Randomized Controlled Trial of Intradialytic Cognitive and Physical Training to Enhance Functional Capacity

Špela Bogataj[1,2], Maja Pajek[2], Aljaž Kren[2,3], Katja Kurnik Mesarič[1] and Jernej Pajek[1,4]

[1]Department of Nephrology, University Medical Centre Ljubljana, Ljubljana, Slovenia; [2]Faculty of Sport, University of Ljubljana, Ljubljana, Slovenia; [3]Faculty of Health Sciences, University of Novo mesto, Novo mesto, Slovenia; and [4]Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

Introduction: Hemodialysis (HD) patients frequently experience cognitive and physical impairments due to various factors, including age, comorbidities, and the demanding nature of the treatment. This study explores the impact of a 12 week integrated cognitive and physical training program on the functional capacity of patients on HD.

Methods: A single blind, randomized controlled trial was conducted with 44 patients on HD. Participants were divided into an experimental (EXP) group that received a combined intervention of intradialytic cycling and cognitive training, and a control (CON) group receiving standard HD treatment. The Trail Making Test (TMT), Timed Up and Go (TUG) test, and TUG dual task test (TUG-dual) were conducted before and after the intervention.

Results: The EXP group demonstrated significant improvements in cognitive function, as evidenced by decreased TMT completion times (TMTA: −3.6 s, $P = 0.006$; TMTB: −14.0 s, $P < 0.001$; TMTB − TMTA: −10.4 s, $P = 0.004$). In contrast, the CON group experienced a significant decline in TMTA and TMTB. In addition, the EXP group exhibited enhanced mobility, with reduced TUG completion times (−0.8 s, $P < 0.001$) and improved cognitive motor performance in the TUG-dual (−1.0 s, $P < 0.001$), whereas the CON group showed no significant changes.

Conclusion: This study demonstrates that a 12 week combined cognitive and physical training program during HD sessions significantly enhances cognitive function and mobility in patients on HD. These findings suggest that integrated interventions can mitigate functional declines in this population and improve their overall quality of life. Further research with larger samples and active control groups is warranted to confirm and expand upon these promising results.

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It is well documented that patients with chronic kidney disease who are treated with HD have impaired cognitive and physical functioning.[1] This occurs naturally due to the biological aging of the HD population, but it is also induced or aggravated due to the disease itself and the physically demanding HD treatment.[2,3]

There is an abundance of studies that show that patients on HD have been successful in at least partly countering this impaired functional capacity by integrating physical exercise either on dialysis or non-dialysis days.[4] For example, a physical exercise program in the form of aerobic and resistance training improved performance on TUG,[5,6] 60 second sit-to-stand test,[6] and hand grip strength test[5] in comparison to the control group. From those studies, only a few also looked at how the physical exercise intervention affected cognitive functioning. The outcomes were inconsistent. The study of Manfredini *et al.*[7] demonstrated an improvement in self reported cognitive function measured by the kidney disease quality of life questionnaire in patients on HD after the 6 month walking program. Patients who participated in 4 months intradialytic cycling program demonstrated a notable decrease in cognitive impairment in contrast to the control group.[8] On the contrary, trials which studied 6 months of low intensity intradialytic resistance exercise,[9] 12 weeks home based aerobic and resistance exercise,[10] and a 12 weeks chair stand exercise program[11] did not observe an effect on cognitive function in patients on HD.

Correspondence: Špela Bogataj, Department of Nephrology, University Medical Centre Ljubljana, Zaloška cesta 7, 1000 Ljubljana, Slovenia. E-mail: spela.bogataj@kclj.si

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Lately, cognitive training has been introduced as a new approach in geriatric research with the aim of mitigating functional (cognitive and physical) decline.[12-14] These studies mostly include frail and sedentary older adults and showed significantly positive results.[15-17]

Until now, the effects of cognitive training, alone or in conjunction with other nonpharmacological interventions in patients on HD remain understudied. We could find only 1 feasibility study[18] that tested the effects of intradialytic cognitive training ($n = 7$) or intradialytic cycling ($n = 6$) on cognitive performance in patients on HD compared with the standard care control group ($n = 7$). At the end of a 12 week intervention, the control group experienced a decline in executive function and psychomotor speed, whereas this deterioration was not observed in either intervention group. The results of the study therefore suggest that cognitive decline in these patients could be prevented by cognitive or physical exercise training. Although this is a very promising outcome, the sample size and consequent lack of statistical power hinder further generalizability and indicate the need for studies incorporating larger samples sizes and potentially, the combination of physical and cognitive interventions.

