ARTIKEL ASLI

Efficacy of 20% Urea Cream in Uremic Pruritus with Uremic Xerosis in Chronic Renal Failure Patients Undergoing Hemodialysis

Yulia Farida Yahya,* Nina Roiana,* Rosi Andarina,* Suprapti, Irsan Saleh,*****

Department of Dermatology and Venereology, Department of Internal Medicine,*** Department of Biomedic Faculty of Medicine Sriwijaya University – General Hospital Moh. Hoesin, Palembang Indonesia*

ABSTRACT

Background: Uremic pruritus (UP) is a chronic itch sensation of the skin which is difficult to treat, in patients with chronic renal failure (CRF) undergoing hemodialysis (HD). Uremic pruritus can cause uremic xerosis (UX) that will decrease quality of life and increase mortality. A 20% urea with creams as the basic material consisting sodium pidolat sodium lactate (NaPCA) and vegetable oils that act as a natural moisturizing factor (NMF) can improve the skin barrier function by increasing skin hydration, reducing transepidermal water loss (TEWL), also can reduce UP with UX. **Purpose:** To determine the efficacy and tolerance of 20% urea in NaPCA and vegetable oils in UP with UX. **Methods**: Randomized, double blind, clinical trial in 65 patients UP with UX in CRF patients. Subjects were divided into two groups, 20% urea in the cream base of NaPCA and vegetable oil (Carmed®, SDM Pharmacy, Indonesia); or placebo in the cream base of NaPCA. To evaluate the efficacy of the two drugs using standard score of visual analog scale (VAS), skin hydration using corneometer (CM) 825, and drug tolerance using quesioner. Assessment was conducted on baseline (day 0), and after treatment on 2nd week and 4th week. **Results:** The VAS score decreased significantly to 2.78 ± 1.070 and the CM score increased significantly to 24.966 in the 20% urea group. There is no adverse effects in both of the 20% urea group and the placebo group. **Conclusion:** Twenty percent urea in the cream base material of NaPCA and vegetable oils can be used as first-line adjuvant therapy, both as a treatment and prevention of PU with UX in CRF patients undergoing HD.

Key words: uremic pruritus, uremic xerosis, 20% urea, NaPCA, vegetable oils.

ABSTRAK

Latar Belakang: Pruritus uremik (PU) merupakan sensasi gatal kronik di kulit yang sulit diterapi, umumnya terjadi pada pasien gagal ginjal kronik (GGK) yang mendapat hemodialisis (HD) dalam jangka waktu lama. Pruritus uremik menyebabkan xerosis uremik (XU), menurunkan kualitas hidup, serta meningkatkan mortalitas. Krim urea 20% dengan bahan dasar krim natrium pidolat natrium laktat (NaPCA) dan minyak nabati dapat memperbaiki fungsi sawar kulit dengan meningkatkan hidrasi kulit, mengurangi *transepidermal water loss* (TEWL), serta mengurangi rasa gatal pada xerosis kulit. **Tujuan:** Mengevaluasi efektivitas dan toleransi krim urea 20% dalam krim NaPCA dan minyak nabati pada pasien pruritus uremik serta mengetahui efek hidrasi pada pasien pruritus uremik. **Metode:** Uji klinis terkontrol, acak, tersamar ganda pada 65 pasien GGK dengan pruritus uremik yang mendapat hemodialisis. Subjek dibagi menjadi 2 kelompok, krim urea 20% dalam dasar krim NaPCA dan minyak nabati (Carmed®, SDM Pharmacy, Indonesia), atau krim plasebo yaitu krim NaPCA saja. Penilaian terdiri dari evaluasi pruritus menggunakan skor *visual analog scale* (VAS), efek hidrasi pada xerosis kulit menggunakan alat korneometer (CM) 825, dan evaluasi toleransi obat menggunakan kuesioner, diukur pada sebelum pengobatan dan setelah pengobatan minggu ke-2 dan ke-4. **Hasil:** Skor VAS menurun signifikan menjadi 2,78 ± 1,070 dan skor CM meningkat signifikan menjadi 24,966 pada kelompok krim urea 20% setelah 4 minggu terapi. **Simpulan:** Krim urea 20% dalam krim NaPCA dan minyak nabati dapat digunakan sebagai terapi ajuvan lini pertama pengobatan dan pencegahan PU pasien GGK dengan HD.

