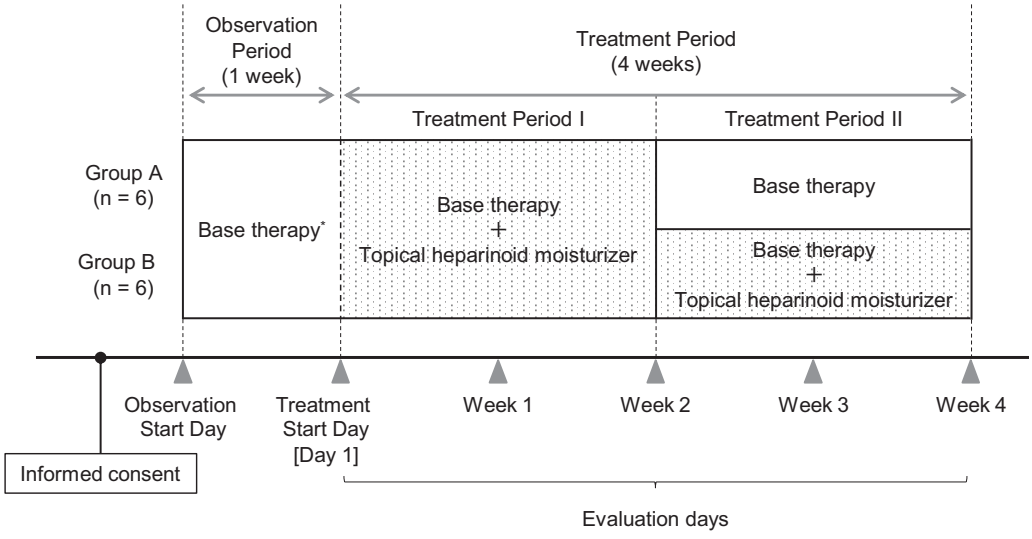

Figure 1. Study schedule.

On each evaluation day, participants were interviewed regarding their study drug adherence during the period since the previous evaluation day. In addition, the unused study drug of each participant was weighed at weeks 2 and 4 to calculate the amounts used in treatment periods I and II.

Primary End Point

On each evaluation day, the investigators measured the water content of the stratum corneum in the hypochondriac region. One site in either the right or left hypochondriac region was designated as the measurement site for each patient and measurement was conducted at that site between 1 and 2 hours after the start of dialysis. A corneometer (Model CM825; Courage-Khazaka Electronic) was used for measurement, which calculates water content of the stratum corneum using a method involving the use of a static capacitor. The corneometer is recommended for the evaluation of cosmetic effects in EU guidance.[15] An increase in a value as measured using this instrument, which indicates an increase in water content of the stratum corneum, suggested that the stratum corneum became flexible and the metabolism in the epidermis improved.[16]

Secondary End Points

On each evaluation day, participants rated their improvement in dryness and itching from the previous evaluation day on a 6-point scale of "disappearance of symptoms," "markedly improved," "improved," "slightly improved," "unchanged," and "exacerbated." Participants also evaluated skin itching at the study drug application site before the start of dialysis on a 100-mm visual analogue scale and then rated the change in duration of itching from the previous evaluation day on a 3-point scale of "shortened," "unchanged," and "prolonged."

The dermatologist independently evaluated the severity of dryness, desquamation, and erythema on 5-point scales using the evaluation criteria in Table S1, based on a photograph of the hypochondriac region (the same site at which water content of the stratum corneum was measured) taken on each evaluation day.

On the final evaluation day, the principal investigator (K.H.) assessed the usefulness of the study drug based on water content of the stratum corneum, dryness/itching improvement rating, itching visual analogue scale, and duration of itching, combined on a 5-point scale of "very useful," "useful," "slightly useful," "not useful," and "harmful."

Adverse events (subjective symptoms and objective findings) that occurred during the study period in participants treated with the study drug were examined.

