Comparison of Moisturizer Containing 5% Urea, Natural Moisturizing Factors, Ceramide, and Glyceryl Glucoside with 5% Urea Lotion for the Treatment of Xerosis in Children with Chronic Kidney Disease

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Background: *Xerosis is a common skin manifestation in chronic renal disease. Itching from dry skin causes skin discomfort, scratch marks, and compromises skin barrier function.*
Objective: *To compare the efficacy of moisturizer containing 5% urea, natural moisturizing factors (NMFs), ceramide, and glyceryl glucoside (GG) with 5% urea lotion for treatment of xerosis in patients with underlying stable chronic kidney disease.*
Material and Method: *We performed a randomized, double-blind, split-side, experimental study in 50 children with xerosis in stable chronic kidney disease. The patients were assigned sequentially by block randomization to use either moisturizing lotion containing 5% urea, NMFs, ceramide, and GG or 5% urea on opposite sides of the lower leg, twice daily for four weeks. The moisturizers were repacked in identical bottles. Clinical severity of xerosis, skin hydration, and transepidermal water loss (TEWL) were evaluated at baseline and at at one, two, and four weeks.*
Results: *Forty-seven of 50 patients completed the study. The mean age was 13.43±2.3years. Both products significantly decreased clinical severity of scaling and roughness from baseline ($p<0.001$). Application of moisturizer containing 5% urea, NMFs, ceramide, and GG resulted in significantly higher skin hydration and lower TEWL compared with 5% urea lotion (both $p<0.01$), from week 1. Regarding the safety of using urea in chronic kidney disease, there were no significant differences in blood urea nitrogen (BUN) and creatinine levels between pre- and post-treatment ($p = 0.627$). No adverse effects were reported.*
Conclusion: *Both moisturizing lotions containing 5% urea, NMFs, ceramide, and GG and 5% urea were effective in improving scaling and roughness, skin hydration, and skin barrier function in stable chronic pediatric kidney disease patients. Additional ingredients, such as NMFs, ceramide, and GG can significantly improve xerosis, skin hydration, and skin barrier function. Products containing 5% urea applied on the lower legs for four weeks do not increase BUN or creatinine levels.*

Keywords: *Xerosis, Glyceryl glucoside, Pediatric*

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Xerosis is a common cutaneous manifestation in chronic kidney diseases in adults and children[1-3]. Itching is the most common symptom of xerosis in patients with chronic renal failure. Itching is significantly increased with an increase in the severity of xerosis[2]. Xerosis can cause skin discomfort, scratch marks, and compromise skin barrier function.

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Urea is a natural moisturizing factor and improves skin barrier function[4]. Urea at a concentration of 5 to 10% is effective in patients with atopic dermatitis (AD)[5], and 5% urea cream can prevent relapse of AD[6]. Glyceryl glucoside (GG) can penetrate the epidermis and increase aquaporin (AQP) 3 mRNA levels, as well as improve skin hydration and barrier function in adults[7]. Treatment of xerosis with topical GG, natural moisturizing factors (NMFs), and ceramide increase skin hydration and barrier function in adults[8].

However, most studies that used GG, NMFs, and ceramide were performed in adults. To the best of

our knowledge, there are no reports on the safety of urea-containing lotion in children with chronic kidney disease. Therefore, the present study aimed to compare the efficacy of moisturizing lotion containing 5% urea, NMFs, ceramide, and GG with 5% urea for the treatment of xerosis in children with underlying stable chronic kidney disease.

