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Efficacy of Calcipotriol 0.005% Ointment for Uremic Xerosis with Pruritus in Chronic Kidney Diseases Undergoing Hemodialysis Patients: *Randomized Double Blind Clinical Trial*

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ABSTRACT

Background: Uremic xerosis with pruritus (UXP) is a chronic cutaneous complication among patients undergoing maintenance renal dialysis. Uremic xerosis level is directly related with pruritus severity or vice versa. Uremic xerosis with pruritus may lead to discomfort and negative psychological effect. The ethiopathogenesis still unknown, Most of treatments are empirical, and there is no effective and safe therapy. Emollient has not been effective enough to improve quality of life. There is some report about efficacy of topical vitamin D in xerosis and chronic pruritus. **Objective**:We evaluate the efficacy of calcipotriol 0.005% ointment for uremic xerosis and uremic pruritus in chronic kidney disease patients undergoing hemodialysis. **Material & methode**: Sixty two patients with UXP were enrolled, randomized double blind study. Patients were divided to two group, calcipotriol 0.005% ointment group or placebo. In baseline, patients were instructed to apply twice daily for four weeks. We assesesment the efficacy and safety of calcipotriol 0.005% ointment and placebo after 2nd and 4th weeks treatment using *overall dry skin score* (ODSS), visual analog scale (VAS), corneometer and sebumeter. We also assessed adverse effect and tolerance this drugs using visual assessment scale. **Results**: Overall dry skin score (ODSS) and visual analog scale (VAS) significantly decreased in calcipotriol 0.005% ointment group than in placebo group ($p < 0.05$). Skin hydration level based on Corneometer score and skin surface lipid based on Sebumeter score was significantly increased in calcipotriol 0.005% ointment group than in placebo group ($p < 0.05$). Cure rate and clinical improvement for calcipotriol 0.005% ointment group was significantly higher than placebo group. There was no adverse effect between two groups after treatment**. Conclusion:** calcipotriol 0.005% ointment is effective than placebo and can be used as alternative or adjuctive treatment and safe and tolerance for UXP.

1. Introduction

Uremic xerosis with pruritus (UXP) is a complication of cutaneous chronic with characteristic dry skin, scaling, rough, poor turgor, elastosis and mild-severe pruritus in chronic kidney disease (CKD) patients undergoing hemodyalisis (HD). Szepietowski explain uremic xerosis is a main factor influencing pruritus. Based on large published series, moderate-severe uremic xerosis with pruritus (UXP) have increase intensity approximately 50-100%[1]. Other studies demonstrated UXP will have a worsening effect by reducing the threshold for itch. Some studies found UXP have an effect in quality of life, both physic and emotional, sleep disorder, depression and mortality risk. [2,3]

In 2005-2008, Dialysis Outcomes & Practice Pattern Study (DOPPS) found UXP in 2140 of 2326 CKD patients undergoing HD. In 2017, 4322 CKD patients undergoing HD in RSUP Moh. Hoesin (RSMH) Palembang, until now prevalence and incident still

unknown[4]

The etiopathogenesis of UXP still unclear. The treatment given is mostly empirical, and there is no effective and safe therapyAlthough emollients can be used to improve subjective and objective symptoms of UXP, it has not been effective enough to improve quality of lifeRecent studies demonstrated topical vitami D can be used both as alternative or adjuvant in several chronic pruritus disease such as atopic dermattis and psoriasis[2,5] Lebwohl et al demonstrated in chronic plaque psoriasis patient[6] Calcitriol is a vitamin D3 metabolite, synthesized in keratinocytes, regulates calcium gradients in the epidermis which are important for keratinocyte differentiation, and potentially as immunomodulators, so that topical vitamin D can improve UXP. Open-label study Jung et al. in 2015 on UXP in CKD patients, the application of calcipotriol 0.005% ointment compared to vehicle, significantly decreasing UXP[8]

Based on the background above, we study about the efficacy of 0.005% calcipotriol ointment for UXP in CKD patients undergoing HD.

