Kidney Medicine

Cannabis-Containing Cream for CKD-Associated Pruritus: A Double-Blind, Placebo Controlled Trial

Suthiya Anumas, Pranporn Kuropakornpong, Panlop Chakkavittumrong, Adis Tasanarong, and Pattharawin Pattharanitima

Rationale & Objective: This study aims to compare the efficacy of a cannabis cream and a placebo in the treatment of chronic kidney disease (CKD)-associated pruritus.

Study Design: A double-blind randomized controlled study.

Setting & Participants: Sixty hemodialysis patients with the worst itching intensity numerical rating scale (WI-NRS) ≥3.

Exposure: Patients received cannabis cream or placebo.

Outcomes: The primary endpoint was the WI-NRS score at week 4. The secondary endpoints included the WI-NRS at week 2, the Skindex-10 score at weeks 2 and 4, and the mean difference score between baseline and week 4 for the WI-NRS and the Skindex-10 score.

Analytical Approach: We used unpaired t tests or Mann Whitney U tests, along with χ^2 or Fisher exact tests as appropriate. The adjusted mean differences were determined using ANCOVA, adjusting for baseline scores.

Results: Among 60 participants, the mean age was 61.6 ± 14.4 years and the mean baseline WI-NRS was 6.7 ± 1.7. The placebo and cannabis cream groups were similar at baseline, although more individuals in the placebo group had diabetes. At 4 weeks, the WI-NRS dropped to 2.6 in the cannabis group and 3.6 in the placebo group (the mean difference after adjustment for baseline scores:−1.1, 95% CI, −2.1 to −0.2; $P = 0.02$). Skindex-10 scores at week 4 were also lower in the cannabis group, but after adjustment for baseline scores, statistical significance was not maintained. No side effects were observed in either group.

Limitations: A single study with a small sample size restricts its generalizability. Variances in participants' diabetes statuses might have affected the itch outcomes. The absence of cannabinoid level assessment in blood prevents conclusive determination of the potential systemic impacts. A 4-week follow-up period inadequately captures long-term effect.

Conclusions: In CKD-associated pruritus, the topical cream containing cannabis significantly reduced the severity of itching symptoms compared to the placebo.

Trial Registration: clinicaltrials.gov Identifier: NCT06159686

Complete author and article information provided before references.

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Chronic kidney disease (CKD)-associated pruritus poses a significant burden on hemodialysis patients, affecting approximately 46% of individuals undergoing dialysis.[1] Eighteen experience extreme itching, 46% encounter work-related disruptions as a result of symptoms, and 58% report concurrent symptoms of depression, all of which have a negative impact on quality of life.[2] Various mechanisms, including inadequate dialysis, increased uremic toxins, inflammatory cytokines, parathyroid hormone, phosphorus, dry skin, mast cell histamine secretion, and an imbalance or dysregulation between different types of opioid receptors, contribute to uremic pruritus.[3-5] Current treatments include antihistamines, gabapentanoids, moisturizer creams, capsaicin creams, and difelikefalin,[1,3,5] with limited success, as approximately only 10% of patients find relief.[6] Cannabinoids were also mentioned in CKD-associated pruritis treatment.[2,7] There was only one study that demonstrated their efficacy by decreasing pruritus in 38% of hemodialysis patients,[8] but they are less commonly used nowadays.

Numerous cannabinoid-containing products have potential uses in a variety of dermatological conditions, such as acne vulgaris, allergic dermatitis, psoriasis, and pruritus.[9-11] One particularly interesting effect is the antipruritic effect, which has been infrequently studied, especially in patients with uremic pruritus. These effects are mediated by neuronal activation and mast cell modulation. Cannabinoid binding to CB1 and CB2 receptors inhibits mast cell differentiation, aggregation, and histamine release, whereas cannabinoid binding to TRP-iron receptors reduces peripheral nerve activation.[9,12,13] Thus, cannabinoids seem to be effective in relieving pruritus through various mechanisms.

