



DIFFERENCES OF IL-6 AND HS-CRP LEVELS AND BLOOD PRESSURE IN ROUTINE HEMODIALYSIS CKD PATIENTS UNDERGOING INTRADIALYTIC AEROBIC CYCLING EXERCISE

Dendy Raharjo^{1*}, Agung Susanto², Bayu Basuki Wijaya³, Eti Poncorini Pamungkasari⁴

Affiliation:

1. Students of Internal Medicine Specialist Education Program, Faculty of Medicine, Sebelas Maret University
2. Division of Kidney Disease and Hypertension Internal Medicine Universitas Sebelas Maret/Dr Moewardi Hospital
3. Geriatric Division of Internal Medicine Universitas Sebelas Maret/Dr. Moewardi Hospital
4. Faculty of Medicine, Universitas Sebelas Maret

Correspondence: Dendy Raharjo, dendyraharjoospd@gmail.com, Student of Internal Medicine Specialist Education Program, Faculty of Medicine, Sebelas Maret University, Kentingan, Jebres, Surakarta, 57126

Received: 4/18/2024

Accepted: 5/06/2024

Published: 5/25/2024



Creative Commons Attribution 4.0 International (CC BY 4.0)



ABSTRACT

Introduction: Chronic kidney disease (CKD) patients receiving hemodialysis (HD) therapy may experience worsening of their condition due to inflammation from various causes. Intradialytic aerobic exercise helps to reduce inflammation. This study aimed to examine the effect of intradialytic aerobic exercise on interleukin-6 (IL-6) and high-sensitivity C-reactive protein (hsCRP) levels as markers of inflammation, as well as its effect on blood pressure in patients who routinely undergo HD.

Methods: This study was a double-blinded randomized control trial (RCT) with a control group and a treatment group that received intradialytic aerobic exercise interventions for 12 weeks; the dose for each session was 30 min at a frequency of 2 times per week. We collected blood pressure data and blood samples for IL-6 and hs-CRP examination using the enzyme-linked immunosorbent assay (ELISA) method before treatment in the first week and after the last treatment in the 12th week. Statistical analysis was performed using the t-test and regression tests.

Results: The mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) values of the treatment group were not significantly different from the control group (146.15 ± 18.39 mmHg vs. 153.77 ± 31.25 mmHg; $p = 0.613$, and 94.62 ± 14.78 mmHg vs. 86.69 ± 12.06 mmHg; $p = 0.089$). The mean post-treatment SBP decreased insignificantly (from 150.77 ± 24.43 to 146.15 ± 18.39 ; $p = 0.438$). The mean post-treatment DBP experienced a non-significant increase (from 89.23 ± 22.24 to 94.62 ± 14.78 ; $p = 0.272$). IL-6 and hs-CRP levels in the treatment group were lower when compared to the control group (4.04 ± 1.48 pg/ml vs. 4.79 ± 3.58 pg/ml; $p = 0.612$, and 17.47 ± 23.59 pg/ml vs. 21.79 ± 21.97 pg/ml; $p = 0.596$). The mean of post-treatment IL-6 and hs-CRP levels were not significantly higher when compared to before treatment (4.04 ± 1.48 pg/ml vs. 3.90 ± 1.35 pg/ml; $p = 0.671$ and 17.47 ± 23.59 pg/ml vs. 8.82 ± 7.65 pg/ml; $p = 0.297$). Neither IL-6 nor hs-CRP affect SBP or DBP.

Conclusion: Intradialytic aerobic exercise for 12 weeks did not significantly affect IL-6, hs-CRP, SBP, or DBP.

Keywords: Chronic kidney disease; hemodialysis; IL-6; hs-CRP; intradialytic exercise.

INTRODUCTION

Chronic kidney disease (CKD) is one of the major causes of death and suffering in the 21st century. It is mostly associated with an increase in various risk factors, including obesity and diabetes mellitus (DM). The number of CKD patients has also increased in recent years, with around 843.6 million people worldwide in 2017 [1]. According to the Centers for Disease Control and Prevention (2021), it is estimated that around 15% of adults in the United States, or around 37 million people, suffer from CKD, of which 2 of 1,000 people are currently living with end-stage CKD, of which 71% are on dialysis [2].

In Indonesia, the number of end-stage CKD patients undergoing hemodialysis (HD) is increasing annually. In 2018, there was a two-fold increase in the number of new patients compared with that in 2017. 2018 recorded 66,433 new patients, compared to only 30,831 in 2017. So the number of active patients in 2018 was 132142, compared to the number of active patients in 2017, which was only 77892 [3].

Hemodialysis has good efficacy and can prolong patient survival, but this procedure can also cause various complications, such as nausea, vomiting, hypotension, headaches, cramps, and low-grade chronic inflammation [4]. This low-grade chronic inflammation is caused by the passage of transmembrane endotoxins during dialysis into the systemic circulation, the activation of neutrophils and monocytes during dialysis, and the activation of proinflammatory cytokines and endothelial changes [5].

An intradialytic aerobic cycling exercise program for 3 months can reduce IL-6 and hs-CRP levels as markers of inflammation [6, 7]. The effects of intradialytic aerobic cycling exercise on blood pressure are still varied and tend not to have a significant effect [6–8]. Given the previously described background, we need to conduct this study to examine changes in inflammatory indicators and their correlation with blood pressure in end-stage CKD patients following a 3-month intervention with intradialytic aerobic cycling exercise.