Kata kunci: pruritus uremik, xerosis uremik, krim urea 20%, krim NaPCA, minyak nabati.

INTRODUCTION

Uremic pruritus (UP) is a chronic itch sensation of the skin in patients with chronic renal failure (CRF) undergoing hemodyalisis (HD).[1-3] It affects 50% of CRF patients undergoing HD that is difficult to treat.[4] Survey conducted by Dialysis Outcomes and Practice Pattern study (DOPPS) showed that the occurence of CRF increase every year despite the advancements of technology in HD. Previous studies have shown the incidence of UP range from 45-52% in patients with CRF undergoing HD.[4,5] Uremic pruritus can cause anxiety, depression, and sleep disturbance that could potentially cause a major negative impact on the quality of life.[2,4]

Xerosis is a common clinical manifestation on the skin. It is most often found in UP patients undergoing HD, which predominantly affects the extensor surface of legs, thigh, and forearms in previous studies with a prevalence of 45-90%.[6] The clinical symptoms consist of mild to severe erythema, scaling, with mild to severe pruritus; and may be accompanied by hyperpigmentation, erosions, or lichenification.[7] According to a hypothesis, UX is a major risk factor of UP.[4,8]

The etiopathogenesis of UP is still unclear. According to some literature, the stratum corneum (SC) is a major component that serves as a barrier function of the skin. The frequent repetitive damage of the skin especially SC and lipid components usually result in prolonged disruption of the skin barrier function, which can be caused by a decrease in the natural moisturizing factor that is found in almost 100% CRF patients undergoing HD.[2,9] The composition of the moisturizer shows different results depending on the active ingredients such as urea and vehiculum used as carrier materials such as gamma linolenic acid in essential fatty acids.[9] In their studies, Okada and Matsumoto found that application of emollients increases the water content in the stratum corneum, which helps in reducing UP with UX patients with CRF on HD.[10]

Urea is a substance that acts as humectant, an active ingredients which has antibacterial and moisturizer effect when combined in vehiculum such as sodium lactate, sodium pidolat, and vegetable oils, can improve barrier function of the skin. This has been proved with 10% urea used on various skin diseases such as ichthyosis, xerosis, psoriasis, and atopic dermatitis. However, in a previous study, a placebo-controlled and double blinded study of 10% urea, 20% urea, and placebo application in 21 healthy volunteers, 20% urea enhances TEWL significantly compared to 10% urea. This study indicates that 20% urea improves cutaneous barrier function and increases antimicrobial defence better than 10% urea in normal human skin.[11]

This study was undertaken to evaluate the efficacy and tolerance of 20% urea with a base cream of NaPCA and vegetable oils as vehiculum in UP with CRF patients undergoing HD. The efficacy, cost, and tolerance will be considered as an adjuvant first-line therapy and also as a prevention in UP patients with CRF undergoing HD.

MATERIALS AND METHODS

This was a placebo-controlled, randomized, double blind, clinical trial design in 67 outpatients UP with UX in CRF undergoing HD at Hemodialysis Division, Internal Medicine Department, Mohammad Hoesin General Hospital, Faculty of Medicine Sriwijaya University. This study was undertaken to determine the efficacy and tolerance of 20% urea in base cream material of NaPCA and vegetable oil (Carmed 20%®) in UP with UX in CRF patients undergoing HD from July until Desember 2015. The sampling technique was conducted in consecutive sampling.

Subjects were randomized to receive 20% urea in base cream of NaPCA and vegetable oil or placebo in base cream material of NaPCA and vegetable oils as control, that fulfilled inclusion criteria: UP patients with UX who agree to be involved in the study and the exclusion criteria: pruritus caused by psoriasis, allergic contact dermatitis, scabies, atopic dermatitis; patients receiving systemic corticosteroid, antihistamines, herbal remedies, vitamins, supplements within 4 weeks prior to the study; patients using topical skin moisturizers, emollients, corticosteroids, retinoids, antipruritus within 2 weeks prior to the study. The study was approved by the local ethics committee and informed consent was obtained.

