

Effect of Pregabalin versus Montelukast on TNF- α and IL-31 for Hemodialysis Patients in Iraq (A single center study)

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ABSTRACT

Uremic pruritus (UP) severely impacts hemodialysis patients' quality of life. Pregabalin, a GABA derivative, inhibits neurotransmitters, while Montelukast blocks leukotriene receptors. This study compares their effectiveness in alleviating this itch and analyzes their distinct impacts on inflammatory markers TNF- α and IL-31.

Methods: This prospective- interventional clinical trial. was conducted at the Iraqi Dialysis Center/ Medical City. Patients on hemodialysis therapy for 3 months or more with uremic pruritus randomly divided in to two groups Group P: which included 25 patients treated with Pregabalin 50mg, one tablet every other day for 4 weeks

Group M: which included 25 patients treated with Montelukast 10mg, one tablet every day for 4 weeks

Control group: which included 25 healthy subject to assess the serum level of TNF- α and IL-31.

The effectiveness of the medications for each patient in group P&M was evaluated every week over four weeks using the 5-dimension itch scale, a concise questionnaire that may be easily completed its. The 5- dimension scores vary between 5 (indicating no pruritus) and 25 (representing the most severe pruritus) then Pruritus intensity measured using numeric rating scale.

The effectiveness of the medications on TNF- α and IL-31 evaluated by taken blood sample for each patient on group P&M before treatment and after 4 weeks of treatment and compared it with control group.

Results: there is a significant ($p < 0.05$) decrease in the 5- dimension

itching score and numeric rating scale in group M after 4 weeks of treatment from the baseline score and showed a significant ($p < 0.05$) decrease in 5- dimension itching score and numeric rating scale in group P after 4 weeks of treatment from baseline score while a comparison of the effect of Montelukast and Pregabalin on the 5- dimension and numeric rating scale score of uremic pruritus in hemodialysis patients was not significantly different ($p > 0.05$). This study, showed a significant ($p < 0.05$) decrease in the level of TNF- α and IL-31 in group M after 4 weeks of treatment from the baseline level while There was no significant different ($p > 0.05$) between two groups (M and P) in decrease of level of TNF α and IL-31 after four weeks of treatment. but there was a significant difference ($p < 0.05$) then, compare the two groups with the control .

Conclusion: Montelukast 10 mg daily or Pregabalin 50 mg every other day: Effectively alleviate itching in dialysis patients with chronic kidney disease who continue to have symptoms. These medications improved pruritus compared to the baseline condition without any therapy. These two medications reduced the levels of TNF- α and IL-31 in hemodialysis patients. No notable significant differences were detected between the two medications. The choice between these options should be individualized based on the patient's specific symptoms, overall health, and response to treatment.

1.Introduction

Uremia, the accumulation of metabolic waste from kidney failure, causes symptoms like nausea, fatigue, and pruritus, reducing quality of life ¹. Chronic kidney disease-associated pruritus (CKDaP) is common yet underdiagnosed, with significant impacts on mortality and well-being ^{2,3}. It affects 40-84% of end-stage renal disease patients, often on the face, chest, and extremities ⁴. The DOPPS study reported 18% of hemodialysis patients are severely troubled by pruritus, linking it to depression and impaired daily function ⁵.

Pathogenesis.

The mechanism of CKDaP remains unclear, with no single comprehensive theory ⁶. Itch, a signal for skin barrier disruption, is closely linked to pain sig-

naling via C-fibers ⁷. CKDaP pathogenesis involves a disruption of balance due to dermatological (e.g., cutaneous barrier dysfunction, xerosis), systemic (e.g., immune dysfunction, pro-inflammatory cytokines), neurological (e.g., neuropathy, opioid system dysregulation), psychogenic, and metabolic factors ⁸.

Dermatologic Factors. Xerosis is common in ESRD, marked by secretory gland atrophy and stratum corneum changes ⁹. While barrier function often remains intact ¹⁰, microangiopathy from uremic factors leads to endothelial dysfunction, hypoxia, and fibrosis ¹¹. Hydrating the skin can alleviate pruritus, though severe xerosis does not always correlate with itch ⁷.

Metabolic Changes. Observations that pruritus diminishes post-kidney transplant suggest inadequate renal replacement contributes to CKDaP ¹². Unidentified metabolites are implicated ¹³. High-permeability hemodialysis filters reduce pruritus severity and levels

Table 1. List of pharmaceuticals and their suppliers

Pharmaceuticals and instruments	Suppliers
Montelukast 10mg	Abdi Ibrahim Pharmaceuticals Co., turkey®
Pregabalin 50mg	Pioneer Pharmaceuticals Co., Iraq®
Tumor necrosis factor- α kit	USCN Business Co.®
IL 31 kit	USCN Business Co.®
centrifuge	Sigma, Germany
Plain tube	China
Disposable syringe 5ml	China

of compounds like PTH and $\beta 2$ -microglobulin, linking dialysis adequacy to itch ¹⁴). CKD-related mineral bone disease, involving hyperphosphatemia and secondary hyperparathyroidism, may contribute via cutaneous calcium deposition ^{15,16}. Zinc deficiency's role is unclear ¹⁷. Iron deficiency anemia may link to pruritus via interleukin-6 (IL-6) and hepcidin elevation ¹⁸.

Inflammation. CKD sustains a systemic micro-inflammatory state contributing to pruritus. While histamine is a well-defined pruritogen, plasma levels don't correlate with itch scores in dialysis patients, and antihistamines are often ineffective ¹⁹. Mast cells, increased in CKDaP skin, release mediators like tryptase, TNF- α , and IL-2 ^{19,20}. These messengers induce neuropeptide production in sensory nerves ⁷. Tachykinins like substance P can enhance pro-inflammatory cytokine production (e.g., IL-2) ²¹. CKD involves T-helper (Th) cell dysregulation, with an elevated Th1/Th2 ratio ²². Increased Th1 activity, marked by elevated CRP, IL-6, IL-2, and IFN- γ , is observed in CKDaP ^{23,24}. Calcineurin inhibitors, which reduce Th1 cytokines, alleviate CKDaP ²⁵. Key pruritogenic cytokines include IL-2, IL-4, IL-13, and IL-31⁷. IL-31 is strongly implicated; its inhibition rapidly alleviates itch ²⁶.

