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The effect of low-intensity intradialytic cycling aerobic exercise on cognitive function in patients undergoing continuous hemodialysis

Andi Sulistyo Saputrana[1,2], I Putu Alit Pawana[1,3], Lydia Arfianti[1,4], Mochammad Thaha[1,5], Atika Atika[6]

[1]Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
[2]Department of Physical Medicine and Rehabilitation, Dr. Soetomo General Hospital, Surabaya, Indonesia
[3]Sport Injury Rehabilitation Division, Department of Physical Medicine and Rehabilitation, Dr. Soetomo General Hospital, Surabaya, Indonesia
[4]Musculoskeletal Rehabilitation Division, Department of Physical Medicine and Rehabilitation, Dr. Soetomo General Hospital, Surabaya, Indonesia
[5]Molecular Cardio-Nephrology, Renal Health and Disease, Department of Internal Medicine, Dr. Soetomo General Hospital, Surabaya, Indonesia
[6]Department of Public Health and Preventive Medicine, Faculty of Medicine, Airlangga University, Surabaya, Indonesia

Andi Sulistyo Saputrana **ORCID ID:** 0009-0006-9858-3292

ABSTRACT

Background. End-stage renal disease (ESRD) patients often experience neurological complications. Mounting evidence suggests cognitive impairment associated with end-stage renal disease is likely related to vascular disruption in the brain, particularly in white matter integrity. Hemodialysis is an independent risk factor for mild cognitive decline (MCD) of ESRD patients and have serious implications for the quality of life. Intradialysis training is the most ideal choice for hemodialysis patients, because not requiring extra time and the patient is also under the supervision of a doctor when doing the exercises.

Method. Eighteen patients with end-stage renal disease (ESRD) were randomized into two groups: a treatment group and a control group, with 9 patients in each group. The treatment group participated in low-intensity aerobic exercise on a cycle ergometer, consisting of two 30-minute sessions per week for 12 weeks. Both groups were instructed to continue their regular hemodialysis and medication regimen. MoCA-INA scores were measured before the intervention and again after 12 weeks for both groups. Comparisons of MoCA-INA scores were made within each group as well as between the two groups before and after the 12-week intervention.

Results. In the treatment group, the MoCA-INA scores showed a significant improvement from baseline to after the intervention ($p < 0.001$; effect size = 1.88). In contrast, the control group did not exhibit a significant change in MoCA-INA scores ($p = 0.468$). Additionally, there was a significant difference in the change in MoCA-INA scores between the treatment and control groups after 12 weeks of intervention ($p = 0.001$).

Keywords: end-stage renal disease, cognitive function, intradialysis exercise

Abbreviations (in alphabetical order):

AVF	– arteriovenous fistula
BDNF	– brain derived nerve factor
CRP	– C-reactive protein
ESRD	– end-stage renal disease
IL-6	– Interleukin-6
MCD	– mild cognitive decline
MMSE	– mini mental state examination
MoCA-INA	– Montreal Cognitive Assessment Indonesia Version
NYHA	– New York Heart Association
TIA	– transient ischemic attack
TNF-alpha	– tissue necroting factor

Corresponding author:
Andi Sulistyo Saputrana
E-mail: asaputrana@gmail.com

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INTRODUCTION

Neurological complications are a common issue for patients with end-stage renal disease (ESRD). This is the condition that gives the nervous system damage. Generally neurovascular patients show worsened neurological symptoms. These however have not been the only the symptoms of change with cases of neuro-DAD. This is because the highly intensified oxidative stress being elevated in ESRD leads to cell injury and CNS complications [1]. This dysregulation leads to comorbid with pathogenetic factors like mineral metabolism implied in these complicated conditions. Commonly neurological disparities in the ESRD include stroke, cognitive deficits, encephalopathy, peripheral and autonomic neuropathy. The condition also affects not only the patient's life quality but also by the risk of mortality through several mechanisms. ESRD is responsible for decreasing nervous functions and increments in fast-growing frailty, vasculature dysfunction as well as augmentation of IL-6, and memory impairment. The increasing body of evidence however raises the possibility that cognitive impairments associated with the ESRD are more likely to the cause of the vascular changes in the brain (specifically degrading the white matter). These symptoms of cognitive impairment which are low levels of physical function, increased endothelial dysfunction, and decreased cognitive function link with weaker syndrome of frailty, poor quality of life, severe sickness, and death [2].