Treatment should be applied twice daily (in the morning and the evening) for a period of four weeks. The subjects were instructed to apply a finger tip unit (0,5 gram) in both of anterior part of lower limb twice daily. Evaluation of treatment was made from the anterior part of lower limbs during baseline the 2nd week and 4th week.

Evaluation of UP with VAS score after treatment means VAS: poor 8-10, good 5-7, and excellent 1-4 on booth right and left of anterior site of lower limbs. Evaluation of UX assessed by skin hydration using corneometer (CM) stated in ug/cm^2 (SM815 Courage & Khazaka Electronic Cologne, Germany). The interpretation of skin hydration on the anterior site of lower limb/cm^2 before treatment: dry <10, moderate 10 -20, oily > 20. Evaluation of UX after treatment using CM with the mean hydration (mg/cm^2): poor <10, fair 10 -20, good > 20 in booth right and left anterior side of lower limbs.

Evaluation of adverse event was recorded, using four-point scale from 0-3 (none, mild, moderate, and severe). The clinical manifestasion were recorded as roughness, scaliness, fissures, thickness, and skin dryness.

Data was analyzed by Statistical Package for Social Science (SPSS) version 19 (SPSS, Inc, Chicago, Illinois), the Wilcoxon test, and Chi-square (x^2). Analysis the efficacy of both drugs, 20% urea

and placebo, was done using independent sample test and the paired t-test. The comparison of both drugs after the treatment used the student's t-test. Analysis of the response to treatment was used two test statistical significance. *p*-values less than 0.05 were considered significant.

RESULTS

This study of clinical trials was randomized and double blind. It was conducted from July to December 2015. The subject of study was 67 UP patients with UX in CRF undergoing HD. Two subjects couldn't continue the study due to passed away. The subjects that completed the study were 65 (n = 65) consisting of 34 males (52.3%) and 31 females (47.7%).

The subjects were divided into two treatment groups, 32 subjects received 20% urea cream (Group A) and 33 subjects received a placebo cream (Group B). In this study, there were 16 male subjects (50%) in the 20% urea group and 18 male subjects (54.4%) in the placebo group, while there were 16 female subjects (50%) in 20% urea group and 15 female subjects (45.5%) in the placebo group (p = 0.719). Their age varies from 30 - 71 years, the most common age group respectively was 51 - 60 years, 24 (37%) subjects, 41 - 50 years, 15 (23%) subjects (p = 0.079). The co-morbidity of the subjects respectively were hypertensive nephropathy 28 (43.1%), diabetic nephropathy 17 (26.2%), chronic glomerulonephritis 11 (16.9%), unknown 5 (7.7%), SLE 3 (4.6%), and polycystic disease 1 (3%) (p = 0.172). Dialysis membrane type consist of 41 (63.1%) subjects used polynephron, followed by 24 polysulphon (36.9%) subjects. All of subjects were being HD 2 times a week, with duration of HD 1-5 years were 38 (58.5%) subjects, < 1 year were 14 (21.5%), > 5 years 13 (20%) subjects. The location of UP were generalized 28 (58.5%) subjects, scattered pruritus 16 (24.6%) subjects and mild pruritus 11 (16.9%) subjects. In this study, the frequency of UP: long episodes (>10 minutes) were 47 (72.3%) subjects and short episodes (<10 minutes) were 18 (27.7%) subjects. The most common skin problems of UP patients with UX in CRF patients undergoing HD were hyperpigmentation with 33 (50.8%) subjects, bacterial infection 13 (20%) subjects, fungal infections 12 (18.5%) subjects, and Kyrle diseases 7 (10.8 %) subjects.

The homogeneity distribution analysis on pruritus severity using VAS and xerosis severity using CM. Before the test of independent samples t-test, normality test with a one-sample Kolmogorov-Smirnov test, to prove that the data prior to treatment between 20% urea groups and placebo group had the same variant, the results of homogeneity tests showed that the drugs were normally distributed and homogeneous.

The analysis of independent samples t-test showed that UP assessment by VAS, the 20% urea group and the placebo group showed a statistical significance before and after treatment, there is a reduction in VAS 5.58 ± 1.249 before treatment and after treatment 2.78 ± 1.070, whereas treatment in the placebo group showed decrease in UP before treatment 5.64 ± 1.365 and after treatment 4.70 ± 1.828, but not statistically significant.