Cannabinoids can be categorized into the following: (1) endocannabinoids, which are produced naturally within humans and animals, such as arachidonoyl glycerol, anandamide, and N-palmitoyl ethanolamide; (2) phytocannabinoids, which are found in the cannabis plant, including cannabidiol (CBD) and Δ-9-tetrahydrocannabinol (THC); and (3) synthetic cannabinoids, which are artificially created cannabinoid, such as dronabinol and nabinoid.[12-14] Abundant research has demonstrated several effects of CBD and THC, such as anti-pruritic properties; however, most of these studies were performed in nondialysis patients.[9]

Szepietowski et al demonstrated the efficacy of an endocannabinoid cream in treating uremic pruritus in hemodialysis patients.[8] *Cannabis sativa* L, belonging to the

PLAIN LANGUAGE SUMMARY

Chronic kidney disease (CKD)-associated pruritus presents a significant burden to hemodialysis patients, with current medications often falling short in alleviating symptoms. Cannabinoids, with their anti-inflammatory, antioxidative, and peripheral nerve activation reduction properties, hold promise in treating CKD-associated pruritus. Especially when applied topically, cannabinoids could provide moisturized skin along with their other effects. We analyzed the efficacy of cannabis cream compared to a placebo, demonstrating that the cannabis cream could improve the severity of itch, as reported by the WI-NRS score at the end of the fourth week of treatment. This innovative therapeutic approach has the potential to pave the way for new drugs aimed at effectively treating CKD-associated pruritus, ultimately reducing symptom severity, and potentially enhancing patients' quality of life.

Cannabaceae family, contains significant amounts of CBD and a small quantity of THC.[13,14] Given the reported efficacy of cannabinoids in pruritus treatment, *Cannabis sativa L*, as a phytocannabinoid source, may offer therapeutic benefits for uremic pruritus. However, no clinical trials have investigated the effects of phytocannabinoids in CKD-associated pruritus.

This study aims to assess the effectiveness of a cannabis-containing cream, which is phytocannabinoid, in comparison with a placebo for treating CKD-associated pruritus among hemodialysis patients.

MATERIALS AND METHODS

Sample Preparation

Cannabinoids from *Cannabis sativa L* seeds were harvested in Tak province, Thailand. They were baked at 55-60 °C for 8-10 hours to remove moisture and then subjected to the screw press technique to extract cannabis oil. Subsequently, the cannabis oil content was quantitatively measured using high-performance liquid chromatography with diode array detection (HPLC-DAD).

Allergic and irritant skin reaction tests were conducted with 1%, 2%, 3%, 4%, and 5% w/w and pure cream base on 30 healthy volunteers at the skin center, Thammasat University Hospital. The results were interpreted according to the International Contact Dermatitis Research Group (ICDRG) criteria,[15] and skin irritation reactions were evaluated using the Toiletry and Fragrance Association criteria.[16] The findings indicated no allergic and irritant skin reactions at any concentration during the drug study (Supplementary File, Tables S1-S5). In this study, we used 5% cannabis oil containing CBD:THC in a ratio of 1.27:0.13 mg/kg mixed with the cream base, totaling 100 g, as the study drug. A pure cream with the same ingredients but without cannabis oil was used as the placebo.

Participants

Adults ≥18 years old, diagnosed with end-stage kidney disease and undergoing long-term hemodialysis thrice-weekly for more than 90 days, were enrolled in this study. All eligible participants received adequate hemodialysis with a single-pooled Kt/V of 1.2 or more and exhibited a WI-NRS score of 3 or higher. Exclusion criteria included a history of cannabis allergy, pregnancy or breastfeeding, dermatologic diseases, and adjustments to medications for controlling itch within the 14 days preceding the study.

Study Design

Random allocation was accomplished through computer-generated permuted blocks of varying sizes, specifically blocks of 4. Eligible participants were then randomly assigned in a 1:1 ratio to receive either a cannabis-containing cream or a placebo. The application of the cream occurred in the morning and evening on the itching areas, excluding the face. The study maintained a double-blind design, ensuring that neither the patients nor the care physicians could distinguish between the 2 regimens. The eligible participants were assessed for the severity of itching symptoms using the WI-NRS and their itch-related quality of life using the Skindex-10 score at baseline, week 2, and week 4 of the study, after randomization. In addition, adverse effects were documented.

Outcomes

The primary outcome was the WI-NRS score at week 4. Secondary outcomes included the WI-NRS at week 2, the Skindex-10 score at weeks 2 and 4, the mean difference score between baseline and week 4 for WI-NRS and the Skindex-10 score, and adverse effects.

Statistical Analysis

We calculated the sample size based on the outcomes of the first 30 participants. We used the mean ± standard deviation (SD) WI-NRS score at week 4, which was 4.1 ± 2.4 for the placebo group and 2.6 ± 1.4 for the cannabis group, to calculate the total sample size. Approximately 60 patients are required to achieve 80% power.