Considering that patients with chronic kidney disease often suffer progressive cognitive impairments while on renal replacement therapy,[19] and that these impairments can cause a further deterioration of mobility, improving or at least preserving cognitive abilities could potentially benefit patients' physical capacity. Considering that the above mentioned pilot study showed promising results from both cognitive and physical training interventions, it would be interesting to additionally investigate their synergetic effects. The aim of the present study was to study the effects of combined cognitive and physical exercise training on executive functions, mobility, cognitive flexibility, and cognitive motor interactions in patients on HD.

METHODS

Study Design

The current study was a single blind, randomized controlled trial designed to evaluate the effects of a bimodal nonpharmacological intervention on cognitive and physical performance in patients on HD. Participants were recruited at a local dialysis center in Ljubljana, Slovenia. To be eligible for the study, patients had to be on HD renal replacement therapy for more than 3 months, have a stable medical condition, have no neurological diseases, and be able to walk independently. Patients with active malignant or infectious disease, uncontrolled hypertension, angina (rating 2–4 on the Canadian Cardiovascular Society scale), heart failure (rating 3–4 on the New York Heart Association scale), severe cognitive impairment or dementia, a history of limb amputation, or any other condition that could render them clinically unstable were excluded from the study. The study strictly adhered to the ethical principles of the Declaration of Helsinki and was approved by the National Medical Ethics Committee (KME 0120-474/2021/4) of the Republic of Slovenia. Before enrollment in the study, all participants provided written informed consent. The clinical trial was duly registered at ClinicalTrials.gov under the identifier NCT05150444.

Participants

The flow of the study is presented in Figure 1. Out of the initial 72 individuals who were screened for eligibility, 44 were randomly assigned to either the EXP or CON group. The final analysis included all patients from the EXP group. In the CON group, 1 patient was lost to all final assessments (due to transfer to another dialysis center), and an additional patient was excluded from TUG tests only (due to mobility problems resulting from a fall in their home environment). Baseline characteristics of included patients are presented in Table 1.

Study Flow and Protocol

The current paper is part of a more comprehensive study protocol that is described in Bogataj et al.[12,20] After screening, all eligible patients who consented to participate underwent an initial test. They were then randomly assigned in a 1:1 ratio to either the EXP or CON group via an online program (www.randomization.com). Patients in the EXP group participated in a 12 week intervention that included sequential physical exercise and cognitive training, with 3 training sessions per week, resulting in a total of 36 training sessions. Patients in the CON group received standard HD treatment. After the intervention phase, all patients were reassessed for the same outcomes as at baseline. Assessments were performed on nondialysis days, always on the same day of the week and at the same time of day. The end point outcome assessors remained blinded to treatment allocation. However, because of the nature of the intervention, it was not possible to blind subjects or their HD providers.

Physical Exercise Training

In the EXP group, aerobic exercise was incorporated into the dialysis routine in the form of cycling sessions