Statistical Analysis

The efficacy analysis set consisted of participants who used the study drug only for the period defined in the study schedule and did not use the prohibited drugs or change the dosage regimen of the restricted drugs or the conditions of dialysis therapy. The safety analysis set consisted of participants who used the study drug after registration and for whom safety data were available for at least one time point after the start of the study treatment.

Mean values and standard deviations of patient demographic characteristics and mean values and 95% confidence intervals (CIs) of the water content of the stratum corneum and itching visual analogue scale were calculated. The results of efficacy end points between the observation start day and week 2 were analyzed as combined values from groups A and B. Efficacy end points were compared within groups using paired t tests and between groups using unpaired t tests at the 2-tailed significance level of 0.05. Bonferroni correction was used for the significance threshold for multiplicity testing.

Ethics

This study was approved by the Institutional Review Board at Nippon Medical School on December 26, 2014 (approval number 226024) and conducted in compliance with the Ethical Guidelines for Clinical Studies (Ministry of Health, Labour and Welfare Notice No. 255, dated July 30, 2003) and its partial amendments and the ethical principles of the Declaration of Helsinki. Written informed consent was provided by all patients.

RESULTS

Patient Demographics

Patient flow through this study is shown in Figure S1, and patient demographics are shown in Table 1. All participants completed this study without withdrawals/dropouts or failure of the restrictions, resulting in all participants being included in efficacy and safety analyses. The sex ratio of patients was 1:1 and mean age was 64.6 ± 11.7 years. Overall, patients were elderly with a higher standard deviation in group B compared to that in group A. Such bias between the 2 groups was due to the small sample size of 6 patients each and to 1 patient being aged in the 30s in group B. Mean duration of kidney failure and dialysis values were 18.7 ± 9.3 and 10.9 ± 6.1 years, respectively. Mean proportion of skin area with dryness and itching to total body surface area was 35.0% ± 22.0%.

Study Drug Adherence and Use

Throughout the treatment period, the drug was topically applied as instructed by all participants in both group A and group B. The mean amount of study drug used was 215.3 ± 69.5 g in treatment period I by group A, 193.3 ± 106.1 g in treatment period I by group B, and 215.7 ± 130.1 g in treatment period II by group B.

Table 1. Patient Demographics

	All Participants (N = 12)	Group A (n = 6)	Group B (n = 6)
Sex			
Male	6 (50.0%)	3 (50.0%)	3 (50.0%)
Female	6 (50.0%)	3 (50.0%)	3 (50.0%)
Age, y	64.6 ± 11.7	66.5 ± 5.1	62.7 ± 16.3
Height, cm	160.4 ± 7.0	160.6 ± 3.5	160.2 ± 9.8
Weight, kg	52.8 ± 11.2	52.9 ± 7.8	52.7 ± 14.7
Duration of kidney failure, y[a,b]	18.7 ± 9.3	11.8 ± 6.2	23.3 ± 8.2
Duration of dialysis, y	10.9 ± 6.1	6.8 ± 5.6	14.9 ± 3.1
Proportion of skin area with dryness/itching to total body surface area, %	35.0 ± 22.0	42.5 ± 24.2	27.5 ± 18.4

Note: Values given as number (percent) or mean ± standard deviation.
[a]Values calculated for patients with available data (treatment period I, 10 patients; treatment period II, group A, 4 patients; treatment period II, group B, 6 patients).
[b]Years since the first diagnosis of kidney failure. All participants in this study had end-stage kidney failure on the observation start day.

Water Content of the Stratum Corneum

Results of the stratum corneum water content measurements are shown in Figure 2. In treatment period I, when all participants were treated with the study drug combined with base therapy, mean water content of the stratum corneum in combined groups A and B was 33.1 (95% CI, 25.6-40.6) arbitrary units (AU) on the observation start day, 31.6 (95% CI, 26.6-36.7) AU on the treatment start day, 49.3 (95% CI, 43.8-54.8) AU at week 1, and 51.2 (95% CI, 47.3-55.1) AU at week 2. Mean water content of the stratum corneum was significantly increased at weeks 1 and 2 ($P < 0.001$ vs treatment start day).

