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Effectiveness of Combined Hemodialysis-Hemadsorption Therapy in Improving Uremic Toxin Clearance, Inflammatory Markers, and Symptoms in Maintenance Hemodialysis Patients

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Keywords
Hemadsorption · Hemodialysis · End-stage renal disease

Abstract

Introduction: Combined hemodialysis (HD) and hemadsorption (HA) therapy has shown the highest clearance rates for middle and large-sized uremic toxin molecules and reduced mortality rates among maintenance HD (MHD) patients. This study aimed to investigate the effectiveness of combined HD and HA therapy in patients undergoing MHD. ***Methods:*** Forty patients with end-stage renal disease (ESRD) were divided into three groups: HD only (14), HD + biweekly HA (14), and HD + weekly HA (12). The duration of the study was 8 weeks. Uremic toxins (β2-microglobulin, leptin, parathyroid hormone), inflammatory markers (interleukin-6, C-reactive protein), and symptoms (appetite, pruritus, sleep quality) were assessed before the start and at the completion of therapy. Changes in the parameters were compared between the three groups. Mean differences of parameters in each group were also compared between before and after therapy. ***Results:*** Decrease in BUN level (−61.34 mg/dL [95% CI: −71.33 to −51.34], $p < 0.0001$) and pruritus score (−3.93 [95% CI: −6.89 to −0.97], $p = 0.013$) was significantly larger in HD + biweekly HA group compared to the others. Only HD + biweekly HA group showed significant reductions in CRP level (−0.10 mg/L [95%: −0.18 to −0.01], $p = 0.034$), VAS appetite score (10.43 [95% CI: 4.99–15.87], $p = 0.001$), and pruritus score (−3.93 [95% CI: −6.89 to −0.97], $p = 0.013$) after therapy. Both HD + biweekly HA (−2.79 [95% CI: −4.97 to −0.60], $p = 0.016$) and HD + weekly HA group (−2.33 [95% CI: −4.59 to −0.08], $p = 0.044$) exhibited a significant improvement in sleep quality score after therapy. ***Conclusions:*** HD combined with a biweekly HA is associated with a greater reduction in BUN level and better improvement of pruritus in ESRD patients compared to HD alone. HD + biweekly HA can significantly reduce CRP levels, alleviate pruritus, improve appetite, and enhance sleep quality.

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Introduction

Mid-term and long-term complications in hemodialysis (HD) patients are associated with low clearance rates of middle- and large-sized uremic toxin molecules when only HD is used [1, 2]. Factors such as β2-microglobulin (β2-MG), leptin, interleukins (ILs), and parathyroid hormone (PTH) are closely related to the severity of chronic kidney disease (CKD) and can increase the risk of overall mortality and cardiovascular mortality [3–5].

The retention of middle- and large-sized uremic toxin molecules is also associated with uremic pruritus and sleep disturbances. Uremic pruritus is triggered by several factors, such as uremic toxins, inflammation, and comorbidities, which include blood urea nitrogen (BUN), β2-MG, calcium, phosphate, PTH, and somatic neuropathy [6]. Up to 80% of CKD patients have a high prevalence of sleep complaints, possibly caused by uremic toxins, pruritus, and social and financial problems [7, 8]. CKD patients also tend to experience anorexia, which may increase with the progression of kidney disease [9].

The management of uremic toxin retention and its complications can be achieved, among other methods, through a combination therapy of HD and hemadsorption (HA), which has demonstrated the highest clearance rates of middle- and large-sized uremic toxin molecules, particularly in maintenance HD (MHD) patients [10–13]. Despite the recommended HD frequency of three times a week, HD is generally conducted at a frequency of twice weekly in Indonesia due to limited resources relative to the number of patients. However, no studies have evaluated the effectiveness and safety of combination therapy with HD + HA in patients undergoing routine twice-weekly HD. Increasing the frequency of HD reduces the accumulation of soluble substances/toxins. Therefore, this study aimed to determine the effectiveness and safety of HD + HA combination therapy in improving the clearance of uremic toxins (β2-MG, leptin, PTH) and inflammatory markers (IL-6, C-reactive protein [CRP]), as well as improving subjective symptoms (appetite, pruritus, and sleep quality), in MHD patients.

Methods

Study Design and Data Collection

This quasi-experimental study involved 40 MHD patients at 3 different hospitals in Indonesia (Dr. Sardjito General Hospital, Gatot Soebroto Army Hospital, and Ciputra Tangerang Hospital). Patients were divided into 3 groups of therapy: HD + biweekly (the frequency of HA treatment was once every 2 weeks), HD + weekly (the frequency of HA treatment was once a week), and HD only (the control group). One attending nephrologist determined each potential subject's clinical suitability to enroll into the study. Meanwhile, the grouping of patients was performed by an independent team with randomization and matching based on age and sex. The study was conducted for 8 weeks. HA was performed with an HA130 disposable HA cartridge (Jafron Biomedical, Zhuhai, China) [14]. The duration of each HD or HD + HA session was 4–5 h. Effectiveness was assessed by improvement in uremic toxin levels (β2-MG, leptin, PTH), inflammatory markers (IL-6, CRP), and subjective symptoms (appetite: visual analog scale, pruritus: 5D itch scale [15], sleep quality: Pittsburgh Sleep Quality Index [PSQI] [16]). The visual analog scale for appetite ranges from 0 (not hungry at all) to 100 (very hungry). We used an Indonesian translated version of the PSQI whose validity and reliability have been evaluated in a previous study [17].

Adverse events were assessed at every therapy session by evaluating any allergic reactions (skin rash and itching all over the body), bleeding spots, hypotension (SBP <90 mm Hg or MAP <65 mm Hg), neutropenia (neutrophil count ≤1,500 cells/μL), thrombocytopenia (<150,000 cells/μL), hypoglycemia (random blood glucose <70 mg/dL), and hypocalcemia (serum calcium level <8.5 mg/dL). Basic information, demographic data, medical history, vital signs, and physical examination data were also obtained. All data were collected at baseline (before the start of therapy) and 3 days after the completion of the therapy. Post-therapy data could not be collected on the day of therapy completion due to technical issue in obtaining the samples.