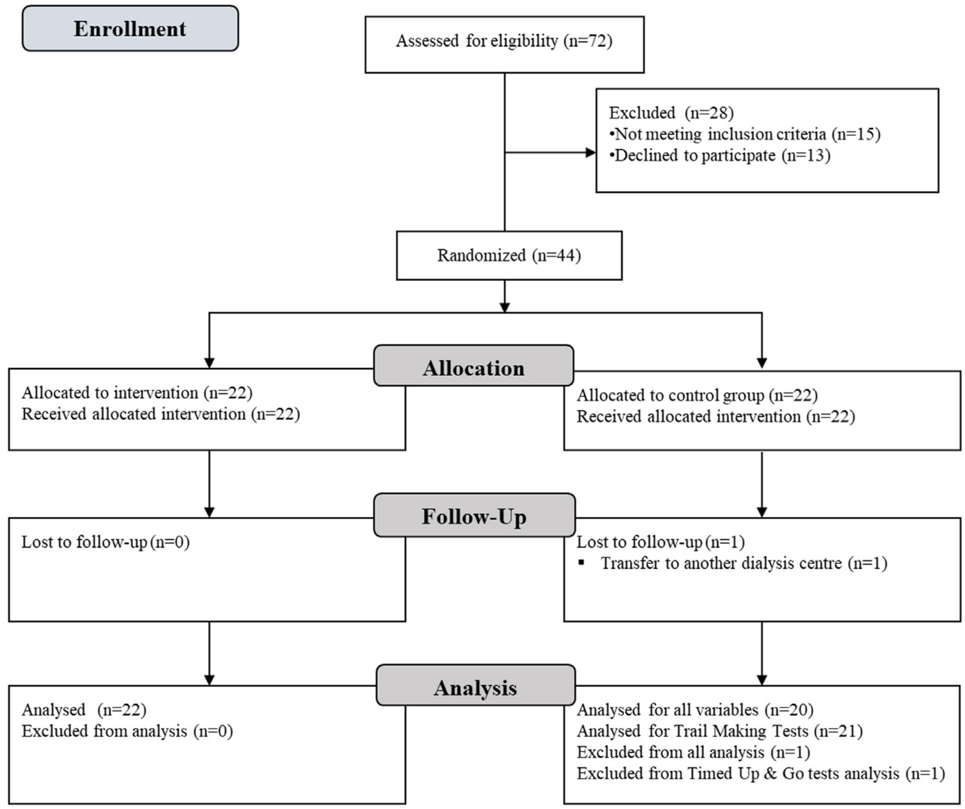

Figure 1. Study flow diagram.

on a customized bed ergometer (BedBike, Lemco, Denmark). These exercise sessions were delivered 3 days a week, lasting for 12 weeks, and took place within the first 2 hours of dialysis. Each session followed a structured format, starting with a 5 minute warm up and concluding with a 5 minute cool down. During the middle part of the exercise session, the aim was to achieve an exercise duration of ~30 minutes. The resistance level was individually tailored based on each participant's rate of perceived exertion, while maintaining an intensity level of 5 on a 10 point Borg scale. This approach was demonstrated to be effective in this particular patient population.[4,21]

Cognitive Training

Following the cycling session, patients in the EXP group engaged in a 30 to 40 minute cognitive training session.[14] Cognitive training was administered via

Table 1. Demographic and clinical characteristics

Characteristics	All participants (N = 44)	Intervention group (n = 22)	Control group (n = 22)	P value
Age (yr)	66.5 ± 11.0	65.7 ± 9.7	67.2 ± 12.5	0.658
Male sex (%)	66%	54%	77%	0.117
Height (cm)	170.3 ± 11.4	169.6 ± 12.5	171.0 ± 10.5	0.687
Weight (kg)	75.6 ± 18.3	77.1 ± 21.9	74.2 ± 14.3	0.595
Dialysis vintage (yr)	6.6 ± 6.1	7.1 ± 7.6	6.1 ± 4.3	0.593
Phase angle (°)	4.4 ± 0.8	4.6 ± 0.8	4.3 ± 0.8	0.242
BIA assessed overhydration (l)	2.2 ± 1.6	1.8 ± 1.6	2.6 ± 1.6	0.108
Hemoglobin (g/l)	113.3 ± 12.4	110 ± 12.7	116.6 ± 11.4	0.094
Albumin (g/l)	36.7 ± 2.8	37.0 ± 2.2	36.3 ± 3.3	0.250
C-reactive protein (mg/l)	5.3 ± 5.5	4.4 ± 3.7	6.1 ± 6.9	0.263
Systolic blood pressure (mm Hg)	156 ± 22	160 ± 22	151 ± 22	0.187
Diastolic blood pressure (mm Hg)	87 ± 11	88 ± 13	85 ± 9	0.470
Charlson comorbidity index	5.7 ± 2.2	5.7 ± 2.5	5.6 ± 1.8	0.837
MoCA (score)	24.7 ± 2.8	25.0 ± 2.8	24.3 ± 2.9	0.433