METHOD

Type and Design of Research

This study was an RCT conducted in the Renal Hypertension Instalation of Dr. Moewardi General Hospital Surakarta for treatment and the Laboratorium Riset Terpadu (LRT) FK-KMK UGM for measuring IL-6 and hs-CRP levels. The treatment was carried out from January 2023 to March 2023, where the subjects performed intradialytic aerobic cycling exercise for 12 weeks with a total duration of 30 minutes for each cycle. Blood samples were collected just before the first intradialytic aerobic cycling exercise in the first week of treatment and shortly after the last intradialytic aerobic cycling exercise in the 12th week of treatment. Blood samples were collected in EDTA tubes and placed in ice boxes to the LRT FK-KMK UGM for IL-6 and hs-CRP examination using the Enzyme Linked immunosorbent assay (ELISA) method.

This study was an RCT conducted in the Renal Hypertension Instalation of Dr. Moewardi General Hospital Surakarta for treatment and the Laboratorium Riset Terpadu (LRT) FK-KMK UGM for measuring IL-6 and hs-CRP levels. From January 2023 to March 2023, the subjects underwent 12 weeks of intradialytic aerobic cycling exercise, each cycle lasting 30 minutes. We collected blood samples just before the first intradialytic aerobic cycling exercise in the first week of treatment and shortly after the last intradialytic aerobic cycling exercise in the 12th week of treatment. Blood samples were collected in EDTA tubes and placed in ice boxes at the LRT FK-KMK UGM for IL-6 and hs-CRP examination using the enzyme-linked immunosorbent assay (ELISA) method.

2.1 Intradialytic Aerobic Cycling Exercise

A 30-minute exercise program consisting of a 5-minute warm-up followed by 20 minutes of cycling at the desired workload and a 5-minute cool-down was carried out while the patient was undergoing hemodialysis. Intradialytic aerobic cycling exercise procedure:

- Vital signs were measured before hemodialysis.

- We took the patient's weight into account to calculate how much fluid the body needs to lose during therapy.
- The patient lied on a hemodialysis bed.
- Connecting the dialysis machine by attaching a blood line (blood tube) and needle to the patient's vascular access, namely access for the blood to exit the dialyzer and access for the blood to enter the body. Once everything is installed, the hemodialysis therapy process can begin.
- The cycling device (Kova Desk Bike KV-DSBK-GR) was standardized and installed to suit each patient's bed for patient comfort and safety.
- The patient warmed up for 5 minutes, followed by cycling for 20 minutes with an intensity of 12 to 15 on the Borg Perceived Exertion Scale, and cooling down for 5 minutes (**Figure 1**).



Figure 1. Intradialytic Aerobic Cycling Exercise in CKD patients

Research Subjects

The participants in this study were end-stage CKD patients who had routinely undergone hemodialysis for at least 3 months with a frequency of 2 times per week and 4-5 hours for each hemodialysis session, and had never participated in other studies related to physical activity in the last 6 months. The participants were non-smokers, willing to participate, signed informed consent, and had never experienced a hemodialysis-related emergency. Calculations using OpenEpi obtained a sample size of 30 patients, but the number of samples included in the final analysis was 28 patients who were divided into the treatment group (n = 13) and the control group (n = 15) because two patients in the treatment group died (**Figure 2**).

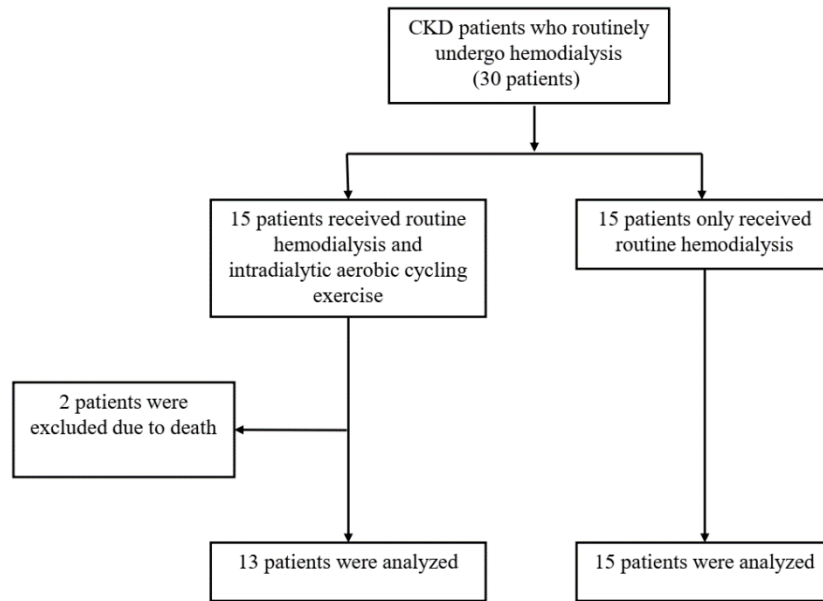


Figure 2. Flowchart of patient selection

Data Analysis Methods

We used the Shapiro-Wilk test to test the normality of the numerical data. Unpaired t-tests and paired t-tests were used for bivariate analysis, while linear regression tests were used for multivariate analysis. Significance is $p < 0.05$. We performed statistical analyses using IBM SPSS Statistics for Windows version 26.