Material and Method

This randomized, prospective, split-side, double-blind study was approved by the Institutional Review Board (IRB), Faculty of Medicine, Chulalongkorn University and adhered to the provisions outlined in the Declaration of Helsinki (IRB No 453/55). According to previous study for repeated-measure analysis, sample size determination would be applied from developed Frison and Pocock formula[9]. In the present study, a value of alternative hypothesis is determined to be 0.4σ[6] and the number of repeated time as 3 for following time at baseline, 7 days, 14 days, and 28 days ($r = 3$). Parameter for comparison between groups is only type of medications, 5% urea lotion and 5% urea, NMFs, ceramide, and GG lotion, therefore the number of this parameter is 1. The analysis requires approximate sample size of 44, 36, 26, and 14 for ρ = 0.6, 0.7, 0.8, and 0.9, respectively. Therefore, the total sample size of patient, when ρ is 0.7 for individual assessment, is 36 per medication group. The patient dropout rate was assumed to be about 10%. Therefore, the total sample number of 40 per medication group would be sufficient to compensate for drop-outs.

Participants

We conducted a study to evaluate children with the clinical diagnosis of xerosis in stable chronic kidney disease at the Department of Pediatrics, King Chulalongkorn Memorial Hospital. Children were aged 6 to 18 years, and were recruited for the present study between December 2012 and April 2014. Stable chronic kidney disease is defined as glomerular filtration rate (GFR) <60 mL/minute/1.73 m^2 for more than three months and have no deterioration of GFR on follow-up at least six months interval. Patients who had any treatment for xerosis within two weeks or other skin lesions, such as infection, eczema, or acute renal failure, were excluded. Informed consent for participation in the study was provided by parents of all children.

Test products

Two moisturizing lotions were tested as follows: 1) urea 5%, NMFs (containing sodium lactate, lactic acid, sodium pyrrolidone carboxylic acid, arginine HCL, serine, alanine, histidine, citrulline, lysine, sodium chloride, glycogen, mannitol, sucrose, glutamic acid, and threonine), ceramide, and GG (Eucerin® Complete Repair; Beiersdorf AG, Hamburg, Germany), and 2) urea 5% that did not contain NMF components. The moisturizer containing 5% urea, NMFs, ceramide, and GG lotion was repacked in bottles that were identical to 5% urea lotion.

Clinical studies

All of the patients were treated with both moisturizers comprising urea 5%, NMFs, ceramide, and GG and 5% urea lotion. Patients were randomized to use moisturizer containing 5% urea, NMFs, ceramide, and GG on the lower part of one leg and 5% urea lotion on the other side of the lower leg in the equal amount, twice daily for four weeks, using bottles that had been sequentially numbered by block randomization before starting the study.

Evaluations

The lesions on each side of the leg were evaluated at baseline and at 1, 2, and 4 weeks after starting treatment with the following assessments. A clinical scoring system modified from Weber et al[7] was used to assess the severity of scaling and roughness by comparing the two sides (Table 1) by the same physician and patients/parents. Skin hydration was measured using a corneometer (Delfin® MoistureMeterSC Compact; Delfin Technologies Ltd., Kuopio, Finland). Five measurements per area were made on each side

Table 1. Clinical grading score for dryness and tactile roughness modified from Weber et al[7]

Score	Scales	Roughness
0 (absent)	No scales	Smooth on tangential tactile evaluation
1 (slight)	Slight scaling, dull appearance	Slightly rough on tangential tactile evaluation
2 (moderate)	Small scales, whitish appearance	Definitely rough on tangential tactile evaluation
3 (severe)	Small and larger scales, a few superficial cracks	Advanced irregularly on tangential tactile evaluation
4 (extreme)	Large scales, redness, cracks	Grossly rough on tangential tactile evaluation

and the mean value of measurements was expressed in arbitrary units (AU). Transepidermal water loss (TEWL) was determined with the Tewameter® TM210 (Courage + Khazaka, Cologne, Germany). Three measurements per area were made and the mean value of measurements was expressed in g/m²h. Serum for blood urea nitrogen (BUN) and creatinine levels were measured before and after 4 weeks of treatment.

Statistical analysis

The characteristics were shown as mean (SD) and percentage for continuous and categorical data, respectively. Differences of efficacy were calculated by using repeated measure ANOVA in SPSS for windows version 17. A *p*-value of less than 0.05 was considered statistically significant.