Continuous variables were expressed as mean ± SD or median and interquartile range (IQR) and compared using an unpaired t test or Mann Whitney U test, as appropriate. Categorical variables were expressed as frequency and percentages and compared using a χ^2 test or Fisher exact test. The outcomes were presented by mean with SD by groups. Comparison of outcome at each week was used as an unpaired t test and reported by an unadjusted mean difference with a 95% confidence interval (95% CI). The adjusted mean difference was used in Analysis of Covariance (ANCOVA), adjusted by score at baseline. All P-values were 2-sided, and $P < 0.05$ was considered statistically significant. All statistical analyses were performed using Stata v.17.0 (StataCorp).

Ethical Consideration

The institutional ethics committee approved the study protocol of Thammasat University No.1, Faculty of Medicine, Thammasat University, Thailand (Approval number: 186/

2565). The trial commenced following approval from the Ethics Committee. Additionally, the trial was registered on ClinicalTrials.gov (Identifier: NCT06159686) to adhere to international standards and ensure transparency. It is noteworthy that while registration on clinicaltrial.gov occurred after trial initiation, it was undertaken to align with broader international research practices and enhance the accessibility of trial information. The guidelines followed the principles set in the Declaration of Helsinki. Writing informed consent was obtained before study participation.

RESULTS

Participants Characteristics

Of the 125 patients screened from September 2023 to November 2023 for entry into the trial, 65 did not meet the criteria for randomization (Fig 1). Of the 60 eligible patients, 30 were randomly assigned to the cannabis group and 30 to the placebo. Each patient was followed at week 2 and week 4. All participants had no history of THC or marijuana use. The mean age of the participants was 61.6 ± 14.4 years, and the median hemodialysis duration was 4 years (interquartile range [IQR], 3-6 years). The median duration of itch was 12 months (IQR, 3.5-15.5). Baseline characteristics were generally well-balanced between the 2 groups, except for a higher prevalence of diabetes in the placebo group. The mean baseline WI-NRS score in the cannabis group was 6.6 ± 1.3, when compared with 6.7 ± 1.9 in the placebo group ($P = 0.66$). The mean baseline Skindex-10 score was 27.4 ± 8 in the hemp group and 29.8 ± 11.2 in the placebo group ($P = 0.23$) (Table 1).