Ethical Clearance

The Research Ethics Commission of the Faculty of Medicine UNS/RS Dr. Moewardi Surakarta (number 1.411/XI/HREC/2022) approved this study after receiving permission from the research supervisor.

RESULTS

Table 1 displays the baseline characteristics of the participants. The mean age of the patients as a whole was 44.89 ± 11.47 years, with the mean age of the treatment group being 42.08 ± 11.95 years, which was lower than the mean age of the control group, which was 47.33 ± 10.45 years. There was no significant difference between the mean ages of the control and treatment groups ($p = 0.233$).

Table 1. Characteristics of participant at baseline

Characteristics	Control Group (n = 15)	Treatment Group (n = 13)	p-value
Age	47.33 ± 10.45	42.08 ± 11.95	0.233†
Gender			0.243#
Man	6 (21.43%)	9 (32.14%)	
Woman	9 (32.14%)	4 (14,29)	

Characteristics	Control Group	Treatment Group	p-value
	(n = 15)	(n = 13)	
HD Duration	5.15 ± 2.41	3.52 ± 3.28	0.262††
Comorbid			1,000#
Yes	4 (11.43%)	4 (11.43%)	
No	11 (39.30%)	9 (32.10%)	
History of COVID-19			0.583#
Yes	1 (3.60%)	2 (7.10%)	
No	14 (50.00%)	11 (39.30%)	
Nutritional status			1,000#
Underweight	1 (3.60%)	1 (3.60%)	
Normoweight	14 (50.00%)	12 (42.86%)	
Overweight	0 (0.00%)	0 (0.00%)	
Obesity	0 (0.00%)	0 (0.00%)	

(†) unpaired t-test, (††) mann-whitney test, (#) chi-square test, HD= Hemodialysis

The control group had the highest proportion of females, with 32.14% of the total number of study subjects (nine patients), while males had a smaller proportion, namely 21.43% (six patients). However, in the treatment group, there was a higher proportion of males (32.14%; 9 patients) than females (14.29%; 4 patients). There was no difference in the sex ratio between the control and treatment groups (p = 0.243).

Both in the control and treatment groups, the majority of the subjects in this study [14 (50.00%); 11 (39.30%)] had never contracted SARS-Cov-2. In the different-proportion test, there was no statistically significant difference between patients with and without SARS-Cov-2 infection in the two study groups (p = 0.583).

This study excluded overweight and obese patients with a BMI > 25 kg/m². We found that one patient (3.60%) in each study group had an underweight nutritional status, while the rest had a normal nutritional status.

Table 2 shows that the results of this study were based on the conditions before treatment. The mean SBP in the control group was not significantly higher than that in the treatment group (151.73 + 24.49 vs. 150.77 + 24.43; p = 0.918). In contrast to the DBP variable, the treatment group had a higher mean DBP than the control group, although the difference was not statistically significant (89.23 + 22.24 vs. 87.00 + 13.17; p = 0.333). The mean IL-6 and hs-CRP levels in the control group were also not significantly higher than those in the treatment group (6.46 ± 4.49 vs 3.90 ± 1.35; p = 0.107 and 18.95 ± 16.72 vs 8.82 ± 7.65; p = 0.059).

Table 2. Blood pressure values, IL-6 levels and hs-CRP levels between study groups at baseline

Parameter	Control Group (n = 15)	Treatment Group (n = 13)	p-value
Blood pressure (mmHg)			
Systolic	151.73 ± 24.49	150.77 ± 24.43	0.918 [†]
Diastolic	87.00 ± 13.17	89.23 ± 22.24	0.333 [#]
IL-6 (pg/ml)	6.46 ± 4.49	3.90 ± 1.35	0.107 [#]
Hs-CRP (pg/ml)	18.95 ± 16.72	8.82 ± 7.65	0.059 [#]

(†) unpaired t-test, (#) mann-whitney test, IL-6= Interleukin-6, Hs-CRP= high-sensitivity C-reactive protein

Table 3 shows that the mean SBP of patients in the treatment group was lower than that of patients in the control group (146.15 ± 18.39 mmHg vs. 153.77±31.25 mmHg). However, this difference was not statistically significant (p = 0.613). However, in the DBP variable, the treatment group had a higher mean blood pressure than the control group (94.62 ± 14.78 mmHg vs. 86.69 ± 12.06 mmHg). This difference was also not statistically significant in the Mann-Whitney U test.

Table 3. Blood pressure values, IL-6 levels, and hs-CRP levels between study groups at the end of the study

Parameter	Control Group (n = 15)	Treatment Group (n = 13)	p-value
Blood pressure (mmHg)			
Systolic	153.77 ± 31.25	146.15 ± 18.39	0.613 [†]
Diastolic	86.69 ± 12.06	94.62 ± 14.78	0.089 [†]
IL-6 (pg/ml)	4.79 ± 3.58	4.04 ± 1.48	0.612 [#]
Hs-CRP (pg/ml)	21.79 ± 21.97	17.47 ± 23.59	0.596 [#]

(†) unpaired t-test, (#) mann-whitney test, IL-6= Interleukin-6, Hs-CRP= high-sensitivity C-reactive protein

IL-6 and hs-CRP levels in the treatment group were found to be lower when compared to the control group, namely 4.04 ± 1.48 pg/ml compared to 4.79 ± 3.58 pg/ml and 17.47 ± 23,59 pg/ml versus 21.79 ± 21.97 pg/ml. In the Mann-Whitney test, there was no significant difference between the mean levels of IL-6 and hs-CRP in the treatment and control groups (p = 0.612 and p = 0.596, respectively).