2. Methods

This is a randomized double-blind clinical trial, placebo-controlled in HD Installation at Mohammad Hoesin general hospital Palembang. The study was conducted from 1 October 2019 to february 2020 Population was all CKD patients diagnosed with UXP undergoing HD at HD Installation RSMH, Palembang. Sample was a population that met inclusion and exclusion criteria. The inclusion criteria, CKD patients undergoing HD with UXP. Informed consent was signing after being given an explanation. Exclusion criteria were patients using systemic corticosteroid treatment, antihistamines, vitamin D 4 weeks before study, patients using topical moisturizer, corticosteroids, antihistamines, vitamin D 2 weeks before study, xerosis or pruritus due to diseases other than CKD and hypersensitivity to study material.

The study sample was taken by consecutive sampling then divided into two treatment groups randomly, ointment group calcipotriol 0.005% and placebo, that only known to the research assistant. Sociodemographic data including age, sex, CKD disease, HD frequency, duration of HD, HD devices, frequency of pruritus, duration of pruritus, distribution of pruritus, sleep disturbances, and other skin diseases were taken. The study subjects were given baby soap and pots containing calcipotriol 0.005% ointment or placebo with the same size, color and shape. Ointment is used twice a day in both lower limbs for four weeks. Uremic xerosis with pruritus assessment was performed using ODSS scores, and VAS scores, skin hydration levels (SHL) using CM825® corneometer and lipid skin surfaces(LSS) level using sebumeter SM815®. The evaluation was conducted on the 2nd and 4th week. Adverse effect and tolerance was assessed using visual assessment scale (VAS) in the 2nd and 4th week after treatment. Statistical analysis was carried out using the statistical package for social sciences (SPSS) version 20.0

3. Results

In this study, UXP patients who fulfilled the inclusion criteria is 65 patients, the number of patients who received calcipotriol 0.005% ointment is 32 patients, and placebo is 33 patients. Three patients dropped out during follow up, one from calcipotriol 0.005% ointment group and two from placebo group because drug non-compliance. Patients who continued the study were 62 people. Data characteristics of patients are shown in table 1.

The analysis of ODSS, VAS, corneometer and sebumeter after 2nd and 4th week evaluation showed there was a reduction of baseline score after treatment in both of calcipotriol 0.005% ointment and placebo group. Analysis with Mann-Whitney test showed the mean of ODSS, VAS, corneometer and sebumeter after treatment was significantly different. ($p < 0.05$).(Table 2)

Clinical improvement of UXP in these studies was assessed by evaluating using ODSS quartile score with interpretation <1 excellent, 1-2 good, >2 no improvement. Analysis Chi-Square showed there are 8 (25.8%) patients who have excellent response in

calcipotriol 0.005% ointment group, 22 (71%) good response and no improvement in 1 (3.2%) patients, meanwhile in placebo group, 27 (87.1%) patients have a good response and no improvement in 4 (12.9%) patients. Calcipotriol 0.005% ointment was significantly more effective in reducing ODSS scores than placebo (*p 0.004*). (Table 3)

Clinical improvement of UXP was assessed by evaluating using VAS quartile score with interpretation < 3 excellent, 3-4 good, > 4 no improvement. Analysis Chi-Square showed 23 patients (74.2%) have an excellent response, 6 patients (19.4%) have a good response and no improvement in 2 patients (6.5%). In placebo group, 6 patients (19.4%) have an excellent response, 12 patients (38.7%) have a good response and no improvement in 13 patients (41.9%). Calcipotriol ointment 0.005% was significantly more effective in reducing VAS scores than placebo (*p 0.000*). (Table 3)