Hemodialysis is a potential cause for mild cognitive decline (MCD) and endangers the lifestyle of ESRD patients [3]. This was the reason for the extended hospital stays and the deaths of many people because of the discomfort it was inflicting it might be pertinent to say that. Be that as it may so far, the pathogenesis of HDPMCD has not been completely revealed to us[4]. An impaired cognitive function, particularly the executive function in the ESRD patient, is one of the risks that get aggravated with the regular hemodialysis by the retention of uremic toxins and recurrent cerebral ischemia in addition to the progression of the patient to the point of the inactive individual. Throughout the continuum of such patients, impairments such as the diminishing of cognition can result in long-term consequences like dementia and death. Exercise training at home, as well as during intradialysis, is a non-pharmacological intervention that is known to maintain cognitive function in ESRD patients [5].

According to Kurella (2010) the cognitive impairment rate among ESRD patients seen in clinical practice is approximately 23 – 28% (n = 80) [6]. Most of the studies published are by Murray (2006) who reported that those receiving dialysis have a prevalence of cognitive impairment that ranged from 20-50% and older patients up to 70% [7]. The reported prevalence of cognitive impairment in dialysis is estimated to be between 40%, but less than 3% of patients are clinically documented as having cognitive impairment [8]. This is evidence that cognitive impairment actually occurs in some ESRD sufferers, but is often undetected.

Intradialysis training is the most ideal choice for hemodialysis patients, because not requiring extra time and the patient is also under the supervision of a doctor when doing the exercises. Intradialysis exercises can also increase solute removal. Aerobic exercise with a cycle ergometer can be done when the patient is undergoing hemodialysis without disturbing the arteriovenous fistula (AVF) in the hand connected to the hemodialysis device [9]. Regular exercise in patients with end-stage renal disease (ESRD) is associated with enhanced dialysis effectiveness and better health-related quality of life. It also helps lower systolic blood pressure, reduce arterial stiffness, and alleviate depression in these patients [10-11]

Intradialytic exercises are often recommended to encourage physical activity among hemodialysis patients. Studies have shown that such exercises effectively reduce fatigue, improve sleep quality, enhance exercise tolerance, and boost both quality of life and psychological well-being. Additionally, research indicates that intradialytic exercise can enhance dialysis efficacy, decrease inflammation, and improve nutrition and bone density [12-13].The intradialysis exercise approach can improve health by efficiently saving time, increasing patient compliance and maximizing the dialysis time period. The researcher aimed to assess cognitive function in ESRD patients on continuous hemodialysis by providing low-intensity intradialysis aerobic exercise intervention. Participants will engage in aerobic exercise on a cycle ergometer twice a week for 30 minutes per session over a period of 24 weeks [14-18]. The outcomes of this intervention will be compared to those of a control group. This study is very important because, it is related to the frequency of dialysis in almost all hospitals in Indonesia which is only 2 times per week. Low intensity intradialysis aerobic exercise is expected to have the same effect as the standard 3×/week exercise prescription.

MATERIALS AND METHODS

This study is a randomized controlled trial using a pre-test and post-test group design. It was conducted at the Hemodialysis Unit at Dr. Soetomo General Hospital, Surabaya, Indonesia, from March to June 2021. Ethical approval was obtained from the Hospital Ethical Committee with the ethical clearance number 0153/KEPK/II/2021.

The study involved 18 ESRD patients selected through consecutive sampling.

Inclusion criteria

The inclusion criteria were: 1) Age between 20 and 50 years, 2) Undergoing routine hemodialysis for at least 3 months, 3) Systolic blood pressure between 110 and 160 mmHg and diastolic pressure between 70 and 90 mmHg, 4) Mild cognitive impairment (Montreal Cognitive Assessment Indonesia Version / MoCA-INA Score 18 - 26), and 5) Voluntary participation by signing an informed consent form.