Neurological Factors. Neuropathy, both peripheral and central, is a component. Peripheral nerve endings may diminish or proliferate irregularly in uremia ²⁷. Capsaicin, which inhibits substance P release, reduces itch, implicating neuropathic changes ²⁵. Dysregulation of the endogenous opioid system is significant. The μ -opioid receptor (MOR) promotes

itch, while the κ -opioid receptor (KOR) inhibits it. Overstimulation of central MOR is suggested in CKDaP ^{2,28,29}. Inflammation modulates the opioid system, with opiates having enhanced effects in inflamed tissue and opioid peptides present in immune cells ³⁰. Cytokines like IL-6 and TNF- α can induce opioid-mediated analgesia in inflammation but hyperalgesia otherwise, complicating the pathophysiology ^{23,30}.

Psychogenic Factors. A bidirectional relationship exists between pruritus and mental health. Depressive symptoms can predict severe pruritus in hemodialysis patients ³¹.

Role of Cytokines in Pruritus. Cytokines are low molecular weight glycoproteins crucial for immune response and cellular communication ^{32,33}. Abnormal cytokine release is a diagnostic marker ³⁴. TH2-type cytokines (IL-31, IL-13, IL-4) from eosinophils, mast cells, and basophils are key ³⁵. IL-4 and IL-13 directly activate sensory neurons via specific receptors ³⁴. In pruritus, afferent neuron activation triggers immune cells to release IL-4, IL-13, and IL-31, which stimulate neuronal receptors, perpetuating the itch-scratch cycle ⁷. TNF- α sensitizes itch-responsive nerve fibers ³⁶. Pro-inflammatory cytokines (IL-2, IL-6, TNF- α) are elevated in CKDaP ³⁶. Serum IL-31 is markedly higher in hemodialysis patients with pruritus, supporting the immunological hypothesis ²⁶.

Treatment.

The unclear etiology of uremic pruritus has led to unsatisfactory therapies. Until difelikefalin's 2021

1. Duration
During the last 2 weeks, how many hours a day did you experience itchiness?
1) < 6 h/day, 2) 6–12 h/day, 3) 12–18 h/day, 4) 18–23 h/day, 5) all day

2. Degree
Please rate the intensity of your itchiness over the past 2 weeks.
1) Not present, 2) Mild, 3) Moderate, 4) Severe, 5) Unbearable

3. Direction
Over the past 2 weeks, has your itchiness improved or worsened compared with that in the previous month?
1) Completely resolved, 2) Much better, but still present, 3) Little bit better, but still present, 4) Unchanged, 5) Getting worse

4. Disability
Please rate the impact of your itchiness on the following activities over the last 2 weeks.

- **Sleep**
1) Never affects sleep, 2) Occasionally delays falling asleep, 3) Frequently delays falling asleep, 4) Delays falling asleep and occasionally wakes me up at night, 5) Delays falling asleep and frequently wakes me up at night
- **Leisure/Social activities**
1) Never affects this activity, 2) Rarely affects this activity, 3) Occasionally affects this activity, 4) Frequently affects this activity, 5) Always affects this activity, *) Not applicable
- **Housework/Errands**
1) Never affects this activity, 2) Rarely affects this activity, 3) Occasionally affects this activity, 4) Frequently affects this activity, 5) Always affects this activity, *) Not applicable
- **Work/School**
1) Never affects this activity, 2) Rarely affects this activity, 3) Occasionally affects this activity, 4) Frequently affects this activity, 5) Always affects this activity, *) Not applicable

5. Distribution
Please indicate the sites on your body where itchiness has been present over the last 2 weeks. If the relevant body part is not listed, choose the site that is anatomically closest. Head/Scalp (), Face (), Chest (), Abdomen (), Back (), Buttocks (), Thighs (), Lower legs (), Tops of feet/toes (), Soles (), Palms (), Tops of hands/fingers (), Forearms (), Upper arms (), Points of contact with clothing (e.g. waistband, undergarment) (), Groin ()

(Ebata, Toshiya et al.: Creation of a Japanese version of the 5D itch scale.
Japanese Journal of Dermatology 2015;125:1035-1040)

Method of calculating each score and the total score

- ◆ Responses 1–5 for questions 1–5 are rated from 1 to 5 points.
- ◆ In Question 4 (Disability), the highest score of each subsection (sleep, leisure/social activities, housework/errands, and work/school) is used.
- ◆ For the distribution of itchiness in Question 5, a total of 0–2 sites of itchiness equates to 1 point, 3–5 to 2 points, 6–10 sites to 3 points, 11–13 sites to 4 points, and 14–16 sites to 5 points.
- ◆ The total score ranges from 5 to 25 points.

Figure 1. Japanese version of the 5-D itch scale ³⁹

FDA approval, no targeted therapy existed ³⁷. Conventional treatments include topical emollients, dialysis modification, antihistamines, phototherapy, and serotonin receptor antagonists. Emerging evidence supports gabapentin, Pregabalin, opioid receptor modulators, and biologics ⁵.

Aim of the study.

1- Evaluate the efficacy of Pregabalin and Montelukast in managing uremic pruritus in hemodialysis patients.

2- To compare the effects of Pregabalin and Montelukast on TNF- α and IL-31, which are elevated in

Table 2. Severity of itching

NRS categories	Severity of itching
0	No pruritus
1-3	Mild
4-6	Moderate
7-8	Severe
≥9	Very severe
10	Maximal pruritus

hemodialysis patients.

2. Materials and Methods

This is a prospective- intervention clinical trial where 80 patients with the age range (of 30-75 years) were included in this study fifty of them were in the study group, five patients were excluded, and the remaining 25 subjects (healthy) were the control group. This study was applied at the Iraqi Dialysis Center/ Medical City. Baghdad/Iraq

Ethical Clearance :-The ethical committee of Baghdad University, College of Medicine, and Ministry of Health Ethical Policy (ethical permission letter No. 1527) obtained written informed consent from all participants before inclusion in the study.

Inclusion Criteria:

- Patients on hemodialysis therapy (HD) for 3 months or more.
- Patients with uremic pruritus (continued symptoms despite adequate dialysis and optimization of metabolic parameters).