In this study, the analysis of the independent samples t-test to assess skin hydration by CM before treatment and after treatment showed that the skin hydration in the 20% urea group was improved significant statistically 17.986 ± 6.9960 to 24.966 ± 6.0084, while treatment in the placebo group showed no statistical improvement of skin hydration 19.924 ± 7.8396 to 19.924 ± 6.1559. This study showed that after the treatment there was more statistically significant increase in skin hydration of 20% urea group than placebo group (p = 0). The paired samples t-test analysis of correlation mean VAS and CM between 20% urea groups and placebo group before and after treatment, showed a statistically significant correlation of VAS and CM of 20% urea group compared with placebo (p = 0).

Clinical improvement in these studies was assessed by evaluating the UP between 20% urea group and placebo group, using VAS with interpretation: 8-10 poor, 5-7 good, and 1-4 excellent. It was found in the 20% urea group that were excellent in 31 (96.9%) subjects, good 0 (0%) subjects, and poor 1 (3.1%) subjects, while treatment with placebo were excellent in 14 (42.4%) subjects, good 17 (51.5%) subjects, and poor 2 (6.1%) subjects. The analysis by Chi-Square test showed that clinical improvement was statistically significant after treatment in the 20% urea group compared to the placebo group (p = 0).

In this study, the assessment of clinical improvement was done by evaluating the increased levels of skin hydration using CM. Interpretation when the value of CM <10 is poor, 10-20 is good, and >20 is excellent. The analysis by Chi-Square test showed clinical improvement in the 20% urea group, respectively they were excellent in 27 (84.4%) subjects, good in 5 (15.6%) subjects, and poor in 0 (0%) subjects, while in placebo group were excellent in 17 (51.5%) subjects, good in 15 (45.5%) subjects, and poor in 1 (3.2%) subject. This showed that there is a significant clinical improvement in 20% urea group compared to placebo group (p = 0) after treatment. In this study, evaluation of the tolerance

and the assessment of adverse effects using VAS: 0-3 = no erythema/slight or spotty erythematous, 4-7 = moderate erythema with fine scaling or diffuse erythematous, and 8-10 = severe erythema, infiltration, vesicles. The analysis by Chi-Square test showed, statistically there is no significant differences in the adverse effects of these drugs, thus showing both drugs can be tolerated well (p = 325).

Table 1. Characteristic sosiodemographic chronic renal failure patients undergoing hemodialysis

Variable	Total n (%)	p value
Sex		
Male	34(52.3)	p = 0.719
Female	31(47.7)	
Age (years)		
<30	6 (9.2)	
31-40	9 (13.8)	
41-50	15 (23.1)	p = 0.079
51-60	24 (36.9)	
61-70	8 (12.3)	
>71	3 (4.6)	
Occupation		
Farmer/fisherman/unskilled laborers	12 (18.5)	
Government employees	30 (46.1)	p = 0.493
Jobless	23 (35.4)	
Etiology of CRF		
Chronic glomerulonephritis	11 (16.9)	
Diabetic nephropaty	17 (26.2)	
Polycystic kidney disease	1 (3)	p = 0.172
Nephropathy hypertension	28 (43.1)	
Systemic lupus erythematosus	3 (4.6)	
Other	5 (7.7)	
Dialyser		
Polynephron	24 (36.9)	p = 0.152
Polysulphon	41 (63.1)	
Frequency of HD		
1x/week	-	
2x/week	65 (100)	p = 0.65
3x/week	-	
Duration of HD		
<1 years	14 (21.5)	
1-5 years	38 (58.5)	p = 0,163
>5years	13 (20)	
Distribution of UP		
Pruritus in single location	11 (16.9)	
Scattered pruritus	16 (24.6)	p = 0.680
Generalized pruritus	28 (58.5)	
UP frequency/day		
Short episode (<10 minutes)	18 (27.7)	p = 0.535
Long episode (>10 minutes)	47 (72.3)	
Co-morbidity		
Hyperpigmentation	33 (50.8)	
Bacterial infection	13 (20)	p = 0.437
Fungal diseases (dermatophytosis, candidosis)	12 (18.5)	
Kyrle diseases	7 (10.8)	