The mean SBP after treatment decreased from 150.77 + 24.43 ± 146.15 + 18.39. However, this decrease was not statistically significant (P = 0.438). While the mean of DBP after treatment (94.62 ± 14.78) was higher than the mean of DBP before treatment (89.23 ± 22.24), However, this increase was not statistically significant (P = 0.272).

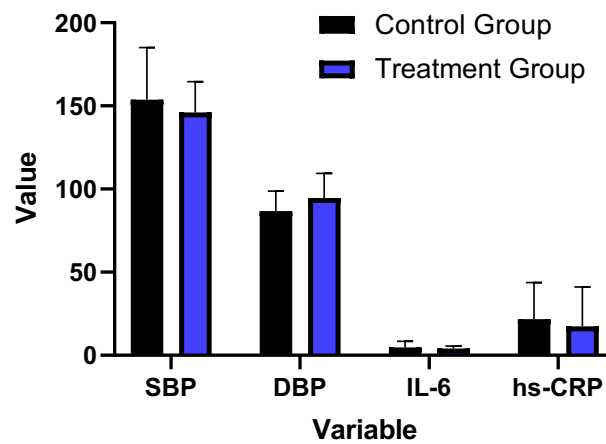


Figure 2. Comparison of SBP and DBP values, IL-6 levels, and hs-CRP levels between study groups after 3 months of treatment

Table 4. Blood pressure values, IL-6 levels, and hs-CRP levels in the treatment group

Parameter	Before Treatment	After Treatment	<i>p-value</i>
Blood pressure (mmHg)			
Systolic	150.77 ± 24.43	146.15 ± 18.39	0.438 [†]
Diastolic	89.23 ± 22.24	94.62 ± 14.78	0.272 [†]
IL-6 (pg/ml)	3.90 ± 1.35	4.04 ± 1.48	0.671 [†]
Hs-CRP (pg/ml)	8.82 ± 7.65	17.47 ± 23.59	0.297 [#]

([†]) paired t-test, ([#]) wilcoxon test, IL-6= Interleukin-6, Hs-CRP= high-sensitivity C-reactive protein

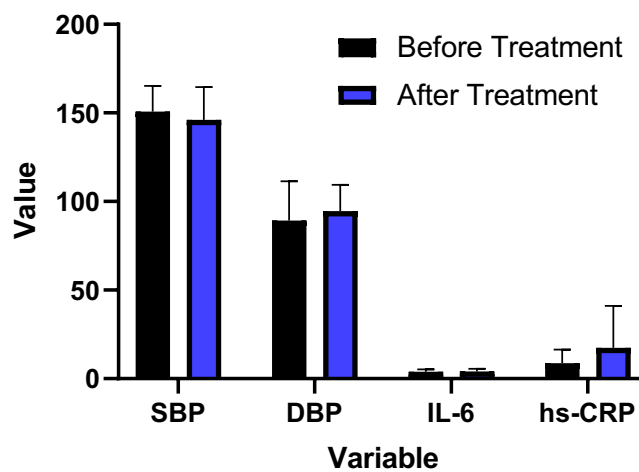


Figure 3. Comparison of SBP and DBP values, IL-6 levels, and hs-CRP levels before and after treatment in treatment group

The mean of post-treatment IL-6 level was not statistically significant higher than the pre-treatment mean of IL-6 level (4.04 ± 1.48 pg/ml vs. 3.90 ± 1.35 pg/ml). The increase in IL-6 levels after treatment was not statistically significant ($p = 0.671$). Post-treatment hs-CRP levels were higher when compared to pre-treatment hs-CRP levels (17.47 ± 23.59 pg/ml vs. 8.82 ± 7.65 pg/ml). The increase in post-treatment hs-CRP levels was also not statistically significant ($P = 0.297$).

As shown in **Table 5**, IL-6 levels did not significantly influence SBP in the group of patients who underwent intradialytic aerobic cycling exercise for 3 months ($B = 7.606$; 95% CI = $-0.672-15.884$; $p = 0.068$). Similarly, hs-CRP levels did not significantly affect SBP ($B = -0.059$; 95% CI = $-0.580-0.461$; $p = 0.804$).

Also, Table 6 shows that the DBP value and IL-6 level did not have a big effect on the DBP value in the group of patients who did aerobic cycling exercise for three months ($B = 2.442$; 95% CI = $-5.217-10.102$; $p = 0.494$). Accordingly, hs-CRP levels did not significantly affect DBP ($B = 0.093$; 95% CI = $-0.389-0.575$, $p = 0.677$).