Exclusion Criteria:

- Elevated intact parathyroid hormone (iPTH) >600pg/ml

“The Kidney Disease Improving Global Outcomes (KDIGO) published a new chronic kidney disease mineral and bone disorder (CKD-MBD) guideline in 2009. The guideline suggested maintaining serum iPTH level in the range of approximately two to nine times the upper normal limit for the assay”¹

High serum phosphorus >5.5 mg/dl²

Patients with liver disease³

Current itching with dermatologic disease other than uremic pruritus³

Materials. Table 1 presents the suppliers of all pharmaceuticals used in the study.

Data Collection.

Data were collected by interviewing using a vocal questionnaire designed for this study and consisting of:

1. Medical history
2. (5-D) itch scale at baseline, after 1 week, 2 weeks, 3 weeks and 4 weeks of therapy and pruritus intensity measured using NRS
3. Collection of blood samples for laboratory investigations.

Medical History.

Each subject's medical history was obtained with a focus on age, sex, dry weight, number of dialysis sessions in a week, duration of time (hours) for each session, and the ultrafiltration volume (UF volume) to calculate the hemodialysis adequacy kt/v single pool. Which remains the best-studied measure of dialysis adequacy globally. Among HD patients, values of spKt/V less than 1.2 are associated with increased mortality. The spKt/V was calculated as follows:

$$\text{spKt/V} = -\ln(R - 0.008 \times t) + (4 - 3.5 \times R) \times \text{UF/W}$$

where R is the ratio of pre- to post-HD concentration of blood urea nitrogen (BUN), t is dialysis session length (in hours), UF is the amount of ultra-

Table 3. Baseline characteristics were comparable in both groups

Group		Montelukast (n=25)	Pregabalin (n=25)	P value
Age		55.76±11.50	54.80±10.785	0.762
Gender	M	8 (42.1%)	11 (57.9%)	0.382
	F	17 (54.8%)	14 (45.2%)	
Dry weight		76.41±19.47	73.08±17.21	0.525
PO4		4.58±1.15	4.7240±1.07	0.659
PTH		377.23±180.15	279.68±215.07	0.089
ALP		135.88±91.34	119.48±78.15	0.498
S.CR		11.67±14.62	7.716±1.83	0.157
Pre-urea		131.72±40.90	133.76±40.37	0.860
Post-urea		54.12±20.09	51.84±16.05	0.660
Hb		9.89±1.55	9.91±1.75	0.953
S. ferritin (ng/ml)		374.3±102.83	378.78±179.426	0.915
Ca		7.8±1.91	7.65±2.31	0.696
Na		138.56±4.14	139.04±3.00	0.641
K		5.41±1.10	6.72±6.78	0.345
Dialysis adequacy		1.10±.35	1.12±.34797	0.820
BMI		30.144±5.55	28.00±5.33	0.171

*Data expressed as mean± standard deviation (SD), chi-square for gender and unpaired t-test were used to determine the differences between the two groups for continuous variable. the groups were balanced in terms of dialysis duration, treatment history, and comorbidities

filtration (L) during the given HD session, and W is post-HD weight (kg) ⁴

Ask the patients about the diseases they suffer from and the treatments they have received. Furthermore, all subjects were asked if any treatment for itching had been taken.

5-D itch scale (Figure 1).

Although itch symptoms are commonly found in general practice, a specific questionnaire to evaluate itch symptoms is quite limited. In 2010, the 5-D itch scale was developed by Elman S et al. in the English language. The 5-D itch scale consists of 8 items in 5 domains as follows: duration, degree, direction, disability, and distribution. The domains of duration, degree, and direction contain 1 item, whereas there are 4 items for determining the disability. A 5-point

Likert scale assesses the items of 4 domains. The distribution domain includes 16 potential itch areas, including 15 body parts and 1 area with clothing or bandage contact. The score of distribution is determined based on the number of areas: 0-2 areas = score of 1, 3-5 areas = score of 2, 6-10 areas = score of 3, 11-13 areas = score of 4, 14-16 areas = score of 5. The 5-D itch scale is a short questionnaire which is easy to complete.³⁸

5-D scores range from 5 (no pruritus) to 25 (most severe pruritus).

The 5-D scale's convergent validity was evaluated using a numeric rating scale (NRS) and other scales. The NRS is a unidimensional scale comprised of 11 points ⁴⁰. $NRS = -2.31 + 0.52 \times (5-D \text{ itch scale})$

Pruritus intensity measured using NRS can be categorized as follows in Table 2.

Table 4. Effect of Montelukast and Pregabalin on 5-D score regarding number of patients

5-Dscore	Montelukast number of patients		Pregabalin number of patients	
	Baseline	Week4	Baseline	Week4
5-10	0	23(92%)	0	24(96%)
11-15	1(4%)	2(8%)	1(4%)	1(4%)
16-20	15(60%)	0	17(68%)	0
21-25	9(36%)	0	7(28%)	0

Table 5. Effect of Montelukast and Pregabalin on NRS depending on the number of patients

NRS	Montelukast number of patients		Pregabalin number of patients	
	Baseline	Week4	Baseline	Week4
1-3 (mild)	0	25(100%)	0	25(100%)
4-6 (moderate)	4(16%)	0	8(32%)	0
7-8 (sever)	18(72%)	0	14(56%)	0
≥9 (very sever)	3(12%)	0	3(12%)	0

Collection of Samples.

Three ml of venous blood samples were taken before starting the hemodialysis session (before treatment). One month later (after treatment), a blood sample from the same patients was retaken to measure TNF- α and IL-31 to comprise the result.

Sampling and Sample Size

About 426 hemodialysis patients referred to Baghdad Teaching Hospital/ Iraqi Center of Dialysis in 2024 and 144 patients had uremic pruritus. 50 patients were finally chosen. All patients included in our study were similar in frequency and

method of dialysis. Patients who experienced other pruritus conditions (non-uremic pruritus) were excluded. Patients were randomly divided into two groups (group M), which included 25 patients treated with Montelukast 10mg, one tablet every day for 4 weeks and (group P), which included 25 patients treated with Pregabalin 50mg, one tablet every other day for 4 weeks.