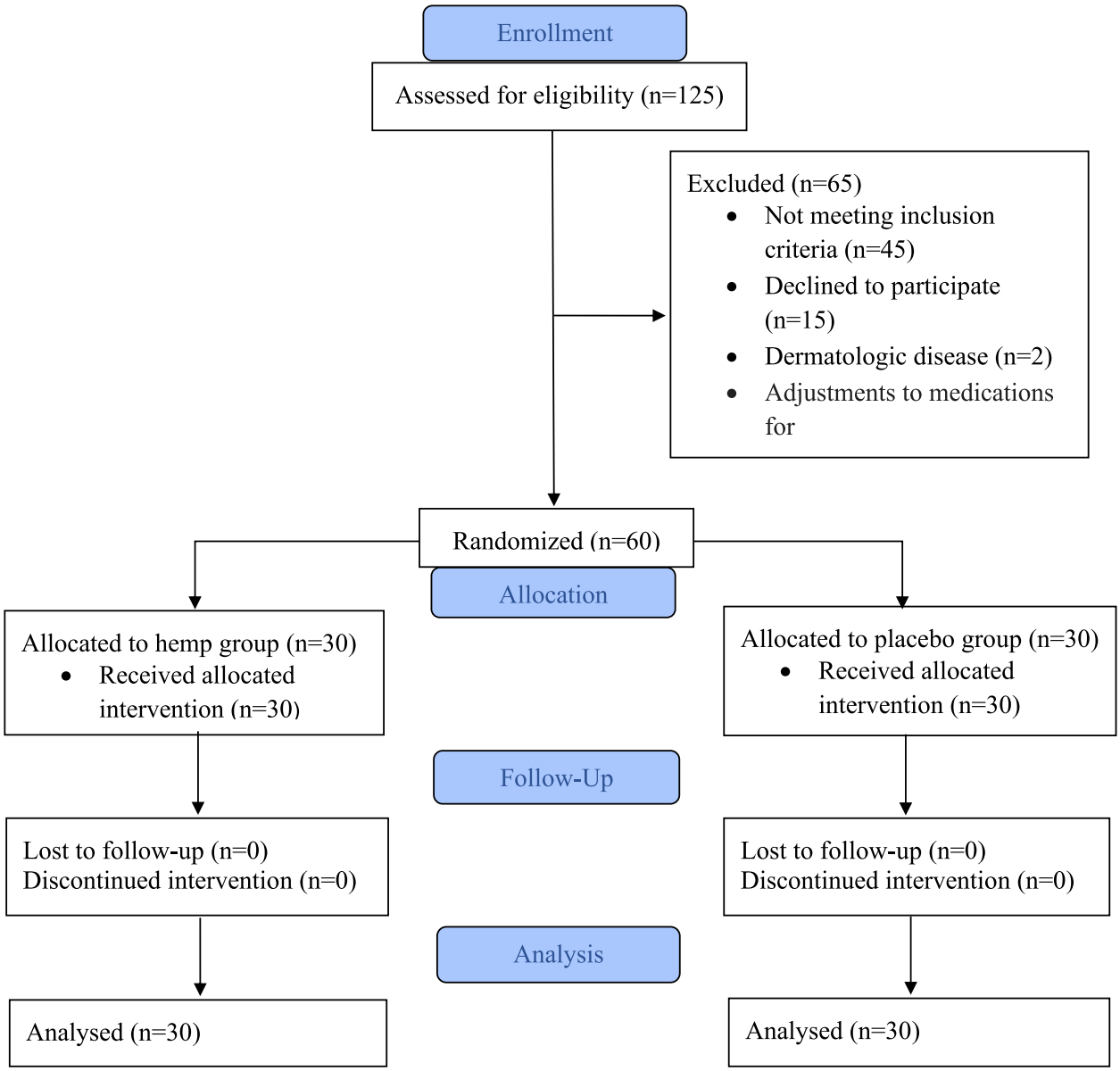

Figure 1. Consort flow diagram.

Table 1. Baseline Characteristics of Patients

Characteristics	Total N = 60	Cannabis Cream n = 30	Placebo n = 30
Age, y, mean ± SD	61.6 ± 14.4	64.3 ± 14.3	58.9 ± 14.1
Male, n (%)	39 (65)	18 (60)	21 (70)
Dry weight, kg, mean ± SD	63.6 ± 13.2	62.4 ± 14.7	64.8 ± 11.6
Dialysis vintage, y, median (IQR)	4 (3-6)	4 (3-6)	4 (3-7)
Vascular access, n (%)			
AVF	42 (70.0)	20 (66.7)	22 (73.3)
AVG	8 (13.3)	5 (16.7)	3 (10.0)
Tunneled cuffed catheter	10 (16.7)	5 (16.7)	5 (16.7)
Native kidney disease, n (%)			
Diabetes nephropathy	36 (60)	14 (46.7)	22 (73.3)
Hypertensive nephropathy	21 (35)	15 (50)	6 (20)
Chronic GN	2 (3.33)	0	2 (6.7)
ADPKD	1 (1.7)	1 (3.3)	0
Underlying disease, n (%)			
Hypertension	57 (95)	29 (96.7)	28 (93.3)
Diabetes mellitus	37 (61.7)	13 (43.3)	24 (80)
Dyslipidemia	25 (41.7)	12 (40)	13 (43.3)
Cerebrovascular disease	6 (10)	3 (10)	3 (10)
Coronary artery disease	10 (16.7)	8 (26.7)	2 (6.7)
Atrial fibrillation	3 (5)	2 (6.7)	1 (3.3)
Gout	8 (13.3)	6 (20)	2 (6.7)
spKt/V, mean ± SD	1.8 ± 0.3	1.8 ± 0.3	1.8 ± 0.4
URR, %, mean ± SD	76.2 ± 6.6	76.2 ± 7.4	76.3 ± 5.9
Duration of itching, months, median (IQR)	12 (3.5-15.5)	6.5 (3-12)	12 (6-24)
Area of itching, n (%)			
Back	46 (76.7)	21 (70)	25 (83.3)
Front	17 (28.3)	10 (33.3)	7 (23.3)
Arms	40 (66.7)	18 (60)	22 (73.3)
Legs	25 (41.7)	13 (43.3)	12 (40)
Face	4 (6.7)	2 (6.7)	2 (6.7)
Medication, n (%)			
Antihistamine	8 (13.3)	5 (16.7)	3 (10.0)
Gabapentin	1 (1.7)	0	1 (3.3)
Cream	24 (40)	14 (46.7)	10 (33.3)
Laboratory			
PTH, pg/mL, median (IQR)	298.4 (167.1-516)	337.3 (190.2-557)	275.2 (126-436)
Transferrin saturation, %, mean ± SD	31.6 ± 15.6	30.4 ± 14.5	32.7 ± 16.7
Ferritin, ng/mL, median (IQR)	311.3 (176.4-507.6)	304 (163-525.1)	311.3 (202.7-471)
Serum albumin, g/dL, mean ± SD	3.9 ± 0.4	3.9 ± 0.4	3.9 ± 0.5
Calcium, mg/dL, mean ± SD	8.9 ± 0.8	8.9 ± 0.8	9.0 ± 0.9
Phosphate, mg/dL, mean ± SD	4.8 ± 1.8	4.8 ± 1.7	4.8 ± 1.9
Hematocrit, %, mean ± SD	30.8 ± 5.0	31.5 ± 5.2	30.2 ± 4.7
Itch score, mean ± SD			
WI-NRS score	6.7 ± 1.7	6.6 ± 1.3	6.7 ± 1.9
Skindex-10 scale total score	28.8 ± 10.0	27.4 ± 8.0	29.8 ± 11.2