In the following 2-week observation period (treatment period II), mean water content of the stratum corneum significantly decreased in group A, in which participants returned to base therapy alone ($P = 0.02$ at week 3: 41.7 [95% CI, 33.6-49.8] AU; $P = 0.005$ at week 4: 39.3 [95% CI, 31.7-47.1] AU vs week 2), but was almost maintained in group B, in which participants continued to apply the study drug ($P = 0.6$ at week 3: 47.7 [95% CI, 40.7-54.8] AU; $P = 0.4$ at week 4: 47.0 [95% CI, 38.0-56.0] AU vs week 2).

Dryness/Itching Improvement Rating

Results for the dryness improvement ratings are shown in Figure 3A. In treatment period I, dryness was at least "slightly improved" at weeks 1 and 2 in many participants. In treatment period II, dryness was aggravated in some patients in group A, but tended to be maintained or improved in group B. Results for the itching improvement rating were similar to those for dryness (Fig 3B).

Itching Visual Analogue Scale/Duration of Itching

Results of the itching visual analogue scale assessments are shown in Figure 4. In treatment period I, the mean itching visual analogue scale score in combined groups A and B on the observation start day was 35.2 (95% CI, 22.7-47.6) mm, that on the treatment start day was 47.8 (95% CI, 33.9-61.6) mm, that at week 1 was 30.8 (95% CI, 17.1-44.5) mm, and that at week 2 was 23.7 (95% CI,

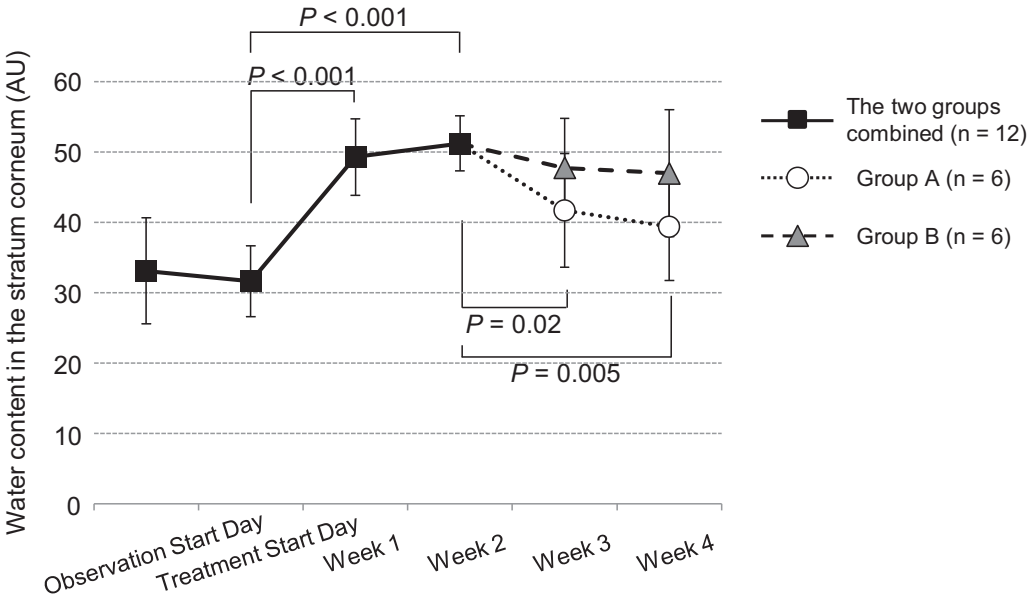

Figure 2. Water content in the stratum corneum in the hypochondriac region was measured on each evaluation day. Data points represent mean ± standard deviation. Statistical significance was evaluated using paired *t* tests. Abbreviation: AU, arbitrary unit.