TNF- α

TNF- α was estimated at the beginning and end of therapy using the USCN® Human TNF- α Kit (using the Sandwich-ELISA principle). The microplate provided in this kit has been pre-coated with an anti-

Table 6. Effect of treatment with Montelukast on uremic pruritus patients

	Baseline	Week1	Week2	Week3	Week4	p-value
5-D score	19.4400±2.21886	10.88±3.45 (44%)	8.96±2.85 (54%)	7.88±2.60 (59%)	6.60±2.02 (66%)	0.000
NRS	7.8132±1.15191	3.34±1.79707 (57%)	2.34±1.48 (70%)	1.78±1.35 (77%)	1.12±1.051 (86%)	0.000

*Values are expressed as mean± stander deviation (SD). n=number of patients. Data was analyzed by paired t-test.

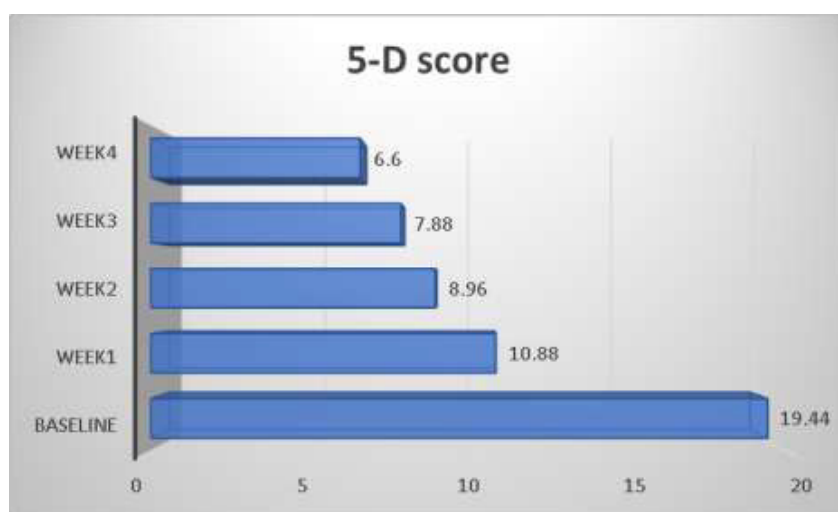
**Figure 2. Effect of Montelukast on 5-D-score****Figure 3. Effect of Montelukast on NRS**

Table 7. Effect of treatment with Pregabalin on uremic pruritus patients

	Baseline	Week1	Week2	Week3	Week4	p-value
5-D score	18.96±2.60576	9.76±3.58562 (49%)	8.56±2.94 (55%)	8.56±2.94 (64%)	6.00±1.89 (68%)	0.000
NRS	7.54±1.35	2.76±1.86 (63%)	2.14±1.53 (72%)	1.24±1.12 (83%)	0.81±.98 (89%)	0.000

*Values are expressed as mean± standard deviation (SD). n=number of patients. Data was analyzed by paired t-test.

**Figure 4. Effect of Pregabalin on 5-D-score****Figure 5. Effect of Pregabalin on NRS**

Table 8. Comparison of the effect of Montelukast and Pregabalin on 5-D score

Group	Montelukast (n=25) (% degree of redaction)	Pregabalin(n=25) (% degree of redaction)	P-value
DB	19.44±2.219	18.96±2.606	0.487
DW1	10.88±3.456 (44%)	9.76±3.586 (49%)	0.266
DW2	8.96±2.850 (54%)	8.56±2.945 (55%)	0.628
DW3	7.88±2.603 (59%)	6.84±2.154 (64%)	0.130
DW4	6.60±2.021 (66%)	6.00±1.893 (68%)	0.284

*Values are expressed as mean± standard deviation (SD). n=number of patients. DB= baseline week. Data was analyzed by independent t-test.

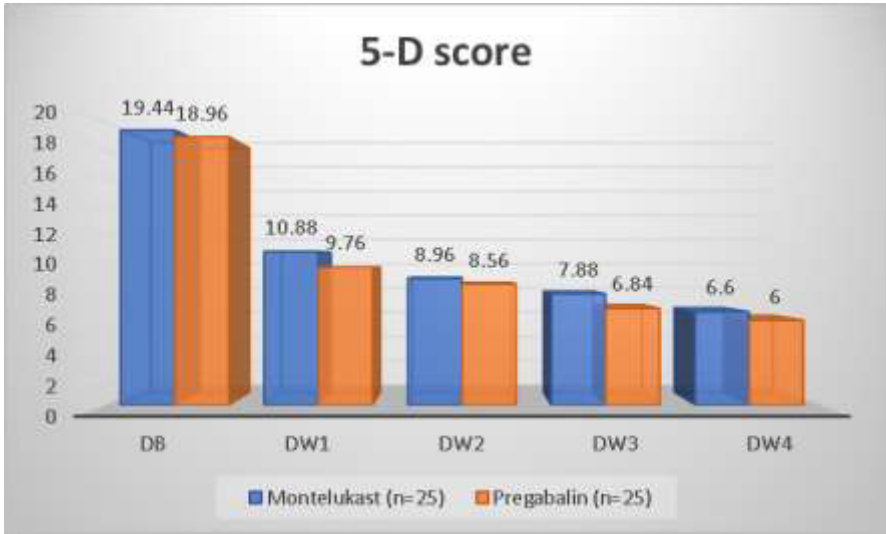


Figure 6. Comparison of the effect of Montelukast and Pregabalin on 5-D score

body specific to TNF- α . Standards or samples are then added to the appropriate microplate wells with a biotin-conjugated antibody specific to TNF- α . Next, Avidin conjugated to Horseradish Peroxidase (HRP) is added to each microplate well and incubated. After the TMB substrate solution is added, only those wells that contain TNF- α , biotin-conjugated antibody and enzyme-conjugated Avidin will exhibit a change in colour. The addition of sulphuric acid solution terminates the enzyme-substrate reaction, and the colour change is measured spectrophotometrically at a wavelength of 450nm $\pm$ 10nm. The concentration of TNF- α in the samples is then determined by com-

paring the optical density (O.D). of the samples to the standard curve ⁴¹.