Note: CRF = chronic renal failure, HD = hemodyalisis, UP = uremic pruritus

Table 2. Comparison of visual analog scale and corneometer between 20% urea group and placebo group after treatment

	Group	Baseline	2nd Week	4th Week	p
Visual analog scale (VAS)	20% urea	5.50±1.249	2.90±1.110	2.78±1.070	p = 0.000
	Placebo	5.64±1.365	4.80±1.950	4.70±1.828	
Corneometer (CM)	20% urea	17.244±6.996	25.355±6.525	24.966±6.004	p = 0.000
	Placebo	19.924±7.839	19.623±6.725	19.355±6.159	

Table 3. Comparison of clinical improvement of visual analog scale in uremic pruritus with uremic xerosis between 20% urea group and placebo after treatment

Clinical improvement	Group treatments				Total (%)		p
	20% urea	n(%)	placebo	n(%)			
Excellent	31	96.9	14	42.4	45	69.2	
Good	0	0	17	51.5	17	26.2	
Poor	1	3.1	2	6.1	3	4.6	p = 0.000
Total	32	100	33	100	65	100	

Table 4. Comparison of clinical improvement skin hydration uremic pruritus with uremic xerosis between 20% urea group and placebo group after treatment

Clinical improvement	Group treatment				Total (%)		p value
	20% urea	n(%)	placebo	n(%)			
Excellent	27	84.4	17	51.5	44	67.7	
Good	5	15.6	15	45.5	20	30.8	
Poor	0	0	1	3.2	1	1.5	p = 0.004
Total	32	100	33	100	100		

Table 5. Adverse effects and tolerance 20% urea group and placebo group after treatment

Adverse event, tolerance (VAS)	Group treatment				Total n%		p value
	20% urea	n(%)	Placebo	n (%)			
No adverse events	32	100	33	100	65	100	
Adverse events	0	0	0	0	0	0	p = 325
Total	32	100	33	100	65	100	

note = VAS: visual analog scale

DISCUSSION

This is a clinical trial randomized, double-blind, placebo-controlled study, comparing between 20% urea cream and vegetable oils with vehicle cream base material NaPCA and vegetable oils as a control in patients with UP with UX in CRF undergoing HD. In this study, a total sample of 65 subjects were divided into 2 treatment groups, one group received 20% urea cream base material of NaPCA and vegetable oils, the other received placebo cream with base material NaPCA and vegetable oils. To found the research objectives, it is needed to know the distribution of the characteristics of UP research subjects by sex, age, duration of HD, occupation, etiology of CRF, frequency of HD, duration of UP, type of dialyser, and co-morbidity of diseases.

The subjects (n = 65) accompanied with skin disease were distributed respectively into hyperpigmentation 33 (50.8%), bacterial infections 13 (20%), fungal infections 12 (18.5%), and Kyrle diseases 7 (10.8%). While previous studies, Dyachenko (2006) revealed that typically the skin diseases were xerosis 95.7%, hyperpigmentation 75.7%, pallor75.7%, ecchymosis 64.3%, and "half & half" nails disorder 18.6%.[12] According Manenti study (2009), UP in CRF patients undergoing HD,

skin disorders manifest generally due to repetitive scratching causing impetigo, prurigo, and lichenification due to skin infections. As a result of the immune system failure that arised from dialysis with characteristic immune defects particularly decreasing activity of B cells and changes in activity of T cell subsets.[7,13] Attia's study (2010) showed specific skin diseases that accompany UP in CRF patients are as xerosis (54%), pallor (42.2%), hair disorders (34%), and hyperpigmentation (22%).[14]In their study, Kyrle diseases or dermatosis perforation revealed 10.8%. Previous study showed Kyrle diseases or dermatosis perforation, although rare, often gives specific manifestations in CRF patients undergoing HD. A study in North America, Kyrle disease incidence was range from 4.5 - 10%.[14,15]

According to statistical analysis there was no significant relationship between the demographics and characteristics in the distribution of UP in CRF patients undergoing HD based on gender, age, duration of HD, occupation, CRF underlying disease, location of UP, frequency of UP, duration of HD, application type of HD, and disease that accompanies CRF.