Patient Eligibility and Drop-Out Criteria

Patients were included if they were aged 18–75 years, had been diagnosed with CKD, and were undergoing routine HD. Patients must have undergone regular conventional HD therapy for a minimum of 2 years, received standard heparin, not used HD catheters or other access, an AV shunt or AV fistula as vascular access, and experienced complaints of decreased appetite, pruritus, or sleep disturbances. Specifically, patients with an estimated blood flow rate (Qb) ≥200 mL/min and a dialysis fluid flow rate (Qd) ≥500 mL/min at screening were also included. Patients were excluded if they had unstable conditions, severe thrombocytopenia (platelet count <50,000/μL), leukopenia (leukocyte count <4,000 cells/μL), leukocytosis (leukocyte count >11,000 cells/μL), autoimmune conditions, pruritus complaints due to skin diseases, other systemic diseases, medications, sleep disturbances due to depression or anxiety, or sepsis. Depression and anxiety were screened by the Patient Health Questionnaire (PHQ)-9 and General Anxiety Disorder (GAD)-7, respectively. The exclusion criteria included non-compliance with the study protocol, refusal to continue therapy (withdrawal from the study), serious or life-threatening adverse events, including severe allergic reactions, or exacerbation into unstable conditions (systemic infections, bleeding, coagulopathy, acute coronary syndrome, stroke, etc.).

Statistical Analysis

Continuous variables are presented as medians and interquartile ranges or means and standard deviations as appropriate. Categorical variables are presented as numbers and

frequencies. The normality of the data distribution was examined with the Shapiro-Wilk test. Continuous variables were compared between each therapy group using one-way ANOVA or the Kruskal-Wallis test in accordance with the normality of distribution. Categorical variables were compared using Pearson's χ^2 test or Fisher's exact test for 2 categories and the Kruskal-Wallis test for >2 categories. Baseline and posttherapy data were also compared using paired *t* tests. Statistical analyses were performed with IBM SPSS statistical software, version 26 (IBM, USA). The results were considered statistically significant if the *p* value was <0.05.

Ethical Considerations

This study protocol was approved by the Ethics Committee of the Faculty of Medicine, Public Health and Nursing Universitas Gadjah Mada (No. KE/FK/1053/EC/2022), and written informed consent was obtained from the participants at the time of enrollment. The study was conducted in accordance with the ethical standards of the institutional research committee, the Declaration of Helsinki for human studies, and Good Clinical Practice (GCP).

Results

Forty-five (45) subjects were initially enrolled in this study. Only 40 subjects were included in the analysis. Five subjects dropped out: 4 died, and 1 withdrew from the study (Fig. 1). Among these 40 subjects, 14 were in the HD group, 14 were in the HD + biweekly HA group, and 12 were in the HD + weekly HA group. Table 1 summarizes the baseline characteristics of the participants. BUN levels, phosphate levels, and pruritus scores were significantly greater in the HD + biweekly HA group (Table 1).

Changes in laboratory parameters measured after 8 weeks of therapy are shown in Table 2. The reduction in the BUN level was significantly different among the three groups, with the HD + biweekly HA group showing the largest decrease (−61.34 mg/dL [95% CI: −71.33 to −51.34], $p < 0.0001$) (Table 2). There was no significant difference in the changes in other laboratory parameters among the three therapy groups. Only the HD + weekly HA group showed a significant difference in the mean hemoglobin level after and before therapy (1.08 g/dL [95% CI: 0.22–1.93], $p = 0.019$). Only the HD (control) group showed a significant difference in the mean leptin level between after and before therapy (−5.05 ng/mL [95% CI: −9.78 to −0.32], $p = 0.038$). The HD + biweekly HA group was the only group that showed a significant difference in CRP level between after and before therapy (−0.10 mg/L [95%: −0.18 to −0.01], $p = 0.034$). Post hoc analyses comparing pairs of two out of the three interventional groups were also performed for each laboratory parameter (Fig. 2). Both HD + biweekly HA and HD + weekly HA demonstrated significantly greater decrease in BUN when each is compared with HD group. Only HD + biweekly group displayed significantly larger reduction in phosphate level compared to HD group.

Table 3 shows the changes in subjective symptom parameters, including the VAS appetite score, 5D itch scale score, and PSQI score, along with its components. The change in pruritus score was significantly different among the three groups, with HD + biweekly HA demonstrating the largest reduction (−3.93, 95% CI: −6.89 to −0.97). There was no significant difference in changes in other subjective symptom parameters. In addition, the HD + biweekly HA group was the only group that showed a significant difference in several parameters after and before therapy: VAS appetite score (10.43% [95% CI: 4.99–15.87], $p = 0.001$), pruritus score (−3.93 [−6.89 to −0.97], $p = 0.013$), sleep duration score (−0.36 [95% CI: −0.64 to −0.07], $p = 0.019$), sleep latency score (−0.64 [95% CI: −1.23 to −0.06], $p = 0.033$), and sleep efficiency (15.17% [4.03–26.30], $p = 0.011$). Both the HD + biweekly HA and HD + weekly HA groups exhibited a significant improvement in sleep quality (PSQI) after therapy compared to before therapy (Table 3). Post hoc analyses comparing pairs of two out of the three interventional groups were also performed for each subjective symptom parameter (Fig. 3). Only HD + biweekly group revealed significantly better improvement in pruritus compared to HD group.

Discussion

This study aimed to evaluate the effectiveness of HD + HA combination therapy in improving the clearance of uremic toxins (β2-MG, leptin, and PTH) and inflammatory markers (IL-6 and CRP) in patients undergoing MHD and to assess how this therapy impacts patients' appetite, pruritus symptoms, and sleep quality. Baseline laboratory values, including hemoglobin, platelet count, leukocyte count, lymphocyte count, neutrophil count, random blood glucose, calcium, creatinine, leptin, β2-MG, PTH, IL-6, and CRP, did not significantly differ among the three groups. However, there was a significant difference in the BUN level, phosphate level, and pruritus score at baseline, which were greater in the HD + biweekly HA group than in the other two groups. These findings should be taken into account when interpreting the results of this study.