Table 5. Effect of IL-6 and hs-CRP levels on systolic blood pressure values in the treatment group

Parameter	B	CI 95%	p-value
IL-6	7.606	-0.672 – 15.884	0.068
Hs-CRP	-0.059	-0.580 – 0.461	0.804

B= Regression Coefficient CI= Confidence Interval, IL-6= Interleukin-6, Hs-CRP= high-sensitivity C-reactive protein

DISCUSSION

This study was a double-blinded randomized control trial with a pre-test and post-test design with a control group. “Blinded “occurred when randomizing the allocation of research subjects to each study group and measuring research outcomes on the SBP, DBP, IL-6, and hs-CRP variables. The research group consisted of two groups: a treatment group and a control group. The treatment group underwent hemodialysis therapy and intradialytic aerobic cycling exercise for 12 weeks, with a total duration of 30 minutes for each cycle. While the control group only received hemodialysis therapy for 12 weeks,.

The randomization of subject allocation to the intervention group in this double-blind RCT study allows for the elimination of confounding variables, which the researcher cannot control and can cause bias. Blinded measurement can help minimize the subjectivity aspect of determining measurement results, which sometimes makes a value tend to be adjusted to the hypothesis. In addition, this study design allows both research subjects, researchers, and research staff to be “blinded.” Another advantage of this study over observational studies is the ability to show causality [9].

The subjects in this study were end-stage CKD patients who had routinely undergone hemodialysis for at least 3 months with a frequency of 2 times per week and 4-5 hours for each hemodialysis session, had never participated in other studies related to physical activity in the last 6 months, were not smoking, were willing to be a participant and signed informed consent, and had never experienced an emergency associated with hemodialysis. At the beginning of the study, 30 patients were divided into treatment ($n = 15$) and control ($n = 15$) groups. However, two patients died at the end of the study, resulting in a total of 28 research subjects included in the data analysis process. The patient died of acute lung edema. This indicates a dropout percentage of 6.7%. According to Bankhead et al. (2017), the general rule states that a dropout of <5% can produce the most minimal bias [10].

In the control group, the majority of research subjects were women (32.14%), whereas in the treatment group, the majority of research subjects were men (32.14%). The mean age of the patients who were the subjects of this study as a whole was 44.89 ± 11.47 years, with the mean age of the treatment group being 42.08 ± 11.95 years, which was lower than the mean age of the control group, which was 47.33 ± 10.45 years. Patients in the control group had a longer history of HD than those in the treatment group (5.15 ± 2.41 vs. 3.52 ± 3.28 years). However, the differences between these two variables were not statistically significant.

This result is consistent with that of a study by Da Cruz et al. (2018). In that study, most of the research subjects in the treatment group (undergoing intradialytic aerobic exercise for 12 weeks) were male (67%), had a had a mean of 43.5 ± 14.4 years, and had a mean history of undergoing HD for 5.2 ± 2.2 years. Whereas in the control group, most of the study subjects were female (80%), aged 39.9 ± 13.5 years, with a history of HD of 5.6 ± 3.0 years [11]. In this study, there was also no significant difference between the age group and the length of HD history. A study conducted by Liao et al. (2016) found that the mean age of the subjects was 62 ± 8 years in the treatment group and 62 ± 9 years in the control group. The mean length of HD history was 71 ± 46 months in the treatment group and 83 ± 71 months in the control group. Most of the subjects in the treatment group were 40% male, whereas in the control group, the majority were female (45%). There were also no significant differences between the study groups in these three variables [6].

At the end of the study, the mean SBP value of patients in the treatment group was lower than that of the control group. In the treatment group, the mean post-treatment SBP also decreased. However, the differences between these two variables were not statistically significant. This result is in line with previous studies that showed no significant difference in the mean SBP of the treatment group compared to that of the control group after 12 weeks of treatment. Although the mean SBP of the treatment group was found to be lower than the control group ($96.6, \pm 64.1$ vs. $132.2, \pm 17.8$; $p > 0.05$) [6], A combined analysis of data from two trials with 50 patients showed that the group of patients who did intraadialytic exercise did not have a significantly lower SBP than the control group (Δ SBP = -2.28 mmHg, $p = 0.700$). Another systematic review that analyzed 287 patients showed an opposite trend. In that study, it was found that intradialytic exercise can significantly reduce SBP [8].

The results of this study on DBP showed that the treatment group had a higher mean blood pressure than the control group. However, this difference was not statistically significant. In the treatment group, the mean post-treatment DBP experienced a non-significant increase compared to the pre-treatment mean DBP. A study of three RCTs with a total of 67 participants showed that the group that did intraadialytic exercise had a small but significant rise in their mean DBP of 2.25 mmHg [8]. These results are in line with that study. In contrast to the results of this study, analysis of data from 7 trials showed that there was a significant decrease in the mean of DBP in the group undergoing intradialytic exercise (Δ DBP = 4.11 mmHg; $p = 0.0007$) [12]. Likewise, an RCT study showed that the control group had a higher mean of DBP when compared to the treatment group, which underwent intradialytic exercise for 12 weeks. Although this difference is not statistically significant [6].

The findings of this study regarding the SBP and DBP variables may be due to poor adherence to antihypertensive medication. Approximately 33.33% of the participants in the control group and 23.08% of the participants in the treatment group did not take medication regularly. In fact, some of them have not taken antihypertensive medications since December 2022.