Exclusion criteria

The exclusion criteria included: 1) Currently participating in a regular aerobic exercise program twice a week; 2) Ischemic heart disease; 3) Class III and IV heart failure according to the New York Heart Association (NYHA) classification; 4) Suspected new stroke or Transient Ischemic Attack (TIA); 5) Hemoglobin <8 mg/dL; 6) Erythema, wounds, ulcers, or gangrene on one or both legs; 7) Limited range of motion in both knees for flexion of more than 45°, extension of more than 10°, hip flexion of more than 45°; 8) Neuromusculoskeletal disease in the lower limbs that interferes with ambulation function; 9) Patient cannot ambulate independently; 10) Uncontrolled hyperglycemia (random blood sugar ≥250 mg/dL); 11) Moderate to severe cognitive impairment; 12) Peripheral polyneuropathy disability degree >4 overall neuropathy disability score; 13) Severe visual impairment; and 14) COVID-19 patients either with or without symptoms (did not pass Dr Soetomo Hospital's COVID screening).

Criteria for drop out were: 1) Not willing to continue the research for any reason; 2) Unable to complete the training according to the established research protocol; and 3) If there are more than two absences from training in a row or a total absence of more than 20% of attendance (maximum 3 times absent from practice). Simple randomization performed to divide subjects into treatment group (n=9) and control group (n=9).

The treatment group engaged in low-intensity aerobic exercise using a cycle ergometer during the first two hours of hemodialysis. The target heart rate was calculated as the resting heart rate plus 30-39% of the resting heart rate, and the activity level was set at 11-12 on the Borg scale. Each exercise session included a 5-minute warm-up, a 20-minute main exercise phase, and a 5-minute cool-down. Participants were introduced to the training protocol during the first session. The intervention consisted of two sessions per week for 12 weeks, with each session lasting 30 minutes, comprising a 5-minute warm-up, 20-minute main exercise, and 5-minute cool-down. The intensity of the aerobic exercise was measured using the target heart rate formula (resting heart rate + 30% resting heart rate) and an activity level of 11-12 on the Borg scale.

Both groups were instructed to continue their hemodialysis and medication regimen as prescribed by their internists. The MoCA-INA scores were measured before the intervention and after 12 weeks for both groups. The MoCA-INA scores were compared within each group and between both groups before and after the 12-week intervention. Data analysis was performed using SPSS version 26. A paired t-test was used to compare the MoCA-INA scores within each group before and after the intervention, while an independent t-test was used to compare the MoCA-INA scores between the two groups before and after the intervention. A p-value of less than 0.05 was considered statistically significant.

RESULTS

At the end of the study, 18 subjects were analyzed. All subjects were able to continue until the end of the study. The subjects consisting of 55.6% (10 subject) male and 44.4% (8 subject) female. The exercises given can be tolerated by the subject. There were no exacerbations in the intervention group during the study period. The monitoring of adverse events reported that there was 1 subject in the treatment group and 1 subject in the control group who complained of muscle cramps after the intervention. Characteristic of the subject is shown on Table 1.

TABLE 1. Characteristic of subjects

Characteristic	Total n= 18	Group		p
		Treatment (n=9)	Control (n=9)	
Age (Years)	38.00 ± 5.07[e]	36.56 ± 4.61[e]	39.44 ± 5.36[e]	0.238[a]
Sex				0.637[c]
Male	10 (55.6%)	6 (66.7%)	4 (44.4%)	
Female	8 (44.4%)	3 (33.3%)	5 (55.6%)	
Education				0.491[b]
• Elementary School	4 (22.2%)	2 (22.2%)	2 (22.2%)	
• Junior High School	1 (5.6%)	-	1 (11.1%)	
• Senior High School	12 (66.7%)	6 (66.7%)	6 (66.7%)	
• Bachelor	1 (5.6%)	1 (11.1%)	-	
Hb (g/dl)	10.29 ± 1.49[e]	11.17 ± 1.39[e]	9.41 ± 1.03[e]	0.008[a]
MoCA-INA (pre-intervention)	23.50(19-26)[d]	23.00(19-25)[d]	24.00 (20-26)[d]	0.392[b]
Duration of Hemodialysis (years)	4.06 ± 2.26[e]	3.77 ± 1.7[e]	4.36 ± 2.79[e]	0.590[a]