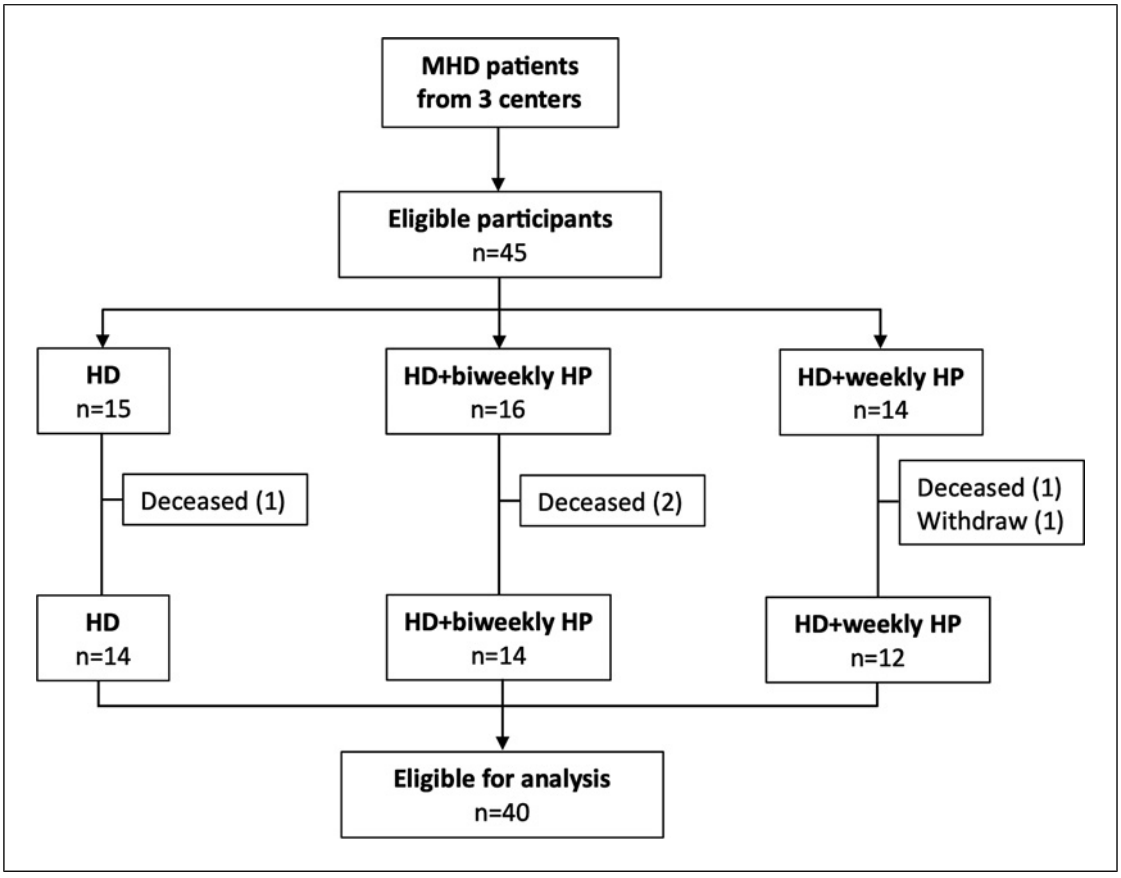

Fig. 1. Participant flowchart.

After 8 weeks of therapy, changes in the laboratory values of uremic toxins (leptin, β2-MG, and PTH) and inflammatory markers (IL-6 and CRP) did not significantly differ among the three groups. The findings of this study contrast with those of the study by Guo et al. [18] in 2011, which revealed that the use of adsorptive dialysis (a combination of HA and HD) resulted in a significant decrease in middle-molecular-weight substance levels compared to those of conventional HD, albeit with the side effects of decreased platelet counts. Another study by Chen et al. [10] in 2011 also showed opposite findings, suggesting that HD + HA combination therapy was significantly superior to HD alone in removing middle- and large-sized uremic toxin molecules after a 2-year observation. The differences in the results between our study and previous ones may be attributed to the different durations of the studies, with this study lasting only 8 weeks, and compensatory mechanisms by homeostatic adaptations in glandular secretion [19].

Geographical context also becomes a crucial consideration. This study was conducted in Indonesia, a developing country with limited resources, where patients typically receive MHD only twice weekly. This study setting differs from others, which commonly involve thrice-weekly therapy. The disparity in HD frequency might influence the outcomes, as an increased frequency of HD may reduce the accumulation of toxin molecules in the blood [20].

Another factor to take into account is the delay in peripheral blood sample acquisition after the completion of therapy. In this study, samples were obtained from patients 3 days after the last dialytic session due to coincidence with a national holiday in Indonesia. The rebound of specific toxin molecules can also lead to differences in outcomes. During HD, increased phosphate clearance can mobilize phosphorus from the deep phosphate pool without losing phosphorus from cellular stores. In the first dialytic session, serum phosphate levels may be deficient due to more significant phosphate mobilization into the extracellular fluid. However, serum

Table 1. Baseline characteristics, laboratory values, and symptom scores of the study participants

	HD (n = 14)	HD + biweekly HP (n = 14)	HD + weekly HP (n = 12)	p value*
Baseline characteristics of the study participants				
Sex, n (%)				
Male	6 (42.9)	7 (50)	8 (66.7)	0.476
Female	8 (57.1)	7 (50)	4 (33.3)	
Age, years				
Median (Q1–Q3)	54 (39–57)	47 (39.75–58.25)	52 (45.75–56)	0.905
Min-max	31–64	29–66	38–60	
Occupation, n (%)				
Office worker	3 (21.4)	4 (28.6)	2 (16.7)	0.523
Fieldworker	4 (28.6)	5 (35.7)	3 (25)	
Not working	7 (50)	5 (35.7)	7 (58.3)	
Comorbidities, n (%)				
Diabetes mellitus	2 (14.3)	2 (14.3)	3 (25)	0.722
Hypertension	13 (92.9)	13 (92.9)	11 (91.7)	0.992
Coronary heart disease	0 (0)	0 (0)	1 (8.3)	0.311
Hepatitis C	4 (28.57)	1 (7.14)	1 (8.33)	0.219
Tuberculosis	0 (0)	0 (0)	1 (8.3)	0.311
Anemia	7 (50)	4 (28.6)	4 (33.3)	0.482
Dental infection	1 (7.1)	0 (0)	0 (0)	0.395
Arthritis	2 (14.3)	0 (0)	0 (0)	0.149
Smoking	2 (14.3)	1 (7.1)	0 (0)	0.395
Anxiety score (GAD-7)	1 (0–2.25)	2 (0–5.25)	0.5 (0.5–2)	0.461
Minimal, n (%)	13 (92.9)	9 (64.3)	10 (83.3)	0.157
Mild, n (%)	1 (7.1)	3 (21.4)	1 (8.3)	
Moderate, n (%)	0 (0)	2 (14.3)	1 (8.3)	
Depression score (PHQ-9)	3 (0–4)	1.5 (0–8)	1.5 (0.25–10)	0.955
Minimal, n (%)	12 (85.7)	9 (64.3)	8 (66.7)	0.419
Mild, n (%)	1 (7.1)	2 (14.3)	1 (8.3)	
Moderate, n (%)	0 (0)	2 (14.3)	2 (16.7)	
Severe, n (%)	1 (7.1)	1 (7.1)	1 (8.3)	
Baseline laboratory values of the study participants				
Hemoglobin, g/dL	9.60±1.53	9.67±1.09	9.05±1.88	0.531
Platelet count, cells/μL	211,000 (175,000–233,250)	208,500 (182,000–259,000)	232,000 (212,250–264,000)	0.269
Leukocyte, cells/μL	6,455 (5,845–7,712.5)	6,515 (6,050–7,752.5)	6,515 (6,375–9,087.5)	0.194
Lymphocyte, %	19.57±8.46	19.71±7.28	20.5±5.14	0.941
Neutrophil, %	66.71±9.05	63.14±7.38	68.00±7.83	0.292
Random blood glucose, mg/dL	91 (75.75–116.75)	102.5 (77.25–123.00)	99.5 (82.00–118.75)	
Calcium, mg/dL	8.89±1.09	8.38±0.95	8.80±0.93	0.365
BUN, mg/dL	58.50 (51.73–66.60)	73 (58.33–103.18)	50.85 (45.43–69.23)	**0.014**
Creatinine, mg/dL	12.58±3.83	14.09±4.26	12.24±2.82	0.400
Phosphate, mg/dL	4.50±1.53	5.96±1.99	4.12±1.51	**0.020**
Leptin, ng/mL	6.3 (1.0–63.4)	9.6 (0.98–72.13)	11.45 (1.53–71.33)	0.968
β2-MG, mg/L	36.32±15.80	34.52±11.59	30.30±11.42	0.503
PTH, pg/mL	117.65 (38.04–376.88)	191.45 (50.98–527.43)	90.29 (31.30–325.93)	0.518
IL-6, pg/mL	6.76 (3.09–9.53)	4.80 (3.78–13.00)	6.33 (3.71–11.58)	0.968
CRP, mg/L	0.25 (0.10–0.55)	0.45 (0.10–0.60)	0.45 (0.30–0.93)	0.288
Baseline symptom scores of the study participants				
VAS Appetite Score	74.5 (50–80.5)	80 (73–84)	80 (62.5–83.75)	0.507
Pruritus score (5D itch scale)	7.5 (7–10.5)	13.5 (9.25–26)	9 (7–11)	**0.034**