An increase in the DBP value without being accompanied by an increase in the SBP value, as in the results of this study, may be related to a family history of hypertension, alcohol consumption, young age, increased blood glucose, increased body mass index, and high triglyceride levels [13]. In this study, patients with a history of alcohol consumption and an increased body mass index were excluded. Meanwhile, the family history of hypertension, blood glucose levels, and high triglyceride levels is unknown. Meanwhile, in the additional regression analysis, younger age significantly affected the DBP score ($B = -0.819$; 95% CI = -1.483 – -0.154 ; $p = 0.021$).

Bias could also arise because people with cardiovascular disorders were still included in the study, and there were variables of nutritional intake that could affect blood pressure, and these variables could not be controlled by the researchers in this study. Increasing the sample size can minimize this emerging bias. Large-scale studies can produce better estimates of the causal effects of the treatment. In addition, increasing the sample size will not only reduce this bias but will also eliminate the effect of variance from sampling error [14].

In the IL-6 level variable, although not statistically significant, the treatment group had lower IL-6 levels when compared to the control group (4.04 ± 1.48 pg/ml vs. 4.79 ± 3.58 pg/ml). The mean IL-6 level after treatment was found to be higher when compared to the mean IL-6 level before treatment (4.04 ± 1.48 pg/ml vs. 3.90 ± 1.35 pg/ml). The increase in the mean post-treatment IL-6 level was not statistically significant.

These results are different from the RCT study conducted by Da Cruz et al. (2018), which found that intradialytic exercise for 12 weeks with a mean duration of 36 minutes for each treatment was able to significantly reduce the mean IL-6 level from 9.22 ± 4.48 to 5.45 ± 3.4 . However, it was higher in the treatment group compared to the control group (5.45 ± 3.4 vs. 4.8 ± 5.5). [11]. Another study with the same duration of intradialytic exercise also found something different from this study's results. The mean IL-6 level in the treatment group (251 ± 123.4) was significantly lower than that of the control group (395.0 ± 161.5). Likewise, the mean IL-6 level was lower in the treatment group after 12 weeks of intradialytic exercise (251.0 ± 123.40 from 354.2 ± 167.10). [15]. Another study conducted by Dungey et al. (2017) with intradialytic cycling treatment 3 times per week with the duration of each session being 30 minutes for 6 months showed that the mean IL-6 level in the treatment group was higher than the control group, although not statistically significant (5.39 ± 3.05 vs. 4.92 ± 2.79) [16].

The mean hs-CRP level in the treatment group was found to be lower when compared to the control group (17.47 ± 23.59 pg/ml vs. 21.79 ± 21.97 pg/ml), although this difference was not significant. Likewise, post-treatment hs-CRP levels were not significantly higher when compared to pre-treatment hs-CRP levels (17.47 ± 23.59 pg/ml vs. 8.82 ± 7.65 pg/ml). Another study in 2021 at other educational centers in Indonesia found no significant decrease in the mean CRP level before and after intradialytic exercise for 12 weeks, from 0.33 ± 0.33 to 0.27 ± 0.16 [17]. The RCT study by Soltani et al. (2020) also found no significant reduction in CRP levels after 12 weeks of treatment (0.93 ± 0.67 to 0.90 ± 0.6) [18].

Elshinnawy et al. (2021) showed different results from those of this study. In this prospective cohort study, intradialytic exercise for 12 weeks significantly reduced CRP levels from 8.2 ± 1.33 to 5.3 ± 1.309 . In addition, at the end of the study, the mean CRP level in the treatment group was significantly lower compared to the control group (5.3 ± 1.309 vs. 7.7 ± 1.11) [15].

The variable levels of IL-6 and hs-CRP in this study, which are different from those of other studies, can be explained by the following factors: Nutritional factors can affect IL-6 levels in HD patients undergoing intradialytic exercise. Ikizler et al. (2018) conducted an RCT that demonstrated a significant decrease in IL-6 levels in subjects following a strict diet and engaging in intradialytic exercise [19]. This was not observed in the control group of patients. Chronic inflammation that occurs in HD patients is a complex syndrome in which the mechanism is closely related to protein-energy malnutrition, which leads to what is called the malnutrition-inflammatory complex syndrome. Protein malnutrition starts early in chronic renal failure [20]. The researchers could not control nutritional factors as a confounding factor in this study.

Greenwood et al. (2021) explained that ideally in the treatment introduction phase, the minimum cycle duration of intradialytic exercise is 21 min/dialysis session (150 min of moderate intensity exercise/7 days). All patients should be able to cycle for 21 minutes at the end of the first 4 weeks, either using the 2-10 minute formula or continuously [21]. In this study, the total duration of intradialytic exercise per 7 days was 60 minutes.

Fluid overload can also cause increased plasma IL-6 levels in CKD patients [22]. Cardiac disorders such as cardiomegaly can interfere with the normal functioning of the kidneys, weakening their ability to remove sodium from the body and triggering mechanisms that cause fluid retention, resulting in a state of fluid overload [23, 24]. In this study, there were 8 patients (4 patients in the control group and 4 patients in the treatment group) who had

cardiomegaly. In addition, this study did not assess the condition of fluid overload or degree of severity in the research subjects.