IL-31

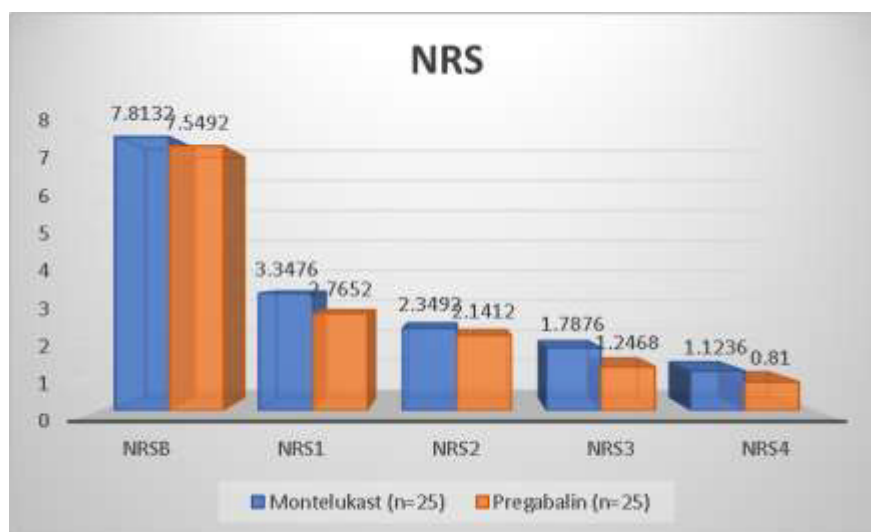
IL-31 was estimated at the beginning and end of therapy using the USCN® Human This kit uses the Sandwich enzyme immunoassay concept. This kit includes a microtiter plate that has been pre-coated with an antibody specific to Interleukin 31 (IL31). Standards or samples are thereafter introduced into the designated microtiter plate wells containing a biotin-conjugated antibody specific to Interleukin 31

Table 9. Comparison of the effect of Montelukast and Pregabalin on NRS

Group	Montelukast (n=25) (% degree of redaction)	Pregabalin(n=25) (% degree of redaction)	P-value
NRSB	7.81±1.15	7.54±1.35	0.462
NRS1	3.34±1.79 (57%)	2.76±1.86 (63%)	0.266
NRS2	2.34±1.48 (70%)	2.14±1.53 (72%)	0.628
NRS3	1.78±1.35 (77%)	1.24±1.12 (83%)	0.130
NRS4	1.12±1.05(86%)	0.81±.98(89%)	0.282

*Values are expressed as mean± standard deviation (SD). n=number of patients. NRSB= baseline week.

Data was analyzed by independent t-test.

**Figure 7. Comparison of the effect of Montelukast and Pregabalin on NRS**

(IL31). Subsequently, Avidin conjugated to Horseradish Peroxidase (HRP) is introduced to each microplate well and allowed to incubate. Upon the addition of the TMB substrate solution, only the wells containing Interleukin 31 (IL31), biotin-conjugated antibody, and enzyme-conjugated Avidin will display a color change. The enzyme-substrate reaction is concluded by the introduction of the sulfuric acid solution, and the colorimetric change is quantified spectrophotometrically at a wavelength of 450 nm ± 10 nm. The concentration of Interleukin 31 (IL31) in the samples is determined by comparing the optical density (O.D.) of the samples to the standard curve.

Statistical Analysis: Data analysis was carried out using the available statistical package SPSS-26 (Statistical Package for Social Sciences-version 26).

- Within each group (group M or P), changes in 5-D score, NRS and the level of TNF-α and IL-31 with respect to baseline were compared using a paired t-test.

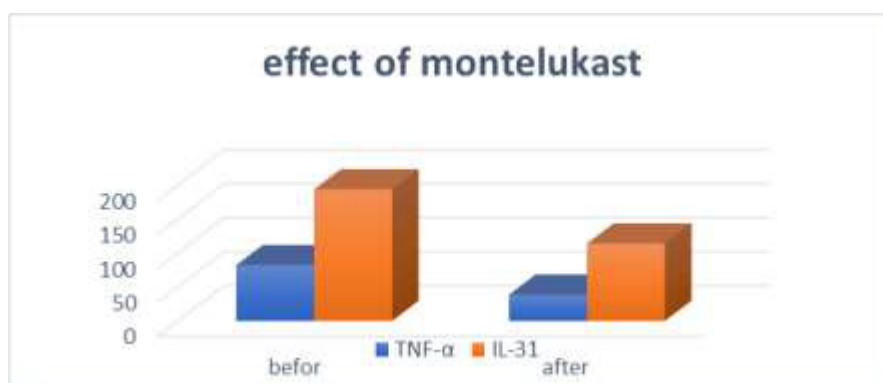
- Comparisons between the two groups (Group M versus Group P) of each parameter (5-D score and NRS) were done by unpaired t-test.

- Comparisons between the three groups (Group M, group P, and control) to estimate the change in the level of TNF-α were made by

Table 10. Effect of Montelukast on TNF- α and IL-31

	Before treatment (N=25)	After treatment(N=25) (% degree of redaction)	p-value
TNF- α	82.21 $\pm$ 41.77	38.65 $\pm$ 28.09 (53%)	0.000
IL-31	193.80 $\pm$ 203.50	114.03 $\pm$ 117.01 (41%)	0.001

*Values are expressed as mean $\pm$ standard deviation (SD). n=number of patients. Data was analyzed by paired t-test.

**Figure 8. Effect of Montelukast on TNF- α and IL-31**

ANOVA(Tukey) test.

- To estimate the change in the level of IL-31, comparisons between the three groups (Group M, Group P, and control) were made using the ANOVA (Tukey) test.

Statistical significance was considered whenever the P value was equal to or less than 0.05.

3. Results

3.1. Patients characteristics

The fifty patients finally chosen were allocated into two groups, Group M and Group P, as described under Material and Methods. Table 3 provides a more detailed summary of the baseline characteristics of the research participants.

There was no significant difference ($p>0.05$) between the two groups in patient characteristics.

Tables 4 and 5 show the number of patients included in this study and the severity of their itching.

In group M, all patients had moderate to severe itching (moderate 4 patients; severe 18 patients; very severe 3 patients) and no patients with mild itching at baseline reading. After 4 weeks of treatment, all patients became mild.