Clinical improvement of UXP was assessed by evaluating using corneometer quartile score with interpretation >44.2 AU excellent, 34.15-44.2 good, <34.15 no improvement. Analysis Chi-Square showed 13 patients (41.9%) have an excellent response and no improvement 5 patients (16.1%) in calcipotriol 0.005% ointment group. In placebo group, there were 4 clinical improvements (12.9%) and no improvement in 27 people (87.1%). Calcipotriol 0.005% ointment was significantly more effective in increasing skin hydration level than placebo (*p 0.000*). (Table 3)

Clinical improvement of UXP based on sebumeter scores was assessed using sebumeter quartile score in 4th weeks with interpretation >3 µg/cm^2 excellent, 2-3 µg/cm^2, <2 µg/cm^2 no improvement. Analysis Chi-Square showed 12 (38.7%) patients have an excellent response, 6 (19.4%) patientshave a good response and no improvement 13 patients (41, 9%) in calcipotriol 0.005%, ointment group. In placebo group, 2 patients (6.5%) have an excellent response, 5 (16.1%) patients have good response and no improvement in 24 patients (77.4%). Calcipotriol 0.005% ointment is more effective than placebo for increasing skin surface lipids level (*p 0.000*). (Table 3)

In this study, evaluation of cure rate for UXP was assesed using cut off of ODSS, VAS, corneometer and sebumeter in 4th weeks treatment. Analysis of UXP cure rate using ODSS found there were 26 patients cured (83.9%) in calcipotriol 0.005% ointment group and 9 patients were cured (29%) in placebo group. The cure rates between calcipotriol 0.005% ointment group and placebo was differences significantly (*p = 0.000*). (Table 4)

Analysis UXP cure rates using VAS showed in calcipotriol ointment group 0.005%, 23 patients cured (74.2%) and 6 patients was cured in placebo group (19.4%). Cure rate between calcipotriol 0.005% ointment group and placebo was significant differences (*p = 0.000*).

Analysis of UXP cure rate using corneometer score found there were 30 patients cured (96,8%) in calcipotriol 0.005% ointment group and 6 patients (19.4%) in placebo group were cured. Cure rate between calcipotriol 0.005% ointment and placebo group were different significantly. (*p 0.000*). (Table 4)

Analysis of UXP cure rate using sebumeter score in calcipotriol 0.005% ointment group found 25 patients (80,6%) cured, meanwhile in placebo group 7 patients (77,4%) was cured Calcipotriol 0.005% ointment than placebo were significantly different cure rate (*p 0.000*).

Evaluation of adverse effect between calcipotriol 0.005% ointment group and placebo was assesed using visual assesment scale. After application for 2nd and 4th weeks, no adverse effects were found (Table 5)

Till the end of this study there is no adverse effects both of drugs, and can be tolerated for used in UXP. inCKD patients underlying hemodialysa

Table 1. Sosiodemographic characteristic

Characteristic	**Number (n)**	***p***
Sex	29 (46.8%)	1.000
- Male	33 (53.2%)	
- Female		
Age (years)		0.960
- 31 - 40	5 (8.1%)	
- 41 - 50	19 (30.6%)	
- 51 - 60	23 (37.1%)	
- 61 - 70	12 (19.4%)	
- >71	3 (4.8%)	
CKD causative disease		0.439
- SLE	1 (1.6%)	
- Hypertension	39 (62.9%)	
- Diabetic nephropathy	16 (25.8%)	
- Polycistic kidney disease	3 (4.8%)	
- Interstitial Nefritis	2 (3.2%)	
- Unknown	1 (1.6%)	
HD duration (years)		
- < 1	11 (17.7%)	0.220
- 1 – 2	18 (29%)	
- > 3	33 (53.2%)	
HD frequency		0.445
- 1x/week	0 (0%)	
- 2x/week	62 (100%)	
- 3x/week	0 (0%)	
Dyalisis membrane		0.62
- *Cuprophane*	0 (0%)	
- *Hemophane*	0 (0%)	
- *Polysulphone*	62 (100%)	
Pruritus distribution		0.445
- 1 Location (inferior extremity)	17 (27.4%)	
- > 1 Location	31 (50%)	
- Generalisata	14 (22.6%)	
Pruritus frequency		0.445
- < 10 minute	29 (46.8%)	
- > 10 minute	33 (53.2%)	
Pruritus duration		0.183
- Intermitten	14 (22.6%)	
- Nocturnal	33 (53.2%)	
- All day	15 (24.2%)	
Sleep disturbances		0.522
- None	20 (32.3%)	
- Annoying	32 (51.6%)	
- Very annoying	10 (16.1%)	
Other cutaneus disease		0.362
- None	40 (64.5%)	
- Purpura	1 (1.6%)	
- Hyperpigmentation	20 (32.3%)	
- Bacterial infection	1 (1.6%)	