Table 1 (continued)

Sleep quality score (PSQI)	11.00±3.64	11.79±3.97	8.58±3.58	0.108
Sleep onset	1.64±0.93	1.79±1.19	1.08±1.00	0.215
Sleep duration	1.57±0.85	1.57±0.85	1.25±0.75	0.528
Sleep latency	1.93±1.14	2.29±0.99	1.33±1.16	0.108
Sleep efficiency, %	68.25±25.68	64.20±28.95	79.47±17.84	0.240
Sleep disturbance	4.07±2.46	6.29±4.86	5.00±3.05	0.431
Daytime dysfunction	1.86±0.77	2.07±0.62	1.75±1.06	0.108

PHQ, Patient Health Questionnaire; GAD, General Anxiety Disorder; IQR, interquartile range; SD, standard deviation. *Pearson's χ^2 test, Fisher's exact test, or the Kruskal-Wallis test (>2 categories) for categorical variables and one-way ANOVA or the Kruskal-Wallis test for continuous variables. *p* values <0.05 (typed in bold) indicate statistical significance. All continuous variables are presented as the mean ± SD or median (IQR) as appropriate for normally distributed data.

Table 2. Comparison of changes in laboratory values of each group after 8 weeks of therapy

Parameters	HD (*n* = 14)	HD + biweekly HP (*n* = 14)	HD + weekly HP (*n* = 12)	*p* value*
Hemoglobin, g/dL	0.72 (−0.85 to 1.53), 0.075	0.45 (−0.63 to 1.53), 0.385	1.08 (0.22–1.93), **0.019**	0.717
Platelet count, cells/μL	5,480.71 (−24,307.07 to 35,268.50), 0.697	27,571.43 (−13,312.64 to 68,455.50), 0.169	−8,416.67 (−59,808.08 to 42.974.75), 0.725	0.473
Leukocyte, cells/μL	923.57 (−1,386.46 to 3,233.60), 0.403	−293.57 (−1,437.36 to 850.22), 0.589	−280.83 (−1,991.34 to 1,429.68), 0.725	0.589
Lymphocyte, %	−1.64 (−6.17 to 2.99), 0.447	−1.36 (−4.39 to 1.68), 0.352	−2.75 (−7.03 to 1.53), 0.185	0.932
Neutrophil, %	−0.14 (−6.42 to 6.14), 0.962	4.21 (−0.77 to 9.20), 0.091	3.42 (−2.64 to 9.47), 0.240	0.502
Random blood glucose, mg/dL	4.57 (−15.33 to 24.47), 0.628	−6.86 (−22.99 to 9.27), 0.375	−14.92 (−53.61 to 23.77), 0.414	0.603
Calcium, mg/dL	2.54 (0.90–4.17), **0.005**	1.94 (1.18–2.71), <**0.0001**	2.63 (0.81–4.44), **0.009**	0.829
BUN, mg/dL	−45.31 (−53.60 to −37.03), <**0.0001**	−61.34 (−71.33 to −51.34), <**0.0001**	−43.37 (−55.79 to −30.95), <**0.0001**	**0.021**
Creatinine, mg/dL	−8.54 (−10.08 to −7.01), <**0.0001**	−9.76 (−11.52 to −8.01), <**0.0001**	−8.46 (−9.82 to −7.10), <**0.0001**	0.459
Phosphate, mg/dL	−2.09 (−2.77 to −1.42), <**0.0001**	−3.53 (−4.48 to −2.58), <**0.0001**	−2.12 (−3.13 to −1.11), **0.001**	0.908
Leptin, ng/mL	−5.05 (−9.78 to −0.32), **0.038**	−8.10 (−16.79 to 0.59), 0.065	2.59 (−23.33 to 28.51), 0.830	0.581
β2-MG, mg/L	−2.73 (−8.86 to 3.41), 0.354	0.89 (−3.65 to 5.42), 0.680	0.83 (−7.31 to 8.97), 0.826	0.645
PTH, pg/mL	49.89 (−12.52 to 112.29), 0.108	51.02 (−178.89 to 280.93), 0.640	−2.98 (−68.16 to 62.21), 0.922	0.355
IL-6, pg/mL	1.85 (−1.61 to 5.31), 0.270	7.60 (−12.38 to 27.58), 0.426	57.27 (−83.76 to 198.29), 0.391	0.707
CRP, mg/L	−0.87 (−0.62 to 0.45), 0.152	−0.10 (−0.18 to −0.01), **0.034**	0.25 (−1.25 to 1.75), 0.595	0.228

Results are given as mean difference (95% CI), *p* value#. #Paired *t* test, statistically significant if the *p* value <0.05 (typed in bold). *One-way ANOVA or Kruskal-Wallis test, statistically significant if *p* value <0.05 (typed in bold).

phosphate levels may be greater in the second dialytic session. As a result, there may be no significant difference in serum phosphate levels at the end of therapy between the HD group and the HDP group [21].