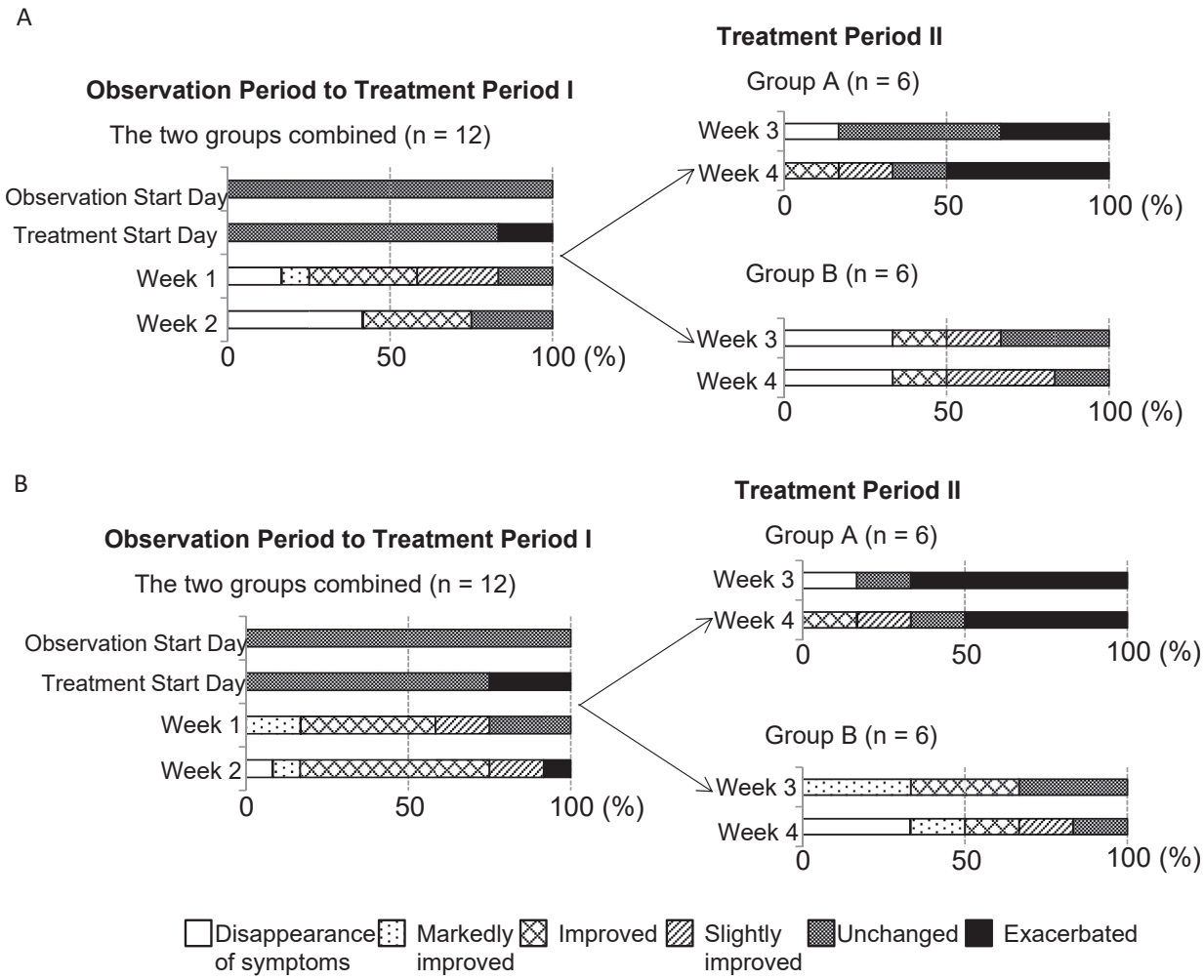

Figure 3. Dryness and itching improvement ratings. Patients assessed the improvement in their skin symptoms from the previous evaluation day: (A) dryness and (B) itching.