In group P, all patients had moderate to severe itching (moderate 8 patients; severe 14 patients; very severe 3 patients), and no patients had mild itching at their baseline reading. After 4 weeks of treatment, all patients became mild.

3.2. Effect of treatment with Montelukast in hemodialysis patients with uremic pruritus

Table 11. Effect of Pregabalin on TNF- α and IL-31

	Before treatment (N=25)	After treatment(N=25) (% degree of redaction)	p-value
TNF- α	102.99 $\pm$ 41.23	51.51 $\pm$ 35.74 (50%)	0.000
IL-31	228.67 $\pm$ 160.85	109.81 $\pm$ 94.60 (52%)	0.000

*Values are expressed as mean $\pm$ standard deviation (SD). n=number of patients. Data was analyzed by paired t-test.

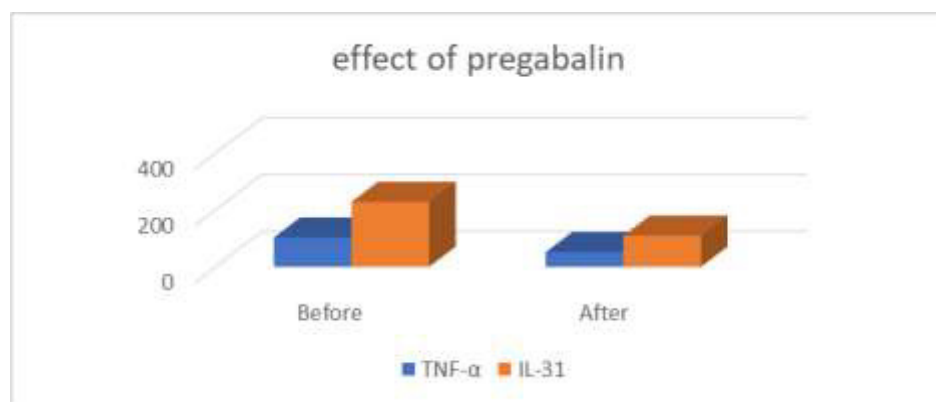
**Figure 9. Effect of Pregabalin on TNF- α and IL-31**

Table 6 and Figures 2 and 3 showed a significant ($p < 0.05$) decrease in the 5-D itching score and NRS in group M after 4 weeks of treatment from the baseline score.

3.3. Effect of treatment with Pregabalin in hemodialysis patients with uremic pruritus

Table 7, figure 4, and figure 5 showed a significant ($p < 0.05$) decrease in 5-D itching score and NRS in group P after 4 weeks of treatment from baseline score.

3.4. Effect of treatment with Montelukast and Pregabalin on 5-D score in hemodialysis patients with uremic pruritus.

After four weeks of treatment, the 5-D score of the

two groups was not significantly different ($p > 0.05$).

Table 8 and Figure 6 explain a comparison of the effect of Montelukast and Pregabalin on the 5-D score of uremic pruritus in hemodialysis patients

3.5. Effect of treatment with Montelukast and Pregabalin on NRS in hemodialysis patients with uremic pruritus.

There was no significant difference ($p > 0.05$) between the two groups in NRS after four weeks of treatment.

Table 9 and Figure 7 explain a comparison of the effect of Montelukast and Pregabalin on the 5-D score of uremic pruritus in hemodialysis patients

3.6. Effect of Montelukast on TNF- α and IL-31

Table 10 and Figure 8 showed a significant ($p < 0.05$)

Table 12. Comparison of the effect of Montelukast and Pregabalín with control in level of TNF-α

TNF-α	Mean Difference (I-J)	P value
Control +M	-23.12±7.4	0.008
Control +P	-35.98±7.46	0.000
M+P	-12.85±7.46	0.204

*Values are expressed as mean± standard deviation (SD). Data was analyzed by one-way ANOVA (Tukey).

Table 13. Comparison of the effect of Montelukast and Pregabalín with control in level of IL-31

IL-31	Mean Difference (I-J)	P value
Control +M	-96.05±24.58	0.001
Control +P	-91.83±24.58	0.001
M+P	4.218±24.58	0.984

*Values are expressed as mean± standard deviation (SD). Data was analyzed by one-way ANOVA (Tukey).

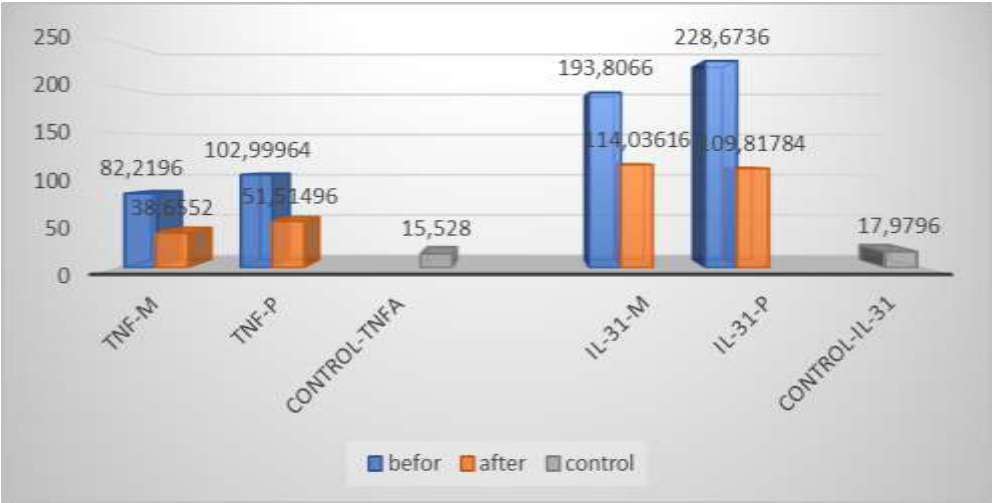


Figure 10. Comparison of the effect of Montelukast and Pregabalín with control in levels of TNF-α and IL-31

decrease in the level of TNF-α and IL-31 in group M after 4 weeks of treatment from the baseline level.

3.7. Effect of Pregabalín on TNF-α and IL-31

Table 11 and Figure 9 showed a significant (p<0.05) decrease in the level of TNF-α and IL-31 in group M

after 4 weeks of treatment from the baseline level.