Results

Sixty patients with stable chronic kidney diseases were enrolled. Ten patients were excluded because of logistical problems. Of 50 patients with xerosis in stable chronic kidney disease, 47 completed the study after they were referred back to a primary care hospital (Fig. 1). The patients' ages ranged from 8 to 17 years, with a mean age of 13.4±2.3 years.

Table 2. Patients' demographic data (n = 50)

Parameter	No. of patients (%)
Age (year), mean ± SD	13.43±2.31
Sex	
Female	39 (78)
Male	11 (22)
Underlying disease	
Systemic lupus erythematosus	32 (64)
Nephrotic syndrome	5 (10)
Chronic kidney disease	10 (20)
Other: IgA nephropathy	3 (6)

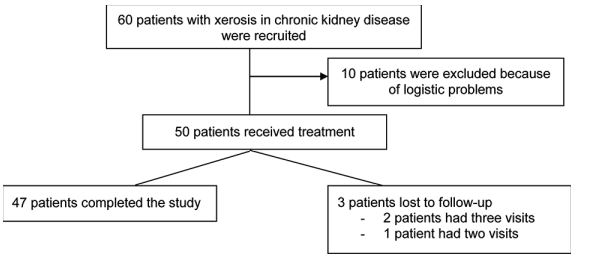

Fig. 1 Flow diagram of the patients' progress throughout the study.

Patients' demographic characteristics are shown in Table 2. Nine patients required hemodialysis and five required continuous ambulatory peritoneal dialysis.

Clinical grading of scaling and roughness as assessed by physicians and patients/parents significantly improved from baseline after using both moisturizers from the first week ($p<0.001$) and continued to improve through weeks 2 and 4, but there was no difference between moisturizers. There were no significantly different assessments between physicians and patients/parents (Table 3, 4).

Skin hydration, as measured by corneometry, was significantly improved ($p<0.001$) after one week of regular, twice-daily use in both moisturizers compared with baseline. Corneometry readings showed that the side that had application of moisturizer containing 5% urea, NMFs, ceramide, and GG was significantly more hydrated than that with 5% urea lotion ($p<0.001$, Fig. 2).

TEWL was significantly decreased after treatment with both moisturizers compared with baseline ($p<0.01$). Application of the moisturizer containing 5% urea, NMFs, ceramide, and GG resulted in significantly decreased TEWL compared with the 5% urea lotion at week 1 ($p = 0.013$), and it continued to be decreased at week 2 ($p<0.002$) and week 4 ($p<0.001$, Fig. 3).

Table 3. Clinical scale score assessed by physicians and patients/parents before and after weeks 1, 2, and 4 of treatment with 5% urea lotion and 5% urea, natural moisturizing factors (NMFs), ceramide, and glyceryl glucoside lotion

Time	Scale score					
	Physicians' evaluation			Patients/parents' evaluation		
	5% urea lotion	5% urea, NMFs, ceramide, and glyceryl glucoside lotion	*p*-value	5% urea lotion	5% urea, NMFs, ceramide, and glyceryl glucoside lotion	*p*-value
Baseline	2.16±0.37	2.16±0.37	1.000	2.14±0.35	2.14±0.35	1.000
Week 1	1.14±0.45*	1.10±0.46*	0.663	1.02±0.47*	0.98±0.43*	0.659
Week 2	0.65±0.52*	0.65±0.52*	1.000	0.63±0.53*	0.63±0.53*	1.000
Week 4	0.51±0.51*	0.47±0.50*	0.684	0.51±0.51*	0.47±0.50*	0.684
p-value[a]	<0.001	<0.001		<0.001	<0.001	

[a] Compared between baseline and weeks 1, 2, and 4 by using repeated measure ANOVA; * $p<0.001$