13.3-34.1) mm. Mean itching visual analogue scale score was significantly decreased at weeks 1 and 2 ($P = 0.02$ at week 1 and $P = 0.001$ at week 2 vs treatment start day). In treatment period II, mean itching visual analogue scale score increased in group A (25.8 [95% CI, 7.0 to 44.6] mm at week 3 and 37.5 [95% CI, 20.5 to 54.5] mm at week 4) and decreased in group B (21.2 [95% CI, 3.8 to 38.9] mm at week 3 and 11.0 [95% CI, −3.0 to 25.3] mm at week 4). There was a significant difference between group A and group B at week 4 ($P = 0.01$; estimated difference, 26.5 [95% CI, 7.3 to 45.7] mm).

Results for the duration of itching are shown in Figure 5. During treatment period I, the duration of itching tended to be shorter compared with the previous evaluation day. In treatment period II, some patients in group A (who returned to base therapy alone) reported prolonged duration of itching compared with the previous evaluation day, whereas patients in group B (who continued study drug application) generally maintained the trend of decreasing duration of itching experienced in treatment period I.

Photographic Evaluation of Skin Symptoms

Results of the photographic evaluation of skin symptoms are shown in Figure 6. After using the study drug with base therapy, the severity of dryness and desquamation tended to improve, resulting in the severity of these symptoms being judged "minor" or "none" at week 2 in all participants. Throughout the study period, erythema was observed in only 1 patient in group A (16.7%) at week 3.

Principal Investigator's Overall Assessment of the Study Drug

Results of the overall assessment are shown in Table 2. The usefulness was high, with a rating of "very useful" achieved in 50.0% of participants in group A and 66.7% of those in group B. These values increased to 66.7% and 100%, respectively, when the rating of "useful" was added.

Safety Evaluation

A mild upper respiratory tract infection was reported in 1 patient during treatment, but was not related to the study drug.

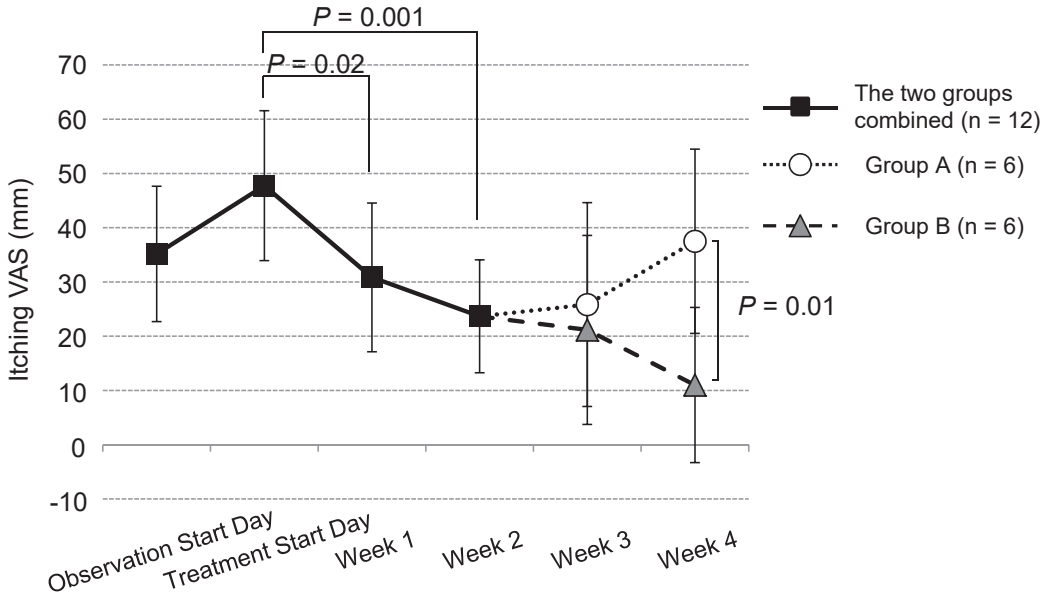

Figure 4. Itching visual analogue scale (VAS) assessments. Participants evaluated the intensity of their itching on each evaluation day. Data points represent mean ± standard deviation. Statistical significance was evaluated using paired *t* tests for intragroup comparisons and unpaired *t* tests for intergroup comparisons.