The rebound phenomenon of β2-MG can lead to differences in the observed levels. An imbalance occurs during dialysis sessions, where the clearance rate of solutes from the extravascular compartment into the plasma is faster than the transfer rate of solutes into the plasma. As a result, the plasma concentration increases after the dialysis session, but the solute levels return to equilibrium after the dialysis session ends. Several previous studies have shown an increase in the plasma β2-MG concentration after high-flux HD. Therefore, the inability of HA to reduce the concentration of β2-MG may be related to significant mass transfer resistance between the vascular and extravascular compartments [22].

In contrast, the HD + biweekly HA group displayed a significant decrease in CRP levels after 8 weeks of therapy compared to before. This finding is consistent

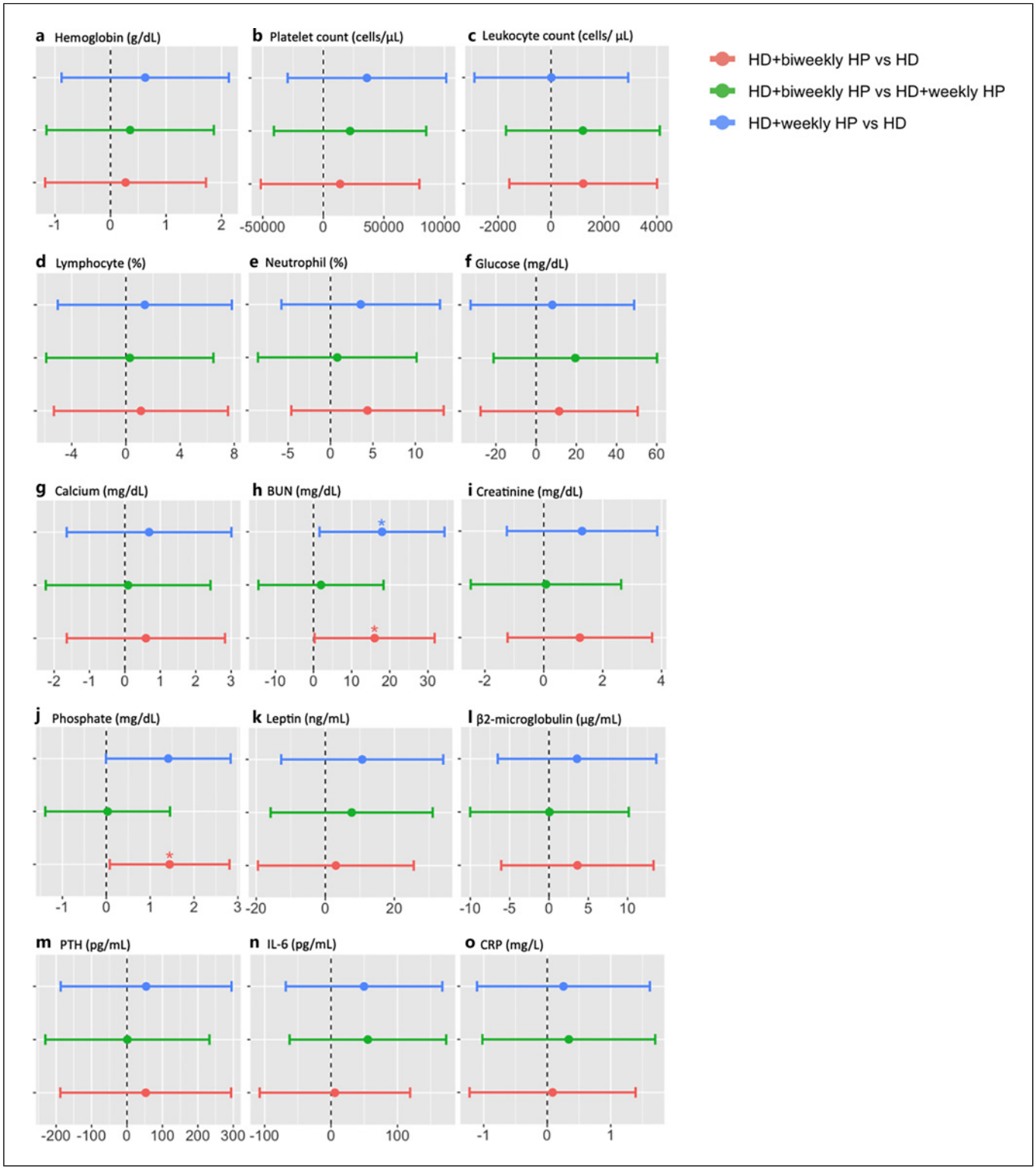

Fig. 2. Plots showing results of post hoc analyses comparing the laboratory parameters among pairs of two groups from the three interventional groups (asterisk mark *indicates $p < 0.05$).

Table 3. Comparison of changes in subjective symptoms 8 weeks after the procedure

Parameters	HD (n = 14)	HD + biweekly HP (n = 14)	HD + weekly HP (n = 12)	p value*
VAS Appetite Score (%)	3.71 (−5.27 to 12.70), 0.388	10.43 (4.99–15.87), **0.001**	6.67 (−3.86 to 17.19), 0.191	0.254
Pruritus score (5D itch scale)	3.43 (−0.39 to 7.25), 0.075	−3.93 (−6.89 to −0.97), **0.013**	−1.75 (−7.59 to 4.09), 0.523	**0.003**
Sleep quality score (PSQI)	−0.71 (−2.46 to 1.03), 0.393	−2.79 (−4.97 to −0.60), **0.016**	−2.33 (−4.59 to −0.08), **0.044**	0.232
Sleep onset	−0.71 (−2.46 to 1.03), 0.136	−0.50 (−1.17 to 0.17), 0.131	−0.42 (−0.99 to 0.16), 0.137	0.622
Sleep duration	−0.14 (−0.45 to 0.17), 0.336	−0.36 (−0.64 to −0.07), **0.019**	−0.42 (−0.92 to 0.09), 0.096	0.368
Sleep latency	−0.36 (−0.72 to 0.01), 0.055	−0.64 (−1.23 to −0.06), **0.033**	−0.33 (−0.96 to 0.29), 0.266	0.476
Sleep efficiency (%)	10.81 (−2.75 to 24.36), 0.109	15.17 (4.03–26.30), **0.011**	9.79 (−2.09 to 21.67), 0.097	0.269
Sleep disturbance	2.00 (−0.42 to 4.42), 0.097	−0.70 (−4.23 to 2.66), 0.630	0.50 (−1.89 to 2.89), 0.653	0.136
Daytime dysfunction	0.07 (−0.41 to 0.55), 0.752	−0.07 (−0.35 to 0.20), 0.583	−0.167 (−0.53 to 0.20), 0.339	0.757