BIA, bioimpedance performed using Body Composition Monitor; Fresenius AG, Bad Homburg, Germany; MoCA, Montreal Cognitive Assessment.
The data is presented as mean ± SD, percentage of subjects, or index. No statistically significant differences were observed between the groups. Phase angle measurements were conducted using an 800 µA current at a frequency of 50 kHz.

tablets, delivering a variety of games that targeted different cognitive subcategories. Each patient had a personalized profile on the CogniFit platform (CogniFit INC; San Francisco, CA), allowing the software to dynamically adjust the game difficulty according to individual performance. This flexible approach ensured that the participants were consistently challenged without feeling overwhelmed. For our study, we chose the Personalized Brain Training package, which is designed to improve a wide range of cognitive skills, including memory, executive functions, perception, reasoning, attention, coordination, visual and spatial skills.

Throughout the sessions, research assistants supervised and assisted the participants, facilitating program initiation, and ensuring that the patients comprehended the instructions for each game. For each new game, the system automatically generated a familiarization trial.

Outcome Measures

As indicated, the current paper is part of a much larger study from which the outcome measures were assessed before and after the 12 week intervention. The results of the primary outcome measure, the Alertness score of the Test of Attentional Performance, were published in Bogataj *et al*.[22] In the current paper, focus is on the following outcome measures: TMT A and B (TMTA and TMTB), TUG test, and the TUG-dual. Other secondary outcome measures of the whole protocol were reported earlier[22-24]: Montreal Cognitive Assessment, Symbol Digit Modalities Test, 10 repetition sit-to-stand test, stork balance test, hand grip strength test, spontaneous gait speed, frailty, bioimpedance analysis, quality-of-life, brain derived neurotrophic factor, C-reactive protein, and interleukin-6. The safety parameters were urea, creatinine, sodium, potassium, hemoglobin, hematocrit, self reported falls, and musculoskeletal injuries.

TMT consisted of 2 parts (TMTA and TMTB). It assessed cognitive function, more specifically visual search speed, processing speed, attention, mental flexibility, and executive function.[25-27] Each part of the test consisted of a sample (as a familiarization) and an actual test. The test was timed, and the time required (in seconds) to complete the test represented the score on the test, with a higher score indicating worse cognitive functions. Errors have to be corrected immediately. The test was performed in a paper-and-pencil form.[25-27] The TMTA consisted of 25 randomly arranged numbers (from 1–25) in circles. The participant had to connect numbers in an ascending order, as quickly as possible. The test assessed visual search and psychomotor speed skills.[25,26] The TMTB consisted of 25 circles containing numbers (from 1–13) and letters (from A–L). The participant had to alternate between numbers and letters in a consecutive order, as quickly as possible. The test assessed mental flexibility and executive functions.[25,26] The TMTA and TMTB tests were conducted on an individual basis by a psychologist in a calm and undisturbed environment. The protocol included clarifying the test's objectives, providing directions, assisting participants with the familiarization sample, and initiating the actual assessment. Cognitive flexibility was calculated by subtracting the TMTA from the TMTB score (TMTB − TMTA). This measure was relatively independent of motor skills. A higher score indicated worse cognitive flexibility.[18,28]

The TUG test was used to assess functional mobility of the patient.[29] During this assessment, participants were instructed to rise from a chair, walk a distance of 3 m, and then return to the seated position. The completion time for the task was measured in seconds, considering the average time taken from 2 attempts.

The TUG-dual required the subject to perform the TUG while subtracting numbers backward in 3s in order to examine cognitive motor interactions. The starting number was different at pretesting and posttesting. The results were recorded in seconds from a single attempt.

Statistics

Statistical analysis was carried out using IBM SPSS statistical software version 29 (IBM Corporation, USA). Normality was confirmed using the Shapiro-Wilk test, with additional visual inspection. A repeated measures analysis of variance (2 × 2) with randomized group (EXP vs. CON) as between subject factor, and time (pretest and posttest) as a within subject factor was performed on both TMT and TUG tests. A paired samples *t* test was used to determine within group differences over time. The study used an intention-to-treat analysis. This approach ensured that all randomized patients who were eligible for final testing were included in the analysis, regardless of whether they received the intervention.