DISCUSSION

The present exploratory study demonstrated that the water content of the stratum corneum in dialysis patients with dry skin significantly increased by week 1 of the moisturizer application in combination with base therapy, and the increased water content was maintained in the group that continued the moisturizer combination therapy but decreased in the group that discontinued the moisturizer. Most participants noticed improvements to their dry skin consistent with increased water content of the stratum corneum at weeks 1 and 2. Skin condition was maintained or further enhanced in the group that continued the moisturizer combination therapy, but was aggravated in some patients in the group that discontinued the moisturizer.

Photographic evaluation of skin symptoms by the investigators revealed that dryness and desquamation were "moderate" in severity in some patients on the treatment start day, but were "minor" or "none" in all patients at week 2. Subsequently, the severity distribution was maintained in patients who continued to use the moisturizer, with an increasing number of patients experiencing disappearance of symptoms, while symptoms were exacerbated in some patients who discontinued the moisturizer; results almost consistent with those for the subjective symptoms. Overall, results from the water content of the stratum corneum and skin assessments suggest that topical heparinoid moisturizer can improve dry skin and keep water content of the stratum corneum high when used continuously by dialysis patients. Severity

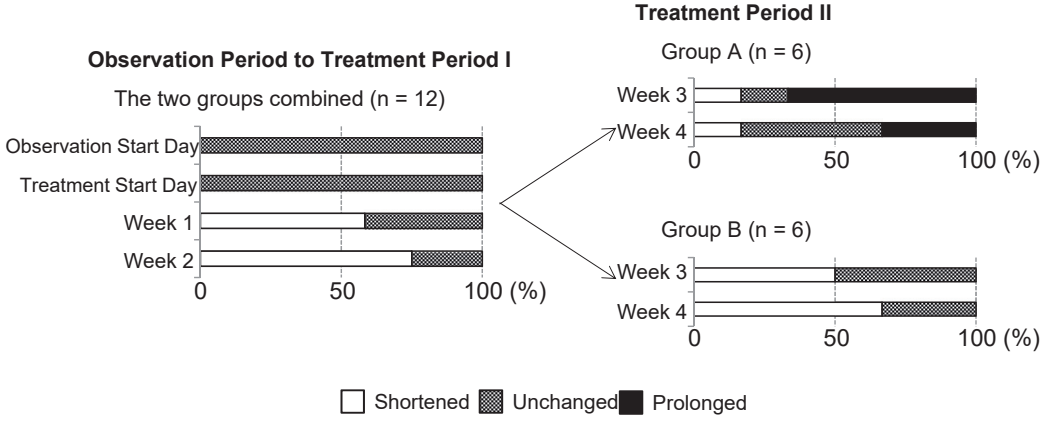

Figure 5. Duration of itching. Patients rated the change in the duration of itching from the previous evaluation day.