Uremic pruritus in CRF patients receiving long-term dialysis is the most common skin disease, reaching more than 90%. It is a distressing, often overlooked condition in patients with CRF and end-stage renal disease. It has been associated with poor quality of life, poor sleep, depression, and mortality. Xerosis is a risk factor most commonly found in UP patients with CRF undergoing HD.[16,17] Xerosis or dry skin resulting in impaired skin barrier function, among others, which decreased skin hydration, was strongly influenced by the NMF. Until now, the pathogenesis of UP with UX in CRF patients receiving HD is still unclear, due to multifactorial role, need to find an effective topical treatment to reduce UP with UX in CRF patients undergoing HD.[18] The variety of topical medications need as UP and UX treatment has various outcomes. Moisturizers are generally used to improve skin barrier on various skin disorders such as ichthyosis, atopic dermatitis, and also UP in CRF patients.[19]

Reports from Okada and Matsumoto (2004) application of emollient component containing NMF including urea, lactic acid, increases the water content in the stratum corneum which decreases UP and UX in CRF patients receiving HD.[10] Other studies Szpietowski et al (2005) showed that in 21 CRF patients with HD, application of topical treatment cream containing the structure of natural lipid and endocannabinoids as an emollient and humectant for 3 weeks, has the effect of moisturizing, and also controls pruritus and xerosis.[19] Another recent study by Heisig et al (2016), using polymerase chain reaction (PCR), showed there were no association in cannabinoid R1 (CNR1) gene polymorphism and the presence of UP.[20]

In this study, analysis by independent samples t-test was used to assess UP with VAS, in the 20% urea group and placebo before and after treatment, showed there was a significant reduction, in VAS 5.58 ± 1.249 before treatment and after treatment 2.78 ± 1.070, whereas treatment with placebo showed no significant reduction in UP before treatment 5.64 ± 1.365 and after treatment 4.70 ± 1.828. It means that there was a significant decrease in UP using 20% urea compared to placebo ($p = 0.000$). A previous study found that treatment with 5% urea cream on xerosis and pruritus in atopic dermatitis (AD) showed significant improvement in skin hydration, reduces xerosis, and relieve itching.[21]

Analysis by independent samples test to assess skin hydration by corneometer (CM), in the 20% urea group and the placebo group before and after treatment, indicated there was a significant increase in skin hydration 17.986 ± 6.9960 before treatment and after treatment 24.966 ± 6.0084, while treatment with placebo showed there were no improvement in skin hydration 19.924 ± 7.8396 before treatment and after treatment of 19.924 ± 6.1559. There was more statististicaly significant increase in skin hydration using 20% urea rather than placebo ($p = 0.000$). In a prior study, UX patients with mild to moderate AD treated with 5% urea and 10% urea lotion on xerosis showed improvements which includes an increased skin hydration, although there were no significant difference both drugs.[22] Previous study showed 20% urea significantly decreased the transepidermal water loss (TEWL) and the expression of microbial defence compared to urea 10%.[11] In this study, 20% urea cream in cream base showed significant clinical improvement and a decrease in xerosis. Thus the 20% urea can be used as a first line topical drug for UP with UX in patients CRF undergoing HD.

The independent samples t-test assessed mean VAS and CM between 20% urea groups and placebo groups before and after treatment. Based on the test of independent samples t test, there is a correlation mean VAS with CM before and after treatment 20% group urea and placebo group ($p = 0.000$). Analysis of paired samples t-test was significantly correlated, showed a clinical improvement decreasing UP with increased skin hydration after treatment in 20% urea group than placebo group ($p = 0.000$). According to a

theory, in CRF ongoing HD, UX is mostly accompanied with UP, because the sebaceous glands become atrophic and there is a decreased secretion of sweat glands, thereby reducing the skin hydration. In previous studies, UP patients who received hemodialysis turned out to be significantly lower compared to the level of skin hydration without UP.[4] Other studies prove there was no correlation between UP and the reduced level of hydration in CRF patients undergoing HD.[23] The provision of 20% urea in the basic cream materials, NaPCA as an emollient and humectan, and vegetable oils as an occlusive ingredients to improve TEWL, improves skin hydration. These conditions improve UX and relieve UP, these findings are consistent with the explanation Kfoury LW et al.[24]