[a]Independent t test, significant if p <0.05
[b]Mann – Whitney U test, significant if p <0.05
[c]Fisher Exact test, significant if p <0.05
[d]Median (min-max)
[e]Mean ± SD

TABLE 2. MoCA-INA score before and after intervention

Group	Pre (Mean ± SD)	Post (Mean ± SD)	p
Control Group (n = 9)	23.44 ± 2.29	24.00 ± 2.64	0.468
Treatment Group (n = 9)	22.56 ± 2.65	27.56 ± 2.29	< 0.001*

**) Paired t test, significant if p <0.05*

TABLE 3. Comparison of ΔMoCA-INA score between groups

	Control (n = 9)	Treatment (n = 9)	p
ΔMoCA-Ina Score	1 ± 2.18	4 ± 2.64	0.001*

**) Independent t test, significant if p <0.05*

Table 2 shows that the MoCA-INA scores before and after the intervention in the treatment group showed a significant difference (p = 0.000; effect size = 1.88), while the control group did not show a significant difference (p = 0.468). Table 3 shows a significant difference in the delta of MoCA-INA scores between two groups (p = 0.001).

DISCUSSION

This is the initial research conducted at RSUD Dr. Soetomo Surabaya that aimed to evaluate effect of low-intensity intradialytic cycling exercise on the cognitive function of patients undergoing continuous hemodialysis. Author have not found a standard protocol regarding intradialysis exercise at Dr. Soetomo Regional Hospital, so author create exercise procotol based on several studies related to intradialysis aerobic exercise[5,19–21]. In this study a lower frequency and intensity protocol was used than the protocols used in previous studies considering hemodialysis schedule at RSUD Dr. Soetomo twice per week and considering the safety of regular hemodialysis patients who have sufficient susceptibility.

The positive impact of intradialytic exercise on hemodialysis patients is well-documented. While previous research has explored aerobic exercise during hemodialysis and its effects on cognitive function, no studies have evaluated its impact on cognition in ESRD patients following the specific exercise protocol used in this study. This study found that after 12 weeks of intradialytic cycling aerobic exercise, the treatment group showed significant improvements in cognitive function compared to the control group. This improvement in general cognitive function was statistically significant and had a large effect size. The findings align with prior research indicating that intradialytic aerobic exercise can prevent cognitive decline related to executive function caused by residual uremia [6,22]. It also helps prevent short-term decreases in psychomotor speed and executive function, with potential greater benefits over a longer duration[19].Another study found that intradialytic exercise enhances cerebral blood flow and cognitive function in hemodialysis patients, suggesting a possible mechanism for mitigating cognitive impairment through physical exercise [20]. Aerobic exercise improves executive function by increasing cerebral blood flow, brain volume in critical areas such as the pre-frontal cortex and hippocampus, Brain-Derived Neurotrophic Factor (BDNF), and neural structure. It also reduces inflammatory biomarkers like C-reactive protein (CRP), Tissue Necrosis Factor (TNF-alpha), and Interleukin-6 (IL-6), thereby enhancing brain plasticity and executive function [5,23]

ESRD patients undergoing regular hemodialysis often experience reduced vascular function, arterial stiffness, systemic inflammation, and increased cognitive impairment. Cognitive decline in these patients is often linked to vascular issues in the brain, particularly affecting white matter integrity [24]. The combination of poor physical function, vascular dysfunction, and cognitive impairment increases the risk of losing independence, reduced quality of life, and higher morbidity and mortality. Factors such as uremic toxin retention, recurrent cerebral ischemia, and sedentary lifestyles exacerbate cognitive impairment in these patients [25].