Results are given as mean difference (95% CI), p value#. *One-way ANOVA or Kruskal-Wallis test, statistically significant if p value <0.05 (typed in bold). #Paired t test or Wilcoxon signed rank test, statistically significant if p value <0.05 (typed in bold).

with a study by Chen et al. [10], which indicated that patients receiving HD + HA therapy experienced a 20.58% decrease in CRP levels. Microinflammation often occurs in MHD patients and can lead to malnutrition-inflammation-atherosclerosis syndrome and increase the risk of mortality in CKD patients. High-sensitivity CRP is a key clinical indicator of microinflammation in HD patients [10]. The combination of HD + HA enhances toxin elimination in vivo and reduces microinflammation levels in uremic patients [23]. The results of this study affirm that HD + HA combination therapy can reduce the levels of inflammatory factors, especially CRP, in CKD patients. This can be achieved through HA with neutral macroporous resin, which effectively adsorbs substances with a molecular weight of 300–5,000 Da, including inflammatory mediators such as CRP [24]. However, the HD + weekly HA group failed to show similar results, indicating that the frequency of HA might impact its effectiveness and that there might be an optimal frequency that should be customized or personalized according to each patient's characteristics.

？有错误 In this study, we found that hemoglobin levels were significantly greater in the HD + weekly HA group than in the HD + ~~weekly HA~~ group. This finding is consistent with a study by Chen et al. [10], which showed that patients receiving weekly HD + HA combination therapy had significantly higher hemoglobin levels than those receiving only HD. Microinflammation can be reduced in uremic patients receiving HD + HA combination therapy [23]. Reducing microinflammation and oxidative stress in vivo can increase hemoglobin levels in research subjects. As a result, erythropoietin resistance may decrease [24].

Calcium and phosphate abnormalities are characteristic of CKD and significantly affect the condition of patients undergoing MHD. Uncontrolled kidney failure often leads to hyperphosphatemia and hypocalcemia in patients undergoing MHD [12]. After 8 weeks, there was a significant difference in the mean calcium levels of all groups after therapy compared to before therapy. This result is consistent with the findings of Nguyen Huu et al. [11], who reported a significant increase in calcium levels in patients receiving HD + HA therapy as well as in patients receiving only HD therapy after 3 years.

We also found a significant decrease in phosphate levels in all groups compared to baseline values. This result aligns with the study by Wang et al. [25] in 2018, which revealed a significant decrease in phosphate levels in both patients who underwent HD only and those who underwent HD + HA combination therapy ($p < 0.05$).

Only the HD + biweekly HA group showed a significant increase in appetite compared to that before the administration of HD + HA therapy. This finding aligns with the research by Wang et al. [25], which showed that there was a significant decrease in the proportion of subjects who experienced a poor appetite after 6 months of HD + HA combination therapy ($p < 0.01$). Similar to our findings regarding CRP levels, HD + weekly HA did not significantly increase appetite scores. Studies have shown that higher levels of CRP are associated with suppressed appetite and food intake in dialysis patients [26, 27].

Sleep disturbances or poor sleep quality are pervasive among patients with CKD, especially those with end-stage renal disease [28]. In this study, both the HD + biweekly HA and HD + weekly HA groups demonstrated significant improvements in the PSQI score after 8 weeks of therapy. These findings are consistent with the findings of Jin [29] and Gu et al. [13], who reported that patients