Cohen's *d* effect size was used to determine the magnitude of observed differences for each group. Effect sizes between 0.2 and 0.5 were categorized as small, effect sizes between 0.5 and 0.8 were considered moderate, and effect sizes greater than 0.8 were regarded as large.[30] The sample size calculation is described in a study protocol paper.[20]

RESULTS

During the study, no musculoskeletal injuries occurred. In the CON group, 1 patient experienced a fall in the home environment.

Table 2. Pre-TMT and post-TMT results per group

Variable	Group	Pretest	Posttest	Mean change (95% CI)	*P* value	ES
TMTA (s)						
	EXP ($n = 22$)	63.6 ± 29.8	60 ± 29.9	−3.6 ± 5.5 (−6.1 to −1.2)	0.006	0.12
	CON ($n = 21$)	64.9 ± 36.8	71.5 ± 38.6	6.6 ± 10.5 (1.8–11.3)	0.009	0.17
TMTB (s)						
	EXP ($n = 22$)	158.7 ± 77.3	144.7 ± 73.2	−14.0 ± 17.2 (−21.7 to −6.4)	< 0.001	0.19
	CON ($n = 21$)	163.0 ± 91.6	170.0 ± 88.8	7.0 ± 13.4 (0.9–13.1)	0.026	0.08
TMTB − TMTA (s)						
	EXP ($n = 22$)	95.1 ± 55.6	84.7 ± 49.9	−10.4 ± 15.2 (−17.1 to −3.7)	0.004	0.20
	CON ($n = 21$)	98.1 ± 67.8	98.5 ± 59.4	0.4 ± 17.9 (−7.7 to 8.6)	0.914	0.01

CI, confidence interval; CON, control group; ES, Cohen's d effect size; EXP, experimental group; TMTA, Trail Making Test A; TMTB, Trail Making Test B.
Values are expressed as mean ± SD.

Compliance to Training Interventions

Compliance with the cycling and cognitive training programs was calculated as the total number of completed sessions divided by the overall number of sessions. The compliance rate for cycling sessions was 79.9% ± 21.2%, with an average session duration of 37.6 ± 12.7 min and an average distance of 10.8 ± 3.6 virtual km. The cognitive training compliance reached 84.2% ± 14.9%, with an average session duration of 34 ± 4.1 min.

Various reasons accounted for skipping cycling sessions, including stomach pain, joint pain, fatigue, upper respiratory tract infection, hematoma, hypertension or hypotension, COVID-19 infection, and dyspnea. As for cognitive training sessions, the main reasons for skipping were fatigue or COVID-19 isolation.

TMT

Pre-TMT and post-TMT scores are shown in Table 2. The repeated measures analysis of variance showed a significant effect of group time interaction for TMTA test results (F [1, 41] = 16.218, $P < 0.001$, $\eta^2 = 0.283$), TMTB test results (F [1, 41] = 19.944, $P < 0.001$, $\eta^2 = 0.327$) and TMTB − TMTA (F [1, 41] = 4.606, $P = 0.038$, $\eta^2 = 0.101$) in favor to the EXP group.

Within group analysis (Table 2) revealed a significant worsening after the 12 weeks intervention in TMTA and TMTB in the CON group. In contrast, subjects in the EXP group significantly improved their performance in all 3 variables as follows: TMTA, −3.6 s (5.7% improvement); TMTB, −14.0 s (8.8% improvement); and TMTB − TMTA, −10.4 s (10.9% improvement).

Timed Up and Go Tests

A statistically significant effect for time group interaction was found for TUG test (F [1, 40] = 8.854, $P = 0.005$, $\eta^2 = 0.181$) and for TUG-dual test (F [1, 40] = 8.457, $P = 0.006$, $\eta^2 = 0.175$). Within group changes are presented in Table 3. In the CON group, pre- to post- change was not statistically significant for both tests, whereas the subjects in the EXP group significantly improved their performance (−0.8 s [9.5% improvement] in the TUG and −1.0 s [10.4% improvement] in the TUG-dual).

Preintervention and postintervention laboratory parameters and body composition values with between group changes are presented in the Supplementary Table S1. No significant changes were found except for a slightly higher albumin increase in the EXP group than in the CON group at the end of the intervention.