3.8. Comparison of the effect of Montelukast and Pregabalín on TNF-α and IL-31 on hemodialysis patients with uremic pruritus.

There was no significant different (p>0.05) be-

tween two groups (M and P) in decrease of level of TNF- α and IL-31 after four weeks of treatment. but there was a significant difference ($p < 0.05$) then, compare the two groups with the control

Table 12 and figure 10 explain a comparison of the effect of Montelukast and Pregabalin with control in level of TNF- α , while table 13 and figure 10 explain a comparison of the effect of Montelukast and Pregabalin with control in level of IL-31 in uremic pruritus in hemodialysis patients.

4. Discussion

Pruritus is a skin condition characterized by an unpleasant itch sensation. It is the consequence of a systemic condition that disrupts the communication between keratinocytes, immune cells, and neurons. In patients with chronic kidney disease (CKD) and, more specifically, patients with end-stage kidney disease (ESKD), uremic pruritus is one of the most prevalent and bothersome manifestations of uremia⁴². The effects of Pregabalin and Montelukast on the treatment of uremic pruritus in hemodialysis patients were evaluated over four weeks in our study and their impact on TNF- α and IL-3

4.1. Patients characteristics

In this study, the level of phosphorous in group M and group P was within limits in normal value which is 5.5 mg/dl for hemodialysis patients⁴³. The level of Ca⁺⁺ in the M group and P group was within limits in normal value. elevated Ca⁺⁺ and phosphorous levels lead to increased itching, as Amany M Abdallah et al. reported a significant association between UP and higher calcium and phosphorous levels⁴⁴. Muhammad Sohaib Asghar et al. suggested treating hyperparathyroidism and hyperphosphatemia with elevated Ca⁺⁺ products, which actually reduce uremic pruritus⁴⁵.

A low level of calcium promotes secondary hyperparathyroidism in patients with CKD. This leads to a higher secretion of parathyroid hormone (PTH), which regulates blood phosphorus levels. The levels of serum phosphorus, calcium, and PTH were found

to be elevated in patients with CKD-Ap. Total parathyroidectomy has been reported to relieve pruritus in patients with secondary hyperparathyroidism⁴⁶ because of that, the patients were selected within limits in normal value in PTH. Fong-Fu Chou, et al suggested that Pruritus in patients with secondary hyperparathyroidism can be reduced by parathyroidectomy⁴⁷.

Also, the adequacy of dialysis (Kt/V) was represented a lower than the accepted level (the minimum single-pool Kt/V level of 1.2)⁴⁸. Optimizing dialysis dosage and increasing the clearance of middle molecules could remove more pruritogenic substances and decrease the severity of pruritus; however, there is no standard dialysis target or dialysis modality for pruritus symptoms⁴⁹.

There was no significant difference between group M and group P so the two groups were in the same condition. Wiraputranto, et al suggest that blood urea level and dialysis adequacy do not play a role in pruritus in hemodialysis patients with chronic kidney disease⁵⁰. While Iman I. Sarhan et al. studied one hundred prevalent hemodialysis patients. They suggested that Inadequate hemodialysis and increased hs-CRP serum levels play important roles in aggravating the intensity and severity of uremic pruritus⁵¹ Patients with chronic liver disease have systemic itching, which significantly reduces their ability to move and sleep. Scratching the irritated parts of the skin does not alleviate the condition. Pruritus is a common complaint among patients with primary biliary cholangitis (PBC) in chronic liver disease⁵². This study found that the Liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were within normal limits.

4.2. Effect of treatment with Montelukast in hemodialysis patients with uremic pruritus

The effect of Montelukast showed a significant decrease of 66% ($p < 0.05$) in the 5-D score after four weeks of treatment. The Numeric Rating Scale (NRS) showed a substantial decrease after four weeks of treatment, decline from a severity level of 7.8 to a mild level of 1.1 ($p < 0.05$).

Montelukast binds to cysteinyl leukotriene receptors specific for leukotrienes D4 and E4. This binding inhibits the subsequent inflammatory responses triggered by these leukotrienes. The presence of these receptors on mast cells may account for the antipruritic activity of Montelukast⁵³ This study was compatible with Mehdi Mahmudpour et al. The impact of Montelukast and placebo was tested in eighty patients suffering from uremic pruritus. The study showed that administering Montelukast 10 mg/d to individuals undergoing hemodialysis can effectively alleviate the intensity of uremic pruritus⁵⁴ and compatible with Chao-qing Gao and colleagues conducted a systematic review and meta-analysis to offer clinical evidence supporting the effectiveness of Montelukast for uremic pruritus (UP) in hemodialysis patients by Seven electronic literature databases⁵⁵.

4.3 Effect of treatment with Pregabalin in hemodialysis patients with uremic pruritus

The findings indicated that the 5-D score of the Pregabalin group saw a substantial decrease of 68% after four weeks of treatment ($p < 0.05$). The Numeric Rating Scale (NRS) showed a substantial decrease after four weeks of treatment, going from a severity level of 7.5 to a mild level of 0.8 ($p < 0.05$).

Pregabalin's mechanism of action in treating uremic pruritus is believed to entail the inhibition of primary afferent neurons' release of calcitonin gene-related peptide, a mediator of itching, and the negative control of voltage-gated calcium channels' $\alpha 2$ delta subunit. It has also been hypothesized that the anti-itch properties of this drug may be mediated through the modulation of μ -opioid receptors (MORs)⁵.

A study conducted by Ravindran et al. examined the impact of gabapentin 100 mg and Pregabalin 25 mg on a group of twenty-one patients suffering from uremic pruritus. The study showed that both gabapentin (100 mg) and Pregabalin (25 mg) effectively alleviate pruritus in dialysis patients compared to the baseline (no medication), and Pregabalin was associated with fewer side effects than gabapentin⁵⁶. Khaled F. El Mulla et al. compared Narrow band-ul-

traviolet B (NB-UVB) and Pregabalin to assess their safety and effectiveness in treating CKD-AP. The study demonstrated that NB-UVB and Pregabalin are both efficacious choices for treating CKD-AP, and phototherapy had a rapid onset of relief of pruritus, fewer adverse effects, and delayed recurrence of pruritus after cessation of therapy but was non-compliant for the patients⁵⁷.