Table 4. Clinical roughness score assessed by physicians and patients/parents before and after weeks 1, 2, and 4 of treatment with 5% urea lotion and 5% urea, natural moisturizing factors (NMFs), ceramide, and glyceryl glucoside lotion

Time	Roughness score					
	Physicians' evaluation			Patients/parents' evaluation		
	5% urea lotion	5% urea, NMFs, ceramide, and glyceryl glucoside lotion	*p*-value	5% urea lotion	5% urea, NMFs, ceramide, and glyceryl glucoside lotion	*p*-value
Baseline	2.14±0.35	2.14±0.35	1.000	2.14±0.35	2.14±0.35	1.000
Week 1	1.12±0.44*	1.08±0.44*	0.650	1.04±0.49*	1.00±0.45*	0.673
Week 2	0.67±0.52*	0.65±0.52*	0.846	0.63±0.53*	0.63±0.53*	1.000
Week 4	0.55±0.50*	0.51±0.51*	0.683	0.53±0.50*	0.47±0.50*	0.541
p-value[a]	<0.001	<0.001		<0.001	<0.001	

[a] Compared between baseline and weeks 1, 2, and 4 by using repeated measure ANOVA; * $p<0.001$

BUN and creatinine levels were measured in 50 patients before the study and in 47 patients at week 4. Three patients did not complete the study because they were referred back to a primary care hospital. Median BUN levels before and after treatment were 24 mg/dl (range 8 to 133 mg/dl) and 24 mg/dl (range 10 to 160 mg/dl), respectively. Median creatinine levels before and after treatment were 0.9 mg/dl (range 0.5 to 11.7 mg/dl) and 0.8 mg/dl (range 0.5 to 11.5 mg/dl), respectively. There were no significant differences in BUN and creatinine levels between pre- and post-treatment ($p = 0.627$). Both study products were well tolerated and there were no reports of adverse events.

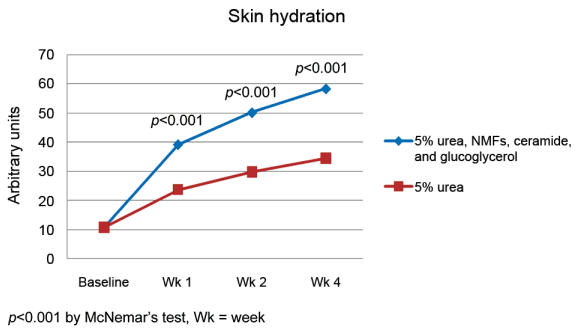

Fig. 2 Comparison of skin hydration between 5% urea lotion and 5% urea, natural moisturizing factors (NMFs), ceramide, and glyceryl glucoside lotion before treatment and at weeks 1, 2, and 4 after treatment.

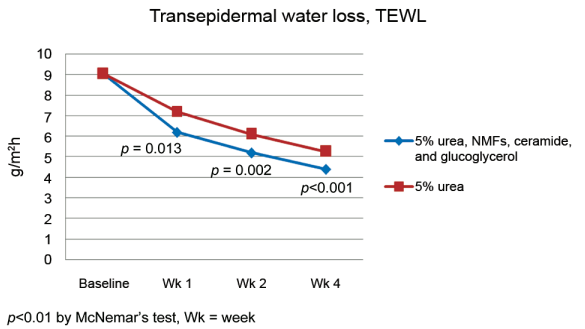

Fig. 3 Comparison of transepidermal water loss (TEWL) between 5% urealotion and 5% urea, natural moisturizing factors (NMFs), ceramide, and glyceryl glucoside lotion before treatment and at weeks 1, 2, and 4 after treatment.

Discussion

This randomized, double-blind, split-side, experimental study showed that 5% urea lotion and moisturizer containing 5% urea, NMFs, ceramide, and GG were effective in improving skin scaling and roughness without difference to 5% urea lotion. Assessment of the severity of scaling and roughness by the physician and patients/parents was designed to decrease bias in assessment. There were no differences in assessment in the present study. Urea is a natural moisturizing factor and can be used as a humectant to increase skin hydration[8]. Urea has been used to treat dry and scaly skin in various dermatological conditions, including skin xerosis and pruritus in hemodialyzed adult patients[10,11]. Urea also improves skin barrier function, decreases the scoring AD index, and prevents relapse in adult AD[4-6].