Safety and Adverse Events

Finally, safety and tolerability are 2 majorly important factors for interventions in every population, but certainly in a chronic kidney disease population receiving HD. From this study, we report that this bimodal cognitive and physical exercise intervention was generally well tolerated by the patients because no intervention related adverse events were reported. One patient from the CON group was lost to follow-up due to transfer to another dialysis center because of colonization and 1 patient did not perform the TUG tests at 12 weeks due to mobility issues resulting from a fall incident in the home environment.

DISCUSSION

The present study examined the effects of a 12 week intervention in the form of intradialytic sequential physical and cognitive training on psychomotor speed, executive functions, cognitive flexibility, mobility, and cognitive motor performance. To our knowledge, this combined intervention has never been tested in patients on HD. Our main findings show that these 12 weeks of physical and cognitive training during dialysis treatment (3 times per week) in the clinic improved performance on the TMTA, TMTB, TMTB − TMTA, TUG and the TUG-dual.

In our study, there was a significant pre- to post-difference in psychomotor speed and executive functions in the EXP group (measured by TMTA and

Table 3. Timed up and go and timed up and go dual task results per group

Variable	Group	Pretest	Posttest	Mean change (95% CI)	*P* value	ES
TUG (s)						
	EXP ($n = 22$)	7.4 ± 1.1	6.7 ± 1.0	−0.8 ± 0.9 (−1.2 to −0.4)	< 0.001	0.67
	CON ($n = 20$)	7.5 ± 2.1	8.2 ± 2.8	0.7 ± 2.2 (−0.4 to 1.7)	0.184	0.28
TUG-dual (s)						
	EXP ($n = 22$)	9.6 ± 2.9	8.6 ± 2.5	−1.0 ± 1.2 (−1.5 to −0.5)	< 0.001	0.37
	CON ($n = 20$)	9.5 ± 3.6	9.9 ± 3.4	0.3 ± 1.7 (−0.5 to 1.2)	0.386	0.11

CI, confidence interval; CON, control group; ES, Cohen's d effect size; EXP, experimental group.
Values are expressed as mean ± SD.

TMTB). We found no such improvement in the standard care control group; conversely, the CON group experienced a significant decline in both cognitive abilities. It is important to recognize that these cognitive skills are intimately linked to various aspects of daily functioning, encompassing the ability to drive safely, prevent falls, effectively react to unforeseen circumstances, engage in social interactions, sustain a satisfactory quality of life, adhere to medication schedules, and comprehend medical instructions.[31,32] Furthermore, the present study demonstrated an improvement in the EXP group in cognitive flexibility as indicated by subtracting TMTA from TMTB time. Cognitive flexibility enables individuals to adapt to changes and helps to pursue complex tasks.[33]

A possible explanation for the EXP group improvements might lay in the underlying mechanisms of physical exercise and cognitive training. Physical exercise has been consistently associated with enhanced cerebral blood flow, neurogenesis, and the release of neurotrophic factors such as brain derived neurotrophic factor, all of which collectively contribute to cognitive vitality and neuroplasticity.[8,34-37] Cognitive training stimulates neural networks involved in executive functions and cognitive flexibility, leading to improved information processing, memory, and decision making capabilities.[38-40] Interestingly, Oswald *et al.*[41] found no cognitive improvements in a group of older adults only performing physical activity, but reported significant improvements in cognitive capacity in the group performing a combined physical and cognitive intervention. They referred to the positive impact of physical activity on brain metabolism leading to neurogenesis and neuroprotection.

Similarly to our study, McAdams-DeMarco *et al.*[19] investigated the effect of either intradialytic cognitive training or intradialytic cycling on TMT results. They demonstrated that after 3 months, a control group experienced a decline in psychomotor speed, executive functions, and cognitive flexibility; whereas both intervention groups preserved those abilities (no significant change compared to baseline). Our study strengthens these preliminary findings by combining both interventions and by applying them in a much larger sample. Comparing both studies, we observe that the time needed to perform the TMT tests at both time points was higher in our study. This can be explained by the older age of our patients (66.5 ± 11.0 years) compared to 50.8 ± 10.0 years old patients from study by McAdams-DeMarco *et