Table 2. Comparison of effectivity between calcipotriol 0.005% ointment and placebo

	Group	Baseline	Week 2	Week 4	p
ODSS	• Calcipotriol 0.05% ointment • placebo	3.32 ± 0.702 3.16 ± 0.688	1.94 ± 0.814 2.42 ± 0.807	0.94 ± 0.727 1.84 ± 0.638	0.000
VAS	• Calcipotriol 0.05% ointment • Placebo	6.61 ± 2.486 6.74 ± 2.352	4.42 ± 2.514 5.45 ± 2.188	1.45 ± 1.588 4.26 ± 2.323	0.000
Corneometer	• Calcipotriol 0.05% ointment • Placebo	14.56 ± 5.882 14.33 ± 4.089	39.17 ± 9.778 23.36 ± 7.470	43.55 ± 7.912 24.68 ± 6.915	0.000
Sebumeter	• Calcipotriol 0.05% ointment • Placebo	0.90 ± 1.012 0.48 ± 0.811	4.87 ± 13.324 0.87 ± 1.024	5.52 ± 11.159 1.16 ± 1.753	0.000

Table 3. Comparison of clinical improvement between calcipotriol 0,005% ointment and place

	Calcipotriol 0.005% ointment			Placebo			p
	n (%)			n (%)			
	Excellent	Good	No improvement	Excellent	Good	No improvement	
ODSS	8 (25.8%)	22 (71%)	1 (3.2%)	0 (58.1%)	27 (87.1%)	4 (12.9%)	0.004
VaS	23 (74.2%)	6 (19.4%)	2 (6.5%)	6 (19.4%)	12 (38.7%)	13 (41.9%)	0.000
Corneometer score	13 (41.9%)	13 (41.9%)	5 (16.1%)	0 (0.0%)	4 (12.9%)	27 (87.1%)	0.000
Sebumeter score	12 (38.7%)	6 (19.4%)	13 (41.9%)	2 (6.5%)	5 (16.1%)	24 (77.4%)	0.000

Table 4. Curerate using corneometer between calcipotriol 0,005% ointment and placebo

	Calcipotriol 0.005% ointment		Placebo		p
	n (%)		n (%)		
	Cured	No	Cured	No	
ODSS	26 (83.9 %)	5 (16.1 %)	9 (29 %)	22 (71%)	0.004
VAS	23 (74.2 %)	8 (25.8 %)	6 (19.4 %)	25 (80.6 %)	0.000
Corneometer score	30 (96.8 %)	1 (3.2 %)	6 (19.4 %)	6 (19.4 %)	0.000
Sebumeter score	25 (80.6 %)	6 (19.4 %)	7 (22.6%)	24 (77.4 %)	0.000

Tabel 5. *Visual assessment scale* (VAS) after application of calcipotriol 0,005% ointment and placebo

Adverse reaction used visual assesment scale	2nd week		4th week	
	Calcipotriol 0.005% oinment	Placebo	Calcipotriol 0.005% oinment	Placebo
• None	0	0	0	0

• Well defined erythem	0	0	0	0
• Well defined erythem with vesicle	0	0	0	0
• Erythem, oedem, vesicle, bullae, erosion	0	0	0	0