Skin hydration and skin barrier function were improved in both study products, but the moisturizer with 5% urea, NMFs, ceramide, and GG was significantly better than the 5% urea lotion. A previous study showed that an increase in urea concentrations from 5 to 10% did not improve efficacy in AD patients[5]. Ceramides are the major intercellular lipids in the stratum corneum and decreased epidermal ceramide content has been linked to water loss and barrier dysfunction[12]. Moisturizer containing ceramide improves skin barrier function of the skin. GG can

increase AQP3 mRNA levels and up-regulate and improve skin barrier function in adults[6,7]. Our study demonstrated that additional ingredients, such as NMFs, ceramide, and GG, significantly improved skin hydration and skin barrier function compared with 5% urea lotion in children with xerosis in stable chronic kidney disease.

We determined the safety of using urea-containing moisturizers in stable chronic kidney disease. We found no significant differences in the levels of the BUN and creatinine before the study and after four weeks of twice-daily use on the lower extremities. No side effects were reported during the study period. Urea is safe and has been used in many moisturizers for sensitive skin in AD[4,5,13].

A limitation of the present study was the small number of patients. Three patients were lost to follow-up.

In conclusion, the present study suggests that both the moisturizer containing 5% urea, NMFs, ceramide, and GG and the 5% urea lotion are effective in improving scaly and rough skin, skin hydration, and skin barrier function in stable chronic pediatric kidney disease patients. Additional ingredients, such as NMFs, ceramide, and GG can significantly improve skin hydration and skin barrier function. Products containing 5% urea that are applied on the lower legs for four weeks do not increase BUN or creatinine levels especially in the patients treated with dialysis.

What is already known on this topic?

Xerosis is a common cutaneous manifestation in chronic kidney diseases in adults and children. Itching is significantly increased with an increase in the severity of xerosis which can cause skin discomfort, scratch marks, and compromise skin barrier function. Treatment of xerosis with topical GG, NMFs, and ceramide increase skin hydration and barrier function in adults. However, most studies that used GG, NMFs, and ceramide were performed in adults. There are no reports on the safety of urea-containing lotion in children with chronic kidney disease.

What this study adds?

Moisturizers containing 5% urea, NMFs, ceramide, and GG lotion and 5% urea lotion were effective in improving scaling and roughness, skin hydration, and skin barrier function in stable chronic pediatric kidney disease patients. Additional ingredients, such as NMFs, ceramide, and GG can significantly improve skin hydration and skin barrier function. Products containing 5% urea applied on the lower legs for four weeks do not increase BUN or creatinine levels.

Acknowledgements

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Potential conflicts of interest

None.

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การศึกษาเปรียบเทียบการใช้สารให้ความชุ่มชื้นที่ประกอบด้วย urea 5%, natural moisturizing factors, ceramide และ glyceryl glucoside กับสารให้ความชุ่มชื้นที่ประกอบด้วย urea 5% ในการรักษาภาวะผิวแห้งในผู้ป่วยเด็กโรคไตเรื้อรัง

ศิริวรรณ วนานุกูล, สุชีรา ฉัตรเพริดพราย, เทอดพงศ์ เต็มภาคย์, ชัยสิทธิ์ ศรีสด, ธวัชชัย ดีขจรเดช

ภูมิหลัง: *ภาวะผิวแห้งพบได้บ่อยในผู้ป่วยโรคไตเรื้อรัง อาการคันจากภาวะนี้ทำให้ไม่สบายตัว เกิดรอยเกาทำให้คุณสมบัติในการปกป้องของผิวเสียไป*