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; AVF, arteriovenous fistula; AVG, arteriovenous graft; GN, glomerulonephritis; IQR, interquartile range; PTH, parathyroid hormone; SD, standard deviation; spKt/V, single-pooled Kt/V; URR, urea reduction ratio; WI-NRS, Worst Itching Intensity Numerical Rating Scale.

Efficacy on Itch Severity

The cannabis cream demonstrated efficacy in relieving itch severity, as indicated by the primary outcome, which revealed a lower WI-NRS score at week 4 when compared with a placebo, with a mean different score (95% CI) was −1.0 (−2.0 to −0.1); P = 0.03. After adjustment for baseline scores, the mean difference (95% CI) was −1.1 (−2.1 to −0.2); P = 0.02. In terms of secondary outcomes, no significant differences were observed between the 2 groups in the WI-NRS score at week 2 and the change at weeks 2 and 4 from baseline (Fig 2; Table 2).

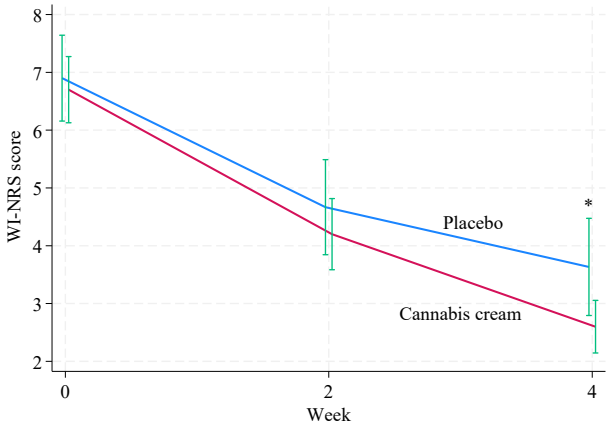

Figure 2. Median WI-NRS score. WI-NRS, worst itching intensity numerical rating scale.

Efficacy on Itch-Related Quality of Life

The cannabis cream demonstrated an improvement in itch-related quality, as indicated by the Skindex-10 score, which showed a lower score in the cannabis group at weeks 2 and 4 when compared with the placebo, with mean differences (95% CI) of −4.5 (−8.8 to −0.1); $P = 0.04$, and −4.4 (−8.3 to −0.5); $P = 0.03$, respectively. However, after adjustment for baseline scores, it did not demonstrate statistical significance. In addition, there were no significant differences between the scores at weeks 2, 4, and baseline (Fig 3; Table 2).

Adverse Effect

No adverse effects were observed in either of the groups.

DISCUSSION

This study demonstrated that a cannabis-containing cream was more effective in relieving the severity of CKD-associated pruritus than a placebo, as indicated by the WI-NRS score at week 4, which was lower in the cannabis group compared to the placebo group.