4. Discussion

This study is clinical trial, a randomized, double blind, placebo-controlled to study the efficacy of calcipotriol 0.005% ointment and placebo in CKD patients undergoing HD with UXP. Total 62 patients were divided into 2 treatment group, one group received calcipotriol 0,005% ointment, the other received placebo. There were 29 male (46.8%) and 33 (53.2%) female included in the study. The mean age of the sample was 52.9 ± 9.87. The causative of CKD respectively are hypertension was 39 (62.9%) and diabetes mellituswas 16(25.8%) and duration of HD are 3 year was 33 (53.2%) and 1-2 years. was 18(29%), the frequency HD 2time/week was 62(100%), distribution pruritusn ≥1 location was 31(50%) patients There is no significant difference characteristic of the patients between of the two treatment group. (Table 1)

Observational data showing the association between lower levels of 25(OH)-VD and various chronic skin diseses such as uremic xerosis and pruritus (UXP)[9] Uremic xerosis with pruritus (UXP) is the most common skin manifestation found in CKD patients undergoing HD. CKD patients has a skin barrier disruption which are the cause of UX. Atrophy of the sebaceous gland associated with a decrease of surface lipid layer causes an increase in TEWL and a decrease of stratum corneum hydration.[10] Uremic xerosis with pruritus is also aggravated by abnormalities function and size of the eccrine gland due to CKD. High-dose diuretics and excess blood filtration also aggravates UXP.[11] , UXP was found in 12-90% of CKD patients.. The pathophysiology of UXP still unclear, Gokuston 2016 study showed there is association of 25(OH)D deficiency with pathogenesis of UXPso an effective topical drug is needed to reduce UXP. [12,13].

In hypothesis Brito study was demonstrate the efect of 25-vitamin D in TLR4, cathelicidin and MCP-1 expressions suggesting that this activated form of vitamin D may minimize infammation. Whether the supplementation of 25-vitamin D in patients UXP with CKD is capable to reduce infammation[14] Various studies tried to prove the effectiveness of topical treatments to reduce UXP, but the results still controversial. Topical vitamin D has been reported effective in reducing pruritus in psoriasis patients[7]. Gokustun et al investigate UP in CKD patients undergoing HD (n = 47) found that there was vitamin D deficiency in CKD patients[13]. Jung et al investigate UXP patients (n = 20) found the effectiveness of calcipotriol 0.005% ointment in reducing UXP in CKD patients[8]. Clinical trials to determine the efficacy of calcipotriol 0.005% ointment against UXP in CKD patients undergoing HD need to be done.

In this study, we assess UXP with ODSS scores, analysis of clinical improvement based on 4th week ODSS score showed that calcipotriol 0.005% ointment was significantly effective in improving UXP than placebo (*p. 0.004*). Analysis of cure rate, the cured patients is 26 (83.9%) patients in calcipotriol 0.005% ointment group and 9 patients (29%) in placebo group. Uremic xerosis with pruritus cure rates based on ODSS scores in the calcipotriol 0.005% ointment group were significantly higher than placebo (p 0.000). Jung et al. in study of CKD patients undergoing HD with UXP, found 7 of 10 patients had over 50 % was repair after application of calcipotriol 0.005% ointment in 4th week compared to baseline[8]. Experimental study of Hong et al. in mice proved the application of topical calcitriol restore epidermal barrier permeability[15]. Calcitriol is a vitamin D3 metabolite, synthesized in keratinocytes, regulating calcium gradients in the epidermis which are important for keratinocyte differentiation, and potentially as immunomodulators[8].