The timing of post-treatment blood sampling can affect the levels of various inflammatory markers, including IL-6. However, until now, there has been no standardization of the right time to obtain blood samples from patients undergoing treatment. According to Da Cruz et al. (2018), the best sampling time is 72 hours after the last exercise session to minimize the pseudo-effect of acute exercise, which can temporarily increase IL-6 levels in response to an exercise recently completed by the research subject [11]. CRP can also increase and reach a peak at 28 hours after exercise [25]. Liao et al. (2016) assert that blood sampling can occur without a specific time lag. This study immediately collected post-treatment data after the completion of the last intradialytic exercise session [6].

In this study, the results of the regression test showed that increased IL-6 levels increased the risk of increasing SBP by 7.6 times, and the risk of increasing DBP was 2.4 times higher. However, this difference was not statistically significant. Similarly, hs-CRP levels did not significantly affect SBP and DBP values in the group of patients who underwent intradialytic aerobic cycling exercise for 3 months. Several previous studies have found that high IL-6 levels correlate with the incidence of hypertension [26]. The cytokine IL-6 has a strong association with angiotensin II-induced hypertension through two molecules, namely IL-6R (also known as IL-6R α , gp80, or CD126) and gp130 (also known as IL-6R β , or CD130) [27]. A large number of studies have shown that higher levels of circulating CRP are associated with higher blood pressure [28]. The various factors previously mentioned for SBP, DBP, IL-6, and hs-CRP levels could cause IL-6 and hs-CRP levels in this study to have no significant effect on SBP or DBP. Furthermore, according to Dungey et al. (2017), it is necessary to study soluble inflammatory markers such as IL-6 and CRP in a large-scale cohort study to address the considerable variation in IL-6 and CRP in HD patients, both intra- and inter-individual. This is related to the presence of daily variations in HD patients such as fluid overload, recurrent infections, or the HD procedure itself, so that the use of large-scale cohort studies can detect long-term changes in circulating CRP and IL-6 [16].

This study has several limitations. First, the inclusion and exclusion criteria used were too lax, unlike other intradialytic exercise studies. This is because this study was conducted in only one hospital or educational center, so there is a risk of a limited number of samples if the inclusion and exclusion criteria are too strict. Therefore, further research should be conducted with more stringent inclusion and exclusion criteria.

Second, the researchers could not control the nutritional intake of the participants. We need more research to regulate the participants' nutritional intake.

Third, there were no other laboratory data included in this study that could affect the results, such as triglyceride or blood sugar levels. Further research also needs to be carried out by entering data on other laboratory results, such as triglycerides and blood sugar.

Finally, hemodialysis does not allow for the performance of intradialytic aerobic cycling exercise, which has a longer total duration of 150 minutes/week. Therefore, in future research, it is necessary to perform a longer duration of intradialytic aerobic cycling exercises during hemodialysis.

CONCLUSION

Intradialytic aerobic exercise for 12 weeks did not significantly affect IL-6, hs-CRP, SBP, or DBP.

ACKNOWLEDGMENTS

We thank all those who helped with writing this manuscript.

CONFLICT OF INTEREST

The author declares there is no conflict of interest.