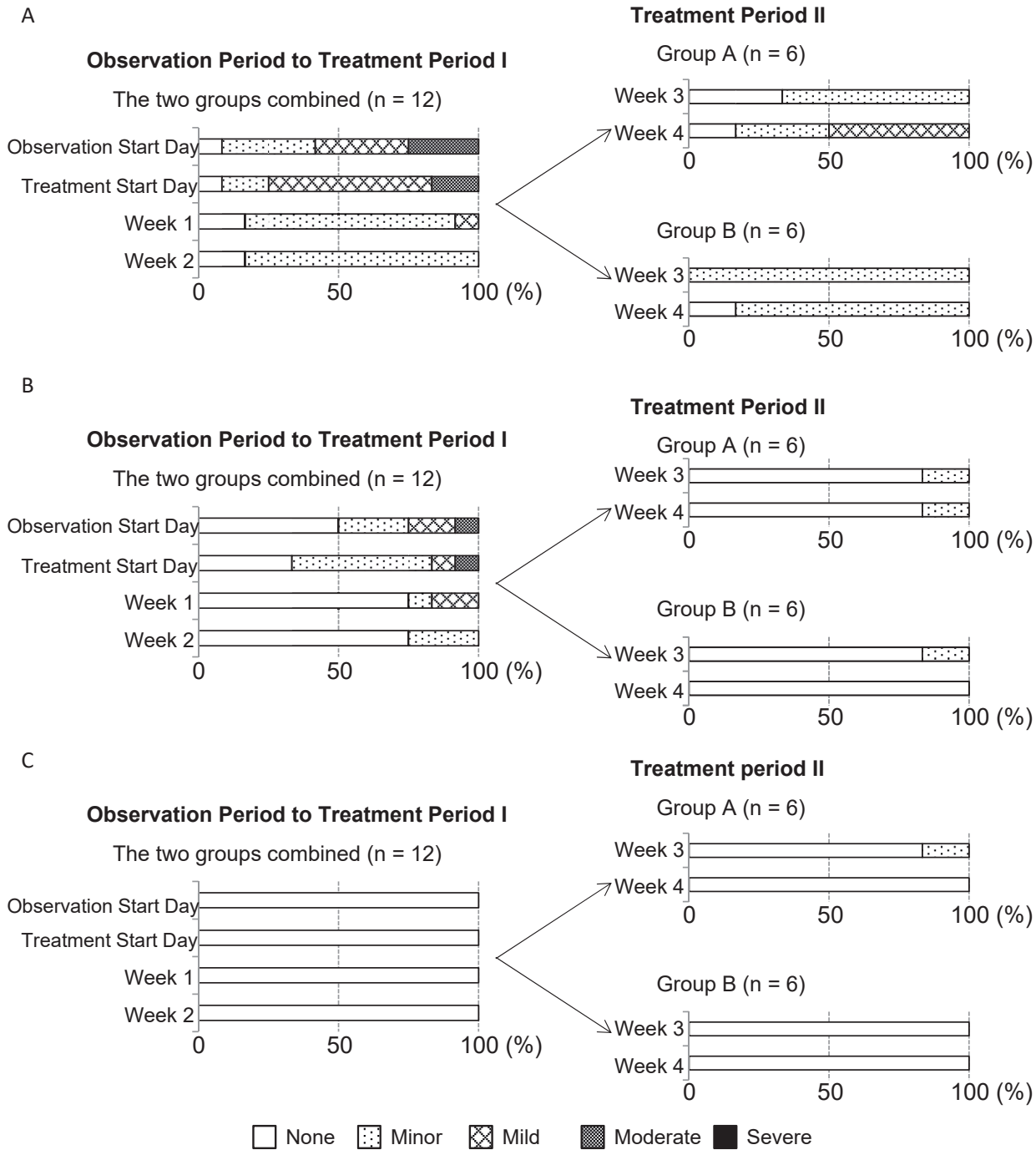

Figure 6. Photographic evaluation of skin symptoms. Dermatologist-evaluated severity of participants' skin symptoms using photographs of their hypochondriac regions on each evaluation day: (A) dryness, (B) desquamation, and (C) erythema.

and duration of itching also tended to improve while combination therapy with the moisturizer was continued, but were aggravated in some participants when the moisturizer was discontinued. This finding is consistent with the change in severity of dry skin, suggesting that continued combination with a moisturizer relieves itching by improving dry skin in dialysis patients.

Investigators' overall assessments revealed that the study drug was "very useful" in more than half the patients in both groups. Moreover, there were no adverse events related to the study drug, suggesting that there is little concern about the safety of topical heparinoid moisturizer combination. Consequently, it was concluded that topical heparinoid moisturizing therapy offers an effective and safe approach to relieving dry skin and keeping the skin of dialysis patients in good condition.