Intradialytic aerobic exercise is a proven non-pharmacological intervention for maintaining overall cognitive function. A study by Stringuetta-Belik (2018) analyzed the effects of intradialytic aerobic exercise using a cycle ergometer during the first two hours of hemodialysis sessions, lasting 30 minutes, three times a week, over four months. The treatment group's Mini Mental State Examination (MMSE) scores improved significantly, from an average of 24.0 ± 3.00 at the beginning to 26.4 ± 2.92 at the end of the intervention [20]. This study also observed increased blood flow velocity in the basilar artery and other cerebral arteries, indicating enhanced cerebral blood flow and a potential mechanism for cognitive function improvement [26]. Increased cerebral blood flow may trigger neurobiological changes such as angiogenesis, neurogenesis, synaptogenesis, and neurotransmitter synthesis, which are associated with improved cognition [27-28]

The initial analysis showed no significant difference in MoCA-INA scores between the two groups (p=0.392). However, by the end of the study, the changes in MoCA-INA scores between the groups were significantly different (p=0.001). This finding is consistent with Stringuetta-Belik's (2018) study, which also reported significant cognitive improvements in the intervention group compared to the control group, as reflected by MMSE scores (p=0.001). Additionally, McAdams-DeMarco (2017) found that hemodialysis patients receiving standard care experienced a greater decline in cognitive functions (executive and psychomotor) than those engaging in intradialysis aerobic exercise (p=0.30) [19]. These studies further validate the cognitive benefits of intradialysis aerobic exercise protocols, demonstrating their effectiveness in preventing cognitive decline and enhancing cognitive function compared to control groups.

In this study, it was observed that two participants experienced mild side effects. One participant from the treatment group and one from the control group reported experiencing leg muscle cramps after exercising. This indicates that both groups had an equal likelihood of experiencing mild side effects, which could be attributed to either the exercise, the hemodialysis treatment, or the symptoms of comorbid conditions. Muscle cramps in hemodialysis patients are the most frequently experienced side effect of hemodialysis. Goudarzian (2015) reported the side effects that can occur during hemodialysis include muscle cramps (72.53%), itching (59.5%), headache (43.6%), back pain (29.57%), hypotension (19.7%), chest pain (14%), shortness of breath (7.04%), nausea and vomiting (6.35%) [29].

In this study, intradialytic cycling exercise has proven to be safe for participants and yields significant positive outcomes. A systematic review and meta-analysis conducted by Pu in 2019 evaluated the safety and effectiveness of intradialytic exercise. Among the 27 randomized controlled trials (RCTs) analyzed, two reported side effects associated with intradialytic exercise, 13 reported no side effects, and 12 did not mention side effects at all. The meta-analysis also demonstrated that intradialytic exercise enhances dialysis adequacy, likely by promoting better circulation and facilitating the removal of toxins and excess water through the dialyzer. Improved dialysis adequacy is linked to lower mortality rates [30].

This study has limitation, including several confounding variables that cannot be controlled, such as exercise outside of hemodialysis, and comorbidities that can influence the MoCA-INA score variable in this study.

CONCLUSION

This study at RSUD Dr. Soetomo Surabaya evaluated the impact of low-intensity intradialytic cycling exercise on cognitive function in ESRD patients undergoing hemodialysis. Implementing a novel exercise protocol tailored to the hospital's schedule, the research found that after 12 weeks, the treatment group exhibited significant improvements in MoCA-INA scores compared to the control group, indicating enhanced cognitive function with a large effect size (p = 0.001; effect size = 1.88). Despite two participants experiencing mild muscle cramps, the exercise was well-tolerated and demonstrated significant benefits, supporting the use of intradialytic aerobic exercise as an effective and safe intervention to improve cognitive function in this patient population.

Authors' contributions:

Conceptualization: ASA, IPAP, LA, MT. Data curation: ASA, IPAP, LA, MT. Methodology: ASA, IPAP, LA, MT, AA. Project administration: ASA. Visualization: ASA. Writing - original draft: ASA. Writing - review and editing: ASA, IPAP, LA, MT, AA. All authors have read and approved the submitted manuscript. The manuscript has not been submitted elsewhere nor published elsewhere in whole or in part.

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