In this study we asses UXP with VAS, analysis of

clinical improvement based on 4th week VAS showed that calcipotriol 0.005% ointment was significantly more effective in reducing UP compared to placebo *(p 0.000)*. Analysis of cure rates, 23 patients (74.2%) calcipotriol 0.005% ointment group were cured. In placebo, 6 patients (19.4%) were cured. The cure rates of UP based on VAS scores in calcipotriol 0.005% ointment group were significantly higher than placebo (p 0.000). Study of Jung et al. CKD patients undergoing HD with UX and UP, there was a significant decrease in VAS scores after application of calcipotriol 0.005% ointment compared to the vehicle in the 2nd and 4th weeks (p <0.05)[8]. Although the etiopathogenesis of UP is still controversial, there is a significant relationship between UX and the severity of UP, so that UX patients are more prone to itching[2]. Vitamin D improves UX by increasing the differentiation of keratinocytes and involved in formation of lipid barriers to restore skin barrier function. Microinflammation is thought to play a role in the pathophysiology of UP. Research shows that there is an increase in the levels of IL-6 and CRP cytokines in serum of CKD patients with UXP[16] A study by Fallahzadeh et al. found a significant increase in serum IL-2 levels in CKD patients with UXP. Vitamin D acts as an immunomodulator. Vitamin D inhibits T cells to producing IL-2 and IL-6[8,17]. In vitro study of Carvalho et al. prove that calcitriol inhibits production of Th1 cytokines and stimulates Th2 cytokines. The administration of calcidiol and calcitriol inhibits TLR7, TLR9, IL-6 and IFN-inhibitor.[18]

In this study, we asses skin hydration (SHL) with a corneometer score, analysis of clinical improvement showed calcipotriol 0.005% ointment was more effective in increasing skin hydration than placebo (p 0.000). Analysis of cure rates, in calcipotriol ointment 0.005% group, the cured sample were 30 patients (96.8%) and placebo 6 patients (19.4%). The cure rate in calcipotriol 0.005% ointment group was significantly higher than placebo *(p 0.000)*. In CKD patients, there was atrophy of ductal sweat glands and sebaceous glands, causing a decrease in SSL production so disrupt the integrity of stratum corneum. Skin barrier damage causes an increase in TEWL and decrease stratum corneum hydration.[10,15] Hong et al. report application of topical calcitriol restore epidermal permeability through activation of vitamin D pathways and increase epidermal lipids, by increasing the production of lamellar bodies and enzyme activity that involved in synthesis epidermal lipid[15, 18]

In this study, we asses SSL levels with a sebumeter, analysis of clinical improvement shows that calcipotriol 0.005% ointment is more effective than placebo in increasing SSL levels (p 0.000). Analysis of cure rate found the cure sample in calcipotriol 0.005% ointment group was 25 patients. (80.6%) and 7 people (22.6%) in placebo group. The cure rate of calcipotriol 0.005% ointment group was significantly higher than placebo (p 0.000). Skin surface lipids had a function as a skin barrier to prevent excess water loss from the epidermis. Study of Hong et al. in mice found an increase in lamellar bodies density after application of calcitriol. Lamellar bodies play a role in the storage and secretion of SSL. Patients with CKD experience a decrease in SSL due to atrophy of the sebaceous glands which is difficult to repair only by giving emollients[14,17]

In this study the evaluation of adverse effects was assessed using the visual assessment scale on 2nd week and 4th week. In both treatment groups, no adverse effects were found. Previous study showing that cholecalciferol repletion has an anti-inflammatory effect and improves vitamin D intracellular regulatory enzymes on lymphocytes from dialysis patients.[19] The study of Lebowl et al. in chronic plaque psoriasis patients showed that calcipotriol 0.005% ointment was safe and effective in long-term treatment[7]. Study of Jung et al in CKD patients undergoing HD with UXP patients did not find adverse effects after application of calcipotriol 0.005% ointment for 4 weeks[8]. The results of this study prove that calcipotriol 0.005% ointment is effective, safe and can be tolerated for UXP in CKD patients undergoing HD.

5. Conclusion

Calcipotriol 0.005% ointment more effective than placebo to reduce UX with pruritus (UXP) in CKD patients undergoing HD based on ODSS, VAS, corneometer and sebumeter. Calcipotriol 0.005% ointment have safe and tolerated for use as an alternative and adjuvant therapy.

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