The proposed mechanisms underlying the efficacy of cannabinoids in the treatment of pruritus center on their binding to CB1 and CB2 receptors, thereby inhibiting mast cell differentiation, aggregation, and histamine release. In addition, cannabinoid interaction with TRP-iron receptors serves to diminish peripheral nerve activation.[2,9,12,13] In the context of CKD-associated pruritus, characterized by histamine release, inflammation, dry skin, and peripheral nervous system stimulation, cannabinoids present potential therapeutic benefits.[4,7]

Various routes of cannabinoid administration can be considered to achieve these effects. However, the transdermal route emerges as a particularly advantageous option owing to the moisturizing properties inherent in the cream base. Transdermal application, elucidated through various mechanisms, including moisturization for dry skin, makes a cannabis-containing cream an

Table 2. Efficacy Outcome

Outcome	Mean ± SD		Unadjusted		Adjusted by Score Baseline		Mean (95%CI) of Change From Baseline		
	Cannabis Cream	Placebo	Mean Difference (95%CI)	P^a	Mean Difference (95%CI)	P^b	Cannabis Cream	Placebo	Difference in Difference (95%CI) P^a
WI-NRS score									
Baseline	6.6 ± 1.3	6.7 ± 1.9							
Week 2	4.2 ± 1.6	4.7 ± 2.2	−0.5 (−1.5 to 0.5)	0.36	−0.6 (−1.5 to 0.4)	0.23	−2.5 (−3.0 to −2.0)	−2.2 (−3.1 to −1.4)	−0.3 (−1.2 to 0.7) 0.57
Week 4	2.6 ± 1.2	3.6 ± 2.2	−1.0 (−2 to −0.1)	0.03	−1.1 (−2.1 to −0.2)	0.02	−4.1 (−4.6 to −3.6)	−3.3 (−4.2 to −2.3)	−0.8 (−1.9 to 0.3) 0.13
Skindex-10 score									
Baseline	27.4 ± 8.0	29.8 ± 11.2							
Week 2	17.6 ± 5.78	22.1 ± 1.9	−4.5 (−8.8 to −0.1)	0.04	−3.12 (−7.7 to 1.5)	0.18	−8.8 (−11.4 to −6.2)	−7.2 (−9.9 to −4.4)	−1.6 (−5.3 to 2.1) 0.38
Week 4	14.0 ± 5.3	18.5 ± 9.2	−4.4 (−8.3 to −0.5)	0.03	−3.5 (−7.4 to 0.3)	0.07	−12.4 (−15.1 to −9.6)	−10.8 (−14.5 to −7.1)	−1.6 (−6.1 to 2.9) 0.48

Abbreviations: CI, confidence interval; SD, standard deviation; WI-NRS, worst itching intensity numerical rating scale.
[a]By 2 independent t test.
[b]*P*-value by ANCOVA.

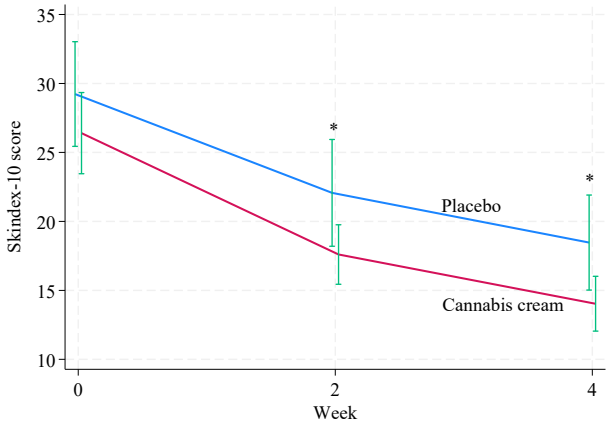

Figure 3. Median Skindex-10 score at baseline, week 2, and week 4 between cannabis and placebo groups.

appropriate approach in the treatment of CKD-associated pruritus.

The comparative analysis of WI-RNS and Skindex-10 in the context of a study evaluating the efficacy of a cannabis-containing cream for CKD-associated pruritus revealed distinct facets of the treatment's impact. WI-RNS, focusing on itching severity scores, demonstrated a noteworthy reduction in scores at weeks 4. This pattern suggests the effectiveness of the cannabis-containing cream in alleviating CKD-associated pruritus, aligning with the proposed mechanistic framework. The evaluation of itch-related quality of life, as measured by Skindex-10, did not exhibit significant improvement at any time after adjusting for baseline scores. However, the observed reduction in Skindex-10 scores suggests a trend toward a positive impact of the cannabis cream on itch-related quality of life, and there was a significant reduction in scores when not adjusted. Confirming the efficacy on itch-related quality of life may prompt considerations regarding the duration of exposure to the cannabis cream.