4.3.Effect of treatment with Montelukast and Pregabalin on 5-D score and

NRS in hemodialysis patients with uremic pruritus. The study showed no significant difference ($p > 0.05$) between the two groups in 5-D scores after four weeks of treatment. Montelukast decreased its 5-D score by 66% after four weeks, while Pregabalin decreased its 5-D score by 68% after four weeks. The study showed no significant difference in NRS between the two groups after four weeks of treatment. Montelukast and Pregabalin decreased NRS after four weeks to 86% and 89%, respectively. Montelukast is a leukotriene receptor antagonist. It works by blocking the action of leukotriene D4. Pregabalin binds to the α -2-delta subunit of voltage-gated calcium channels, reducing excitatory neurotransmitter release and inhibiting the transmission of pain and itch signals. Both medicines may indirectly lower the inflammatory markers that cause itching in uremic patients. A study by Christopher Boehlke et al. evaluated the efficacy of various pharmaceutical interventions in the prevention or treatment of pruritus when compared to a placebo, no treatment, or an alternative treatment. The results showed that various interventions (such as GABA analogs, kappa-opioid receptor agonists, cromolyn sodium, Montelukast, fish oil/omega-3 fatty acids, and topical capsaicin) were effective in treating uremic pruritus when compared to a placebo. GABA analogs were the most effective in reducing pruritus⁵⁸.

4.4. Effect of Montelukast on TNF- α and IL-31

The immune system may also participate in the pathogenesis of uremic pruritus. Studies comparing

hemodialysis patients with and without uremic pruritus showed significantly enhanced T helper 1 cells and serum interleukin (IL)-6, IL-2, and IL-31 levels in patients with uremic pruritus⁵⁹.

TNF- α levels are often elevated in ESKD patients and are believed to contribute to the pathogenesis of UP. TNF- α sensitizes itch nerve terminals (c-fibers) in the skin, leading to a stronger sensitivity to a specific stimulus⁶⁰. Safaa Shehab Ahmed et al. showed that in HD patients with UP, serum levels of IL-6, IL-13, and TNF- α all considerably increase. Additionally, there is a significant correlation between the severity of pruritus and IL-13 and TNF- α (59). Mei-Ju KO et al. suggested that no differences were noted for all 8 cytokines (interleukin (IL)-2, interferon- γ , IL12p70, IL-4, IL-5, IL-6, tumor necrosis factor- α , and IL-10) between patients with and without uremic pruritus for 74 patients experiencing uremic pruritus⁽⁶⁰⁾. According to research, UP is caused by systemic inflammatory T helper cell dysregulation and the release of several cytokines, including IL13, IL31, and IL33, which activate peripheral nerve terminals and cause pruritus. Świerczyńska et al. evaluated the serum level of IL-31 in 175 adult subjects: HD patients with pruritus, HD patients without pruritus, and healthy controls. The study showed a significant correlation between the IL-31 serum level and itch intensity²⁶.

This study showed a significant decrease in the level of TNF- α and IL-31 in group M after four weeks of treatment from the baseline level. By inhibiting leukotriene receptors, Montelukast functions as an antiinflammatory drug and is a critical regulator of immune cell migration to inflammatory areas⁶¹. This study aligned with the findings of Günizi et al., who identified a significant reduction in inflammatory mediators in the interstitial cystitis group after therapy with Montelukast⁶². Nouran El-Shehaby et al. suggested that a ten-day regimen of Montelukast, in conjunction with antibiotics, decreased TNF α levels in late preterm infants diagnosed with sepsis⁶¹.

4.5. Effect of Pregabalin on TNF- α and IL-31

This study showed a significant decrease in the level of TNF- α and IL-31 in group P after four weeks

of treatment from the baseline level. Pregabalin decreased the level of TNF- α . At the same time, IL-31 had been reduced to. The specific mechanism of this anti-inflammatory effect remains unclear. It may result from a direct impact on the activity of certain transcription factors, particularly nuclear factor-kappaB (NF- κ B). Additionally, there is a growing body of evidence supporting the expression of voltage-dependent calcium channels in immune cells. Consequently, it is conceivable that Pregabalin could also affect the voltage-dependent calcium channels in immune cells, as it alters the function of the voltage-dependent calcium channels in the brain^{63,64}.

This study aligned with the findings of Azadeh Motavallian and colleagues demonstrated that Pregabalin administration positively impacts the treatment of experimental colitis, potentially attributable to its anti-inflammatory properties, evidenced by decreased colonic levels of TNF- α , IL-6, IL-1 beta, and myeloperoxidase activity⁶⁵. Kilic et al proposed that Pregabalin exhibits antiinflammatory effects across all dosages⁶⁶. Nevertheless, this impact resembled that of indomethacin, a nonsteroidal anti-inflammatory drug employed in clinic.

4.6. Comparison of the effect of Montelukast and Pregabalin on TNF- α and IL-31 on hemodialysis patients with uremic pruritus

The comparison of the effect of Montelukast and Pregabalin on the level of TNF- α and IL-31 showed no significant difference but the serum level of TNF- α and IL-31 in patients still higher than the control level. Pregabalin and Montelukast reduce IL-31 and TNF- α levels in pathological states by inhibiting distinct inflammatory pathways Pregabalin in the neurological system and Montelukast in leukotriene-mediated allergy reactions. Nonetheless, these medications may not completely restore cytokine levels to those observed in healthy control groups⁶⁷. Chronic inflammatory disorders may result in persistent inflammatory signals due to tissue injury, nerve irritation, or immune system dysfunction. This persistent immune activation can sustain elevated

cytokine levels relative to healthy individuals, even after the inflammatory response is markedly diminished by treatment.

5. Conclusion

This study has shown that Montelukast 10 mg daily and Pregabalin 50 mg every other day effectively alleviate itching in dialysis patients with chronic kidney disease (CKD) who continue to have symptoms.

These medications improved pruritus compared to the baseline condition without any therapy.

Moreover, these two medications reduced the levels of TNF- α and IL-31 in hemodialysis patients.

No notable disparities were detected between the two medications. The choice between these options should be individualized based on the patient's specific symptoms, overall health, and response to treatment.

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