The independent samples t analysis were used to evaluate UP comparison between of 20% urea group and placebo group. This study showed treatment with 20% urea cream has clinical improvement: excellent, good, and poor respectively. Excellent in 31 (96.9%) subjects, good in 0 (0%) subjects, poor in 1 (3.1%) subject, while treatment with placebo group, excellent in 14 (42.4%) subjects, good in 17 (51.5%) subjects, poor in 2 (6.1 %) subjects. The analysis by Chi-Square after the treatment showed more significant clinical improvement on 20% urea group compared to placebo group (p = 0.000). According to Pan (2013), 5 - 10% urea cream in the basic materials NaPCA is used as an anti-pruritic, in addition to its function as humectant and emollient to promote skin hydration and improve xerosis.[25]

Analysis by Chi-Square test showed clinical improvement of 20% urea group respectively excellent in 27 (84.4%) subjects, good in 5 (15.6%) subjects, and poor in 0 (0%) subjects, while treatment with placebo group showed excellent in 17 (51.5%) subjects, good in 15 (45.5%) subjects, poor in 1 (3.2%) subject. The analysis by Chi-Square test showed that after the treatment there was significant clinical improvement on 20% urea group compared to placebo group (p = 0.000). Emollients are the main ingredients used to treat xerosis and other clinical symptoms which needed moisturizer ingredient combined with NMF component.[26,27]

According to Del Rosso (2011) generally UX has a relationship with UP, resulting in loss of NMF components influencing the increase in TEWL, so moisturizer is needed to give good results in the treatment of UX while improving TEWL.[9] According to this study there are three combinations of 20% urea as a moisturizer in the basic cream materials NaPCA as an emollient and humectant and vegetable oil as an occlussive ingredient. TEWL plays a role in the reduction of UX. Lately there is an evidence of protein Aquaporin 3 (AQP3) in the stratum basal keratinocytes knock-out mice (AQP3), which serves as glycerol's transport as a humectant in the process of skin hydration and elasticity of the skin. This research enables the development of new topical drugs for the treatment of various skin diseases.[28]

In this study, evaluation assessment of tolerance and adverse effects of both drugs uses the evaluation visual analog score (VAS) 0-3 = no erythema/erythematous weak either in the form of spotty, 4-7 = erythema moderately subtle or diffuse erythematous scaly, smooth scaling, 8-10 = severe erythema, infiltration, vesicles.

The analysis by Chi-Square test showed both drugs signficantly have no adverse effects. This study proves that the drugs were well tolerated in UP with UX in CRF patients ongoing HD (p = 325). Both of topical 20% urea cream and a placebo cream can be used as a moisturizer to improve skin hydration and TEWL repair in patients with UP and xerosis. Buraczewska's studies (2006) showed examination of TEWL and susceptibility to irritants, proved artificial moisturizer that contains 5% urea and vegetable oil can reinforce the barrier function of the skin in normal skin and repair impaired barrier function of the skin in atopic dermatitis patients.[24] Previous study, Pan (2013) explained that topical treatment for xerosis using basic cream is better than foam or solution.[19] Several clinical studies on hydrating effects, using 15% urea 2 times/day showed reduced TEWL in all xerosis patients, the other study using 10% urea cream showed lowered TEWL and dryness, there is no adverse effects in both drugs.[22]

Prior studies showed the function of moisturizer depends on its materials, if it contains natural ingredients, it serves as humectants, emollients, and occlusive which significantly affect the barrier function of the skin.[29,30] Other studies, Buraczewska (2008) proves improvement of the skin barrier function depends on increased skin hydration and decreased TEWL. Urea has been used safely and effectively in patients with wide variety of skin diseases.[31]

Urea is endogenous metabolite known to enhance stratum corneum and improves permeability in skin barrier function and it appears to exhibit antimicrobial activity. Hence the hypothesized that urea is not merely a passive metabolite, but a small molecule regulator of epidermal stucture and function. Urea both stimulates expression of, and is transported into keratinocyte by two urea transporters (UT), UT-A1, UT-2 and by Aquaporin3,7,9 (AQP).[11,32] The recent study in knocked out mice showed AQP3 is a

key player in epidermal biology and potential target for drug development.[25] Further study is needed for a new topical treatment containing substance that acts directly on the receptor AQP3 at the level of transcription that regulates the skin barrier function.

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