Drawing from the study by Fishbane et al,[17] they established the efficacy of difelikefalin, a κ opioid receptor antagonist administered intravenously, in ameliorating uremic pruritus. Notably, Fishbane et al identified a clinically meaningful improvement in itch intensity as indicated by a 3-point decrease in the WI-NRS score within the patient population under consideration.[17] In our study, focusing on the cannabis group, we observed a substantial decrease in the mean change at week 4 from baseline, with a 95% confidence interval of −4.1 (−4.6 to −3.6). This observed reduction aligns with the threshold established by Fishbane et al[17] for a clinically meaningful improvement and suggests a trend toward a greater score reduction when compared with the placebo group. However, there was no significant difference from the placebo group.

Szepietowski et al[8] performed a study aimed at assessing the efficacy and tolerance of an endogenous cannabinoid cream for managing uremic pruritus in 21 hemodialysis patients. Their findings revealed that the endocannabinoid cream exhibited effectiveness in addressing both pruritus and xerosis,[8] a result consistent with our study demonstrating the efficacy of cannabinoids in uremic pruritus treatment. It is noteworthy that our study diverged in the use of phytocannabinoids rather than endocannabinoids, and additionally, we incorporated a control group with an extended follow-up duration. This distinction in methodology introduces a nuanced perspective and contributes to a more comprehensive understanding of the potential therapeutic applications of cannabinoids in the context of CKD-associated pruritus.

Paramount among our considerations was the evaluation of irritant and allergic reactions before initiating the trial in hemodialysis patients. To ascertain the irritant and allergic reaction profile of the cannabis-containing cream and its placebo counterpart, we performed preliminary tests involving 30 healthy volunteers. This meticulous examination revealed the absence of any irritant or allergic reactions to either the cannabis-containing cream or the pure cream-based placebo among the healthy volunteer cohort. In addition, throughout the clinical trial involving hemodialysis patients, a thorough assessment of adverse effects was performed. Of importance, no adverse effects were observed in this patient population during the trial period. These findings provide evidence to confidently assert that the cannabis cream used for treating CKD-associated pruritus in hemodialysis patients could have no adverse effects. This critical aspect enhances the overall feasibility and acceptability of the cannabis cream as a therapeutic intervention in this specific patient demographic. However, to confirm the safety, it may need a longer duration and a larger population.

Our study holds notable strengths, chiefly as the first investigation into the efficacy of phytocannabinoids in the treatment of CKD-associated pruritus among hemodialysis patients. Moreover, we implemented a rigorous research design, employing a randomized, double-blinded, controlled trial framework. This approach effectively mitigated confounding variables and minimized biases.

Nevertheless, certain limitations warrant consideration. First, the study's sample size was relatively modest, and the patient population was confined to a single center. Although our study design upheld internal validity, the generalizability of the findings to broader populations may be influenced by this limited scope. Second, unfortunately, there are some differences in the diabetes status of participants that may affect the itch outcome. Third, we did not measure cannabinoid levels in the blood, so we cannot conclusively determine whether systemic effects may be present. Lastly, the follow-up period was constrained to a duration of 4 weeks. This abbreviated timeframe may constrain the ability to extrapolate long-term outcomes or assess sustained efficacy over an extended duration. Future research endeavors with larger and more diverse cohorts, encompassing multiple centers, and extending the follow-up duration, would contribute to a more comprehensive understanding of the utility and sustained effects of

phytocannabinoids in the treatment of CKD-associated pruritus in hemodialysis patients.

In conclusion, this study demonstrated that a cannabis-containing cream might be an effective treatment for CKD-associated pruritus in hemodialysis patients with limited adverse side effects. Further studies with larger sample sizes and longer durations of follow-up are suggested to ensure the reliability of the results, especially regarding itch-related quality of life.

SUPPLEMENTARY MATERIALS

Supplementary File (PDF)

Table S1: List of Materials.

Table S2: Evaluation Criteria of the International Contact Dermatitis Research Group (ICDRG) for the Signs of Allergic Reactions.

Table S3: Criteria of the Cosmetic, Toiletry and Fragrance Association (CTFA) for Skin Irritant Reactions.

Table S4: The Result of the Skin Allergic Reaction Test from 30 Healthy Volunteers (ICDRG).

Table S5: The Result of Skin Irritation Test from 30 Healthy Volunteers.

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