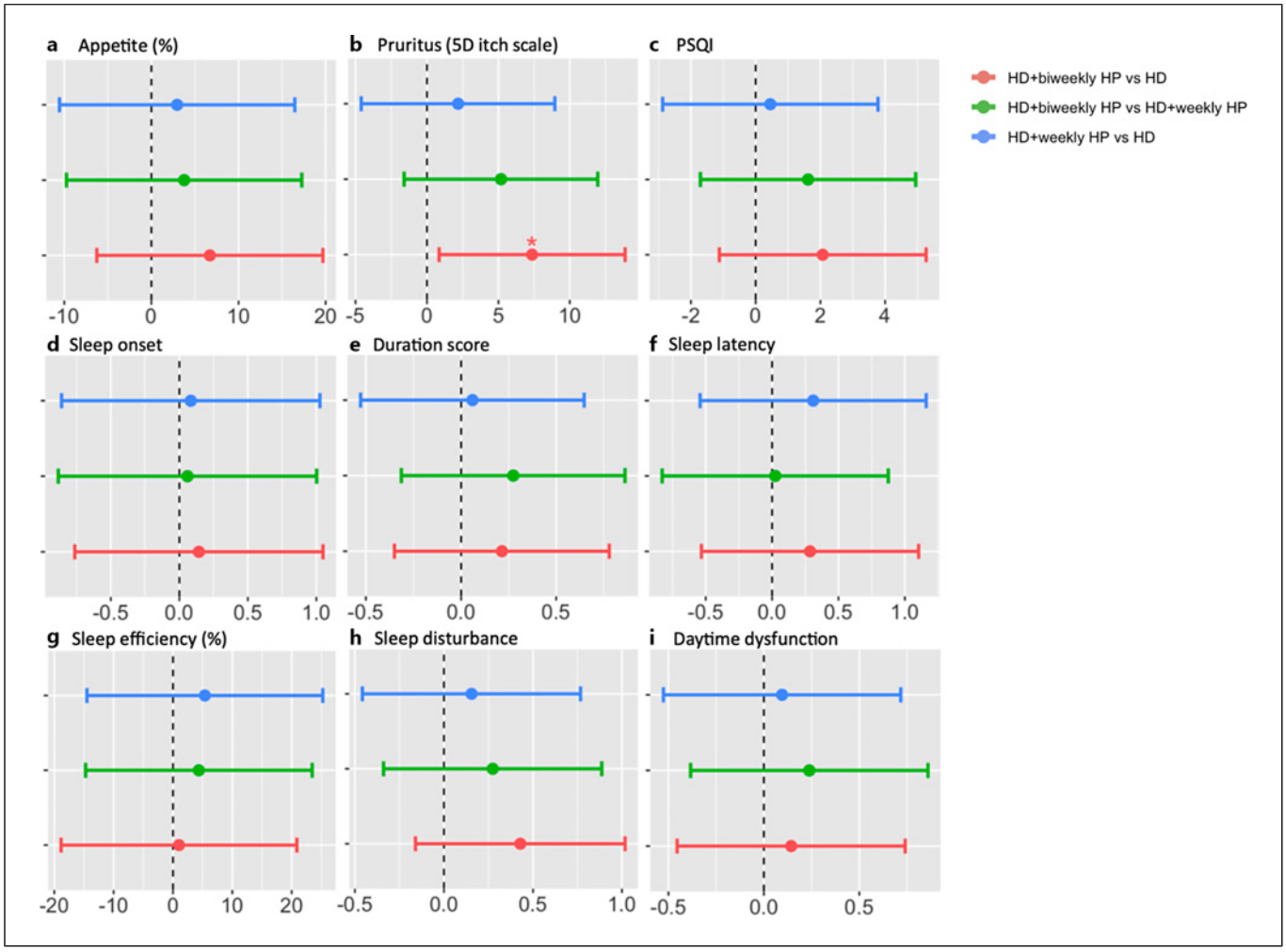

Fig. 3. Plots showing results of post hoc analyses comparing the subjective symptom parameters among pairs of two groups from the three interventional groups (asterisk mark *indicates $p < 0.05$).

receiving HD + HA therapy with HA sessions every 2 weeks have significantly greater sleep duration and sleep efficiency than patients receiving only HD therapy [13, 29]. Poor sleep quality in CKD patients is associated with high-sensitivity CRP and the neutrophil-to-lymphocyte ratio [30]. In this study, the HD + biweekly HA group experienced a significant decrease in CRP levels. This may contribute to the improvement in sleep quality after 8 weeks of therapy.

Changes in the pruritus score (5D itch scale) were significantly different among the three groups. HD + biweekly HA demonstrated the greatest improvement, with a score reduction of 3.93 (95% CI: −6.89 to −0.97). HD + biweekly HA was also the only group to show a significant difference in pruritus score before and after therapy. This result is consistent with the study by Jin [29], in which pruritus scores according to the Worst Itching Intensity Numerical Rating Scale were found to be significantly lower in subjects receiving HD + HA therapy (HA carried out once every 2 weeks) than in patients receiving HD alone [23]. This could be attributed to the difference in the study duration: the previous study was conducted over 2 years, while this study lasted for 8 weeks. These results are also in line with the findings of Li et al. [31], in which pruritus scores significantly decreased after 8 weeks of HD + HA therapy, with HA being carried out once every 2 weeks. Nguyen Huu et al. [11] also demonstrated a significant decrease in pruritus symptoms among patients receiving HD + HA therapy over 3 years.

More complex factors may contribute to the pathogenesis of pruritus in HD patients. Studies have revealed

that various inflammatory factors play a role in the pathogenesis of uremic pruritus. Recurrent pruritus symptoms are caused by a complex microenvironment formed by inflammatory factors and sustained inflammatory conditions [31].

Overall, HD combined with biweekly HA can significantly reduce CRP levels and alleviate symptoms among CKD patients, such as lowering pruritus, increasing appetite, and improving sleep quality. Compared with the control group and the HD + weekly HA group, the HD + biweekly HA group also exhibited a greater reduction in BUN. This finding suggests that additional HA therapy is still effective when administered every 2 weeks instead of once a week. This therapy is suitable for application in low- to middle-income countries with limited resources, including Indonesia, which might find it difficult to fund and provide access to HA therapy.

The strength of this study lies in its multicenter nature. This study is the first in Indonesia to examine the effectiveness of combined HD and HA therapy with varying treatment frequencies. Moreover, patient selection was performed through matching, ensuring a similar distribution of demographic characteristics such as sex and age in all three groups. The limitations of this study include its short follow-up duration of 8 weeks, relatively small sample size, and lack of blinding. The findings in this study might not very well apply to patients with standard thrice-weekly HD regimen since it only included patients undergoing twice-weekly HD. Future studies with larger sample sizes, longer follow-up duration with multiple time point outcome measurements, blinding methods, and patients undergoing standard thrice-weekly HD will be needed. Future studies should further explore the impact of HA frequency on its effectiveness to determine the optimal frequency of HA for each patient. It will also be worthwhile to conduct a cost-effectiveness analysis of HA and determine which patients will benefit most from HA therapy.

Conclusions

Administration of additional HA therapy every 2 weeks can significantly reduce CRP levels, alleviate pruritus, improve appetite, and enhance sleep quality among end-stage renal disease patients on MHD.

Statement of Ethics

This study protocol was approved by the Medical and Health Research and Ethics Committee (MHREC) of the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada (No. KE/FK/1053/EC/2022). Written informed consent was obtained from each participant at the time of enrollment. The study was conducted in accordance with the ethical standards of the institutional research committee, the Declaration of Helsinki for human studies, and Good Clinical Practice (GCP).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

M.P., A.R.P.H., and W.W.: conceptualization, data curation, formal analysis, investigation, methodology, validation, and writing – original draft, review, and editing; P.D.S.: validation, review, and editing; J., I.P., and Y.W.: data curation.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

References

1 Massy ZA, Liabeuf S. Middle-molecule uremic toxins and outcomes in chronic kidney disease. Contrib Nephrol. 2017;191:8–17. https://doi.org/10.1159/000479252

2 Wolley MJ, Hutchison CA. Large uremic toxins: an unsolved problem in end-stage kidney disease. Nephrol Dial Transplant. 2018;33(Suppl l_3):iii6–11. https://doi.org/10.1093/ndt/gfy179

3 Alix PM, Guebre-Egziabher F, Soulage CO. Leptin as an uremic toxin: deleterious role of leptin in chronic kidney disease. Biochimie. 2014;105:12–21. https://doi.org/10.1016/j.biochi.2014.06.024

4 Ureña-Torres PA, Vervloet M, Mazzaferro S, Oury F, Brandenburg V, Bover J, et al. Novel insights into parathyroid hormone: report of the parathyroid day in chronic kidney disease. Clin Kidney J. 2019;12(2):269–80. https://doi.org/10.1093/ckj/sfy061

5 Nissenson AR, Fine RN, Mehrotra R, Zaritsky J. Handbook of dialysis therapy E-Book. Elsevier Health Sciences; 2022.

6 Attia EA, Hassan AA. Uremic pruritus pathogenesis, revisited. Arab J Nephrol Transplant. 2014;7(2):91–6.

7 Sabry AA, Abo-Zenah H, Wafa E, Mahmoud K, El-Dahshan K, Hassan A, et al. Sleep disorders in hemodialysis patients. Saudi J Kidney Dis Transpl. 2010;21(2):300–5.