REFERENCES

1. Jager KJ, Kovesdy C, Langham R, Rosenberg M, Jha V, Zoccali C. A single number for advocacy and communication—worldwide more than 850 million individuals have kidney diseases. *Kidney Int* [Internet]. 2019;96(5):1048–50. Available from: <https://doi.org/10.1016/j.kint.2019.07.012>
2. Centers for Disease Control and Prevention. Chronic Kidney Disease in the United States, 2021. Cdc [Internet]. 2021;1:1–6. Available from: <https://www.cdc.gov/kidneydisease/publications-resources/ckd-national-facts.html%0Ahttps://www.cdc.gov/kidneydisease/publications-resources/2019-national-facts.html>
3. PERNEFRI. 11th report Of Indonesian renal registry 2018. *Indones Ren Regist*. 2018;14–5
4. Rocco M V, Daugirdas JT, Greene T, Lockridge RS, Chan C, Pierratos A, et al. Long-term Effects of Frequent Nocturnal Hemodialysis on Mortality: The Frequent Hemodialysis Network (FHN) Nocturnal Trial. *Am J kidney Dis Off J Natl Kidney Found*. 2015 Sep;66(3):459–68.
5. Costa-Hong V, Bortolotto LA, Jorgetti V, Consolim-Colombo F, Krieger EM, De Lima JJG. Oxidative stress and endothelial dysfunction in chronic kidney disease. *Arq Bras Cardiol*. 2009;92(5):413–8.
6. Liao MT, Liu WC, Lin FH, Huang CF, Chen SY, Liu CC, et al. Intradialytic aerobic cycling exercise alleviates inflammation and improves endothelial progenitor cell count and bone density in hemodialysis patients. *Med (United States)*. 2016;95(27).
7. Sovatzidis A, Chatzinikolaou A, Fatouros IG, Panagoutsos S, Draganidis D, Nikolaidou E, et al. Intradialytic cardiovascular exercise training alters redox status, reduces inflammation and improves physical performance in patients with chronic kidney disease. *Antioxidants*. 2020;9(9):1–15.
8. Young HML, March DS, Graham-Brown MPM, Jones AW, Curtis F, Grantham CS, et al. Effects of intradialytic cycling exercise on exercise capacity, quality of life, physical function and cardiovascular measures in adult haemodialysis patients: A systematic review and meta-analysis. *Nephrol Dial Transplant*. 2018;33(8):1436–45.
9. Misra S. Randomized double blind placebo control studies, the “Gold Standard” in intervention based studies. *Indian J Sex Transm Dis AIDS*. 2012 Jul;33(2):131–4.
10. Bankhead C, Aronson J, Nunan D. Attrition bias [Internet]. Catalogue of Bias Collaboration. 2017 [cited 2023 Jun 6]. Available from: <https://catalogofbias.org/biases/attrition-bias/>
11. Da Cruz LG, Zanetti HR, Andaki ACR, Da Mota GR, Neto OB, Mendes EL. Intradialytic aerobic training improves inflammatory markers in patients with chronic kidney disease: A randomized clinical trial. *Motriz Rev Educ Fis*. 2018;24(3):1–5.
12. Pu J, Jiang Z, Wu W, Li L, Zhang L, Li Y, et al. Efficacy and safety of intradialytic exercise in haemodialysis patients: A systematic review and meta-analysis. *BMJ Open*. 2019;9(1).
13. Mahajan S, Zhang D, He S, Lu Y, Gupta A, Spatz ES, et al. Prevalence, Awareness, and Treatment of Isolated Diastolic Hypertension: Insights From the China PEACE Million Persons Project. *J Am Heart Assoc*. 2019 Oct;8(19):e012954.
14. Markoulidakis A, Holmans P, Pallmann P, Busse M, Griffin BA. How balance and sample size impact bias in the estimation of causal treatment effects: A simulation study. 2021; Available from: <https://doi.org/10.21203/rs.3.rs-1742290/v1%0Ahttp://arxiv.org/abs/2107.09009>
15. Elshinnawy HA, Fayeze MM, Farrag DAB, AbdElgawad MAE. The effect of intradialytic exercise on inflammatory markers in hemodialysis patients. *Egypt Rheumatol Rehabil* [Internet]. 2021;48(1):36. Available from: <https://doi.org/10.1186/s43166-021-00084-z>
16. Dungey M, Young HML, Churchward DR, Burton JO, Smith AC, Bishop NC. Regular exercise during haemodialysis promotes an anti-inflammatory leucocyte profile. *Clin Kidney J*. 2017;10(6):813–21

17. Arum Mayangsari J, Subadi I, Nugraheni N, Mardiana N, Thaha M. Effect of Intradialytic Aerobic Exercise on C-Reactive Protein End Stage Renal Disease Patients. *Int J Res Publ.* 2022;94(1):89–94.
18. Soltani P, Saeedi N, Mashaykhi N, Rostami A, Tajfar M. Evaluating the effect of intradialytic exercise on blood pressure, inflammatory markers and dialysis adequacy. *J Prev Epidemiol.* 2020;5(2):e21–e21.
19. Alp Ikizler T, Robinson-Cohen C, Ellis C, Headley SAE, Tuttle K, Wood RJ, et al. Metabolic effects of diet and exercise in patients with moderate to severe CKD: A randomized clinical trial. *J Am Soc Nephrol.* 2018;29(1):250–9.
20. Achinger SG, Ayus JC. Inflammation from dialysis, can it be removed? *Nephrol Dial Transplant.* 2013;28(4):770–3.
21. Greenwood SA, Koufaki P, Macdonald J, Bhandari S, Burton J, Dasgupta I, et al. The PrEscription of intraDialytic exercise to improve quAlity of Life in patients with chronic kidney disease trial: study design and baseline data for a multicentre randomized controlled trial. *Clin Kidney J.* 2021;14(5):1345–55.
22. Su H, Lei CT, Zhang C. Interleukin-6 signaling pathway and its role in kidney disease: An update. *Front Immunol.* 2017;8(APR):1–10.
23. Miller WL. Fluid volume overload and congestion in heart failure. *Circ Hear Fail.* 2016;9(8):1–9.
24. Rangaswami J, Bhalla V, Blair JEA, Chang TI, Costa S, Lentine KL, et al. Cardiorenal Syndrome: Classification, Pathophysiology, Diagnosis, and Treatment Strategies: A Scientific Statement From the American Heart Association. Vol. 139, *Circulation.* 2019. 840–878 p.
25. Cerqueira É, Marinho DA, Neiva HP, Lourenço O. Inflammatory Effects of High and Moderate Intensity Exercise—A Systematic Review. *Front Physiol.* 2020;10(January):1–14.
26. Agita A, Thaha M. Inflammation, Immunity, and Hypertension. *Acta Med Indones.* 2017;49(2):158–65.
27. Senchenkova EY, Russell J, Yildirim A, Granger DN, Gavins FNE. Novel role of T cells and IL-6 (interleukin-6) in angiotensin II-induced microvascular dysfunction. *Hypertension.* 2019;73(4):829–38.
28. Smith GD, Lawlor DA, Harbord R, Timpson N, Rumley A, Lowe GDO, et al. Association of C-reactive protein with blood pressure and hypertension: Life course confounding and Mendelian randomization tests of causality. *Arterioscler Thromb Vasc Biol.* 2005;25(5):1051–6.