วัตถุประสงค์: *เพื่อศึกษาเปรียบเทียบประสิทธิภาพของโลชั่นที่ประกอบด้วย urea 5%, natural moisturizing factors, ceramide และ glyceryl glucoside lotion กับโลชั่นที่ประกอบด้วย urea 5% ในการรักษาภาวะผิวแห้งในผู้ป่วยเด็กโรคไตเรื้อรังที่มีอาการคงที่*

วัสดุและวิธีการ: *การศึกษานี้เป็นการทดลองชนิด randomized, double-blind, split-side ในผู้ป่วยเด็กโรคไตเรื้อรังที่มีอาการคงที่ จำนวน 50 ราย ที่มีภาวะผิวแห้ง ผู้ป่วยจะได้รับการสุ่มให้ได้รับ 1) สารให้ความชุ่มชื้นที่ประกอบด้วย urea 5%, natural moisturizing factors, ceramide และ glyceryl glucoside และ 2) สารให้ความชุ่มชื้นที่ประกอบด้วย urea 5% ทาคนละข้างของขา วันละ 2 ครั้ง นาน 4 สัปดาห์ โดยที่ขวดที่บรรจุสารทั้ง 2 ชนิด มีรูปแบบและขนาดเหมือนกัน ผู้ป่วยจะได้รับการประเมินภาวะผิวแห้ง ความชุ่มชื้นของผิว และค่าการสูญเสียน้ำผ่านผิว (transepidermal water loss, TEWL) ก่อนการศึกษาและหลังทาสารให้ความชุ่มชื้นในสัปดาห์ที่ 1, 2 และ 4*

ผลการศึกษา: *จำนวนผู้ป่วยทั้งหมด 47 ราย จาก 50 ราย ที่ทาสารให้ความชุ่มชื้นจนสิ้นสุดการศึกษา อายุเฉลี่ยเท่ากับ 13.43±2.3 ปี ผลิตภัณฑ์ทั้ง 2 ชนิด สามารถลดความรุนแรงของภาวะผิวแห้งเปรียบเทียบกับก่อนการศึกษาอย่างมีนัยสำคัญทางสถิติ ($p<0.001$) สารให้ความชุ่มชื้นที่ประกอบด้วย urea 5%, natural moisturizing factors, ceramide และ glyceryl glucoside เพิ่มความชุ่มชื้นของผิวและลดค่าการสูญเสียน้ำผ่านผิวได้มากกว่าสารให้ความชุ่มชื้นที่ประกอบด้วย urea 5% อย่างเดียวอย่างมีนัยสำคัญทางสถิติ ($p<0.001$) ตั้งแต่สัปดาห์ที่ 1 ในด้านความปลอดภัยของการใช้ urea ในผู้ป่วยโรคไตเรื้อรังพบว่า ค่า BUN และ creatinine ในเลือดไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ ระหว่างก่อนการศึกษาและสิ้นสุดการศึกษา ($p = 0.627$) และไม่พบผลข้างเคียงใด ๆ จากการทาสารให้ความชุ่มชื้นทั้ง 2 ชนิด*

สรุป: *สารให้ความชุ่มชื้นทั้ง 2 ชนิด มีประสิทธิภาพในการลดขุย ความหยาบของผิว เพิ่มความชุ่มชื้น และเพิ่มคุณสมบัติในการปกป้องของผิวในผู้ป่วยเด็กโรคไตเรื้อรังที่มีอาการคงที่ สารที่เพิ่มเติมลงไป ได้แก่ natural moisturizing factors, ceramide และ glyceryl glucoside มีประสิทธิภาพในการเพิ่มความชุ่มชื้นและเพิ่มคุณสมบัติในการปกป้องของผิว ในด้านความปลอดภัยการทาผลิตภัณฑ์ที่มี urea 5% ที่ขา นาน 4 สัปดาห์ ไม่มีผลต่อระดับ BUN และ creatinine ในเลือด*