8 Perl J, Unruh M, Chan C. Sleep disorders in end-stage renal disease: "Markers of inadequate dialysis?" Kidney Int. 2006;70(10):1687–93. https://doi.org/10.1038/sj.ki.5001791
9 Carrero JJ. Mechanisms of altered regulation of food intake in chronic kidney disease. J Ren Nutr. 2011;21(1):7–11. https://doi.org/10.1053/j.jrn.2010.10.004
10 Chen SJ, Jiang GR, Shan JP, Lu W, Huang HD, Ji G, et al. Combination of maintenance hemodialysis with hemoperfusion: a safe and effective model of artificial kidney. Int J Artif Organs. 2011;34(4):339–47. https://doi.org/10.5301/IJAO.2011.7748
11 Nguyen Huu D, Dao Bui Quy Q, Nguyen Thi Thu H, Phan The C, Nguyen Thi Hong Q, Nguyen Duc L, et al. A combination of hemodialysis with hemoperfusion helped to reduce the cardiovascular-related mortality rate after a 3-year follow-up: a pilot study in vietnam. Blood Purif. 2021;50(1):65–72. https://doi.org/10.1159/000507912
12 Zhang ZY, Li MX, Yu H, Zhao J, Xiao FL, Xuan F, et al. Combination of multiple hemodialysis Modes: better treatment Options for patients under maintenance hemodialysis. Ther Clin Risk Manag. 2021;17:127–33. https://doi.org/10.2147/TCRM.S288023
13 Gu YH, Yang XH, Pan LH, Zhan XL, Guo LL, Jin HM. Additional hemoperfusion is associated with improved overall survival and self-reported sleep disturbance in patients on hemodialysis. Int J Artif Organs. 2019;42(7):347–53. https://doi.org/10.1177/0391398819837546
14 Jafron Biomedical. HA130 disposable hemadsorption cartridge [Internet]. 2023 [cited 2023 Dec 25]. Available from: https://www.jafroninternational.com/therapiesproducts/products/ha_series/19.html
15 Elman S, Hynan L, Gabriel V, Mayo M. The 5-D itch scale: a new measure of pruritus. Br J Dermatol. 2010;162(3):587–93. https://doi.org/10.1111/j.1365-2133.2009.09586.x
16 Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989;28(2):193–213. https://doi.org/10.1016/0165-1781(89)90047-4
17 Alim IZ, Elvira SD, Amir N. Noorhana. Uji validitas dan reliabilitas instrumen pittsburgh sleep quality index versi Bahasa Indonesia = Test validity and reliability of the instrument pittsburgh sleep quality index Indonesia language version. 2015. Available from. https://lib.ui.ac.id
18 Guo A, Meng J, Li D, Liu W, Wang S, Gao F, et al. Adsorptive dialysis for cleaning uremic middle molecular substances. Chin J Tissue Eng Res. 2011;15(12):2261.
19 Zhang J, Yuan Y, An X, Ouyang C, Ren H, Yang G, et al. Comparison of combined blood purification techniques in treatment of dialysis patients with uraemic pruritus. Int J Clin Exp Med. 2016;9(5):8563–8.
20 Shafiee MA, Chamanian P, Shaker P, Shahideh Y, Broumand B. The impact of hemodialysis frequency and duration on blood pressure management and quality of life in end-stage renal disease patients. MDPI; 2017. p. 52.
21 Minutolo R, Bellizzi V, Cioffi M, Iodice C, Giannattasio P, Andreucci M, et al. Post-dialytic rebound of serum phosphorus: pathogenetic and clinical insights. J Am Soc Nephrol. 2002;13(4):1046–54. https://doi.org/10.1681/ASN.V1341046
22 Ward R, Greene T, Hartmann B, Samtleben W. Resistance to intercompartmental mass transfer limits beta2-microglobulin removal by post-dilution hemodiafiltration. Kidney Int. 2006;69(8):1431–7. https://doi.org/10.1038/sj.ki.5000048
23 He H, Xie Y. Effect of different hemodialysis methods on microbiota in uremic patients. BioMed Res Int. 2020;2020:6739762–8. https://doi.org/10.1155/2020/6739762
24 Cheng W, Luo Y, Wang H, Qin X, Liu X, Fu Y, et al. Survival outcomes of hemoperfusion and hemodialysis versus hemodialysis in patients with end-stage renal disease: a systematic review and meta-analysis. Blood Purif. 2022;51(3):213–25. https://doi.org/10.1159/000514187
25 Wang Y, Chen Y, Mao L, Zhao G, Hong G, Li M, et al. Effects of hemoperfusion and continuous renal replacement therapy on patient survival following paraquat poisoning. PLoS One. 2017;12(7):e0181207. https://doi.org/10.1371/journal.pone.0181207
26 Vannini FD, Antunes AA, Caramori JC, Martin LC, Barretti P. Associations between nutritional markers and inflammation in hemodialysis patients. Int Urol Nephrol. 2009;41(4):1003–9. https://doi.org/10.1007/s11255-009-9563-8
27 Zabel R, Ash S, King N, Bauer J. The relationship between subjective appetite sensations, markers of inflammation and appetite in dialysis patients. J Hum Nutr Diet. 2009;22(4):343–50. https://doi.org/10.1111/j.1365-277X.2009.00968.x
28 Harris TJ, Nazir R, Khetpal P, Peterson RA, Chava P, Patel SS, et al. Pain, sleep disturbance and survival in hemodialysis patients. Nephrol Dial Transplant. 2012;27(2):758–65. https://doi.org/10.1093/ndt/gfr355
29 Jin HM. Hemadsorption improves sleep disturbance and survival in maintenance hemodialysis patients. Oxford University Press; 2018.
30 Empitu MA, Kadariswantiningsih IN, Thaha M, Nugroho CW, Putri EAC, Hakim ZE, et al. Determiner of poor sleep quality in chronic kidney disease patients links to elevated diastolic blood pressure, hs-CRP, and blood-count-based inflammatory predictors. Indones Biomed J. 2019;11(1):100–6. https://doi.org/10.18585/inabj.v11i1.452
31 Li WH, Yin YM, Chen H, Wang XD, Yun H, Li H, et al. Curative effect of neutral macroporous resin hemoperfusion on treating hemodialysis patients with refractory uremic pruritus. Medicine. 2017;96(12):e6160. https://doi.org/10.1097/MD.0000000000006160