As participants were instructed in this study, the proper dose of moisturizer applied over an area twice that of the adult

Table 2. Investigators' Overall Assessment of the Study Drug

	Very Useful	Useful	Slightly Useful	Not Useful	Harmful
Group A	3 (50.0%)	1 (16.7%)	2 (33.3%)	0 (0.0%)	0 (0.0%)
Group B	4 (66.7%)	2 (33.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Note: Values given as number (percent) of participants.

palm is considered to be ~0.5 g. However, patients are occasionally not conscious of the application dose, which sometimes results in the actual application of a smaller amount of moisturizer than the proper dose. The investigation of drug adherence conducted on each evaluation day demonstrated that all participants applied the study drug as instructed. The amount used was ~200 g in both groups and periods, with no differences noted. This value was an appropriate amount to be used over 2 weeks in a population of patients with dryness and itching over 35.0% of their total body surface area, considering that the amount used per week by an adult man when applied twice daily at the proper dose over the whole body excluding the scalp would be ~282 g.[17]

Thus, the present study demonstrated the possible usefulness of a moisturizer for dialysis patients with dry skin, largely due to continued application of the moisturizer by participants in an appropriate manner throughout the study period. For a moisturizer to sufficiently exert its effect, patients need to be aware of and comply with the appropriate dosage. Methods to promote proper use by patients include video instruction on topical application and periodic confirmation of drug adherence, as was done in the present study. Furthermore, it would also be effective for health care providers engaged in dialysis therapy to adopt appropriate moisturizer administration methods and apply moisturizer to the skin of patients on the day of dialysis. To keep the skin of dialysis patients in good condition, it is essential that health care providers should not only propose moisturizer application, but also involve patients in their efforts toward successful moisturizing therapy.

The strength of this study is that differences in the skin condition of dialysis patients between those treated with the moisturizer and those without were evaluated using water content of the stratum corneum, which is a frequently used objective method in dermatology.

A limitation of this study is that the present results are unlikely generalizable because the sample size was small and included only Japanese patients. We did not plan to analyze the data using any statistical test other than t test due to the exploratory nature of this study and the small sample size; however, nonparametric tests appear to be necessary for the verification testing as well. Furthermore, it would be worthwhile to compare the efficacy of a heparinoid-containing preparation in skin dryness of dialysis patients with other moisturizers, including urea, in the future.

The present exploratory study demonstrated that repeated application of a topical heparinoid moisturizer increased the water content of the stratum corneum and subsequently improved itching in dialysis patients. Photographic evaluation of skin symptoms also demonstrated that dryness and desquamation tended to improve with application of the topical heparinoid moisturizer. Another study with a larger sample size should be conducted.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1: Evaluation criteria for the severity of skin symptoms.

Figure S1: Patient flow diagram.

ARTICLE INFORMATION

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Support: Maruho Co, Ltd, the sponsor of this study, had a role in the study design and publication. Language editing assistance was provided by ASCA Corp.

Financial Disclosure: Maruho Co, Ltd paid commission grants for this study to the Departments of Nephrology and Dermatology, Nippon Medical School, and the Kidney Disease Clinic of Nippon Medical School. Dr Yoshida reports honoraria and funding from Maruho for travel related to a presentation on this study at Kidney Week 2017. Dr Tsuruoka reports advisory fees from Maruho related to this study. Mr Fujimoto and Ms Kishida are employees of Maruho. The remaining authors declare that they have no relevant financial interests.

Acknowledgements: We thank Dr Chikara Ishihara for expert assistance and the staff of the Kidney Disease Clinic of Nippon Medical School.

Prior Presentation: Some of the data in this study were presented at a meeting of the Japanese Society of Dialysis Therapy, Kanagawa, Japan, June 16 to 18, 2017, and at Kidney Week 2017, New Orleans, LA, October 31 to November 5, 2017.

Peer Review: Received December 2, 2018. Evaluated by 2 external peer reviewers, with direct editorial input from the Statistical Editor, an Associate Editor, and the Editor-in-Chief. Accepted in revised form April 29, 2019.

Data Sharing: Individual participant data will not be shared, but the study protocol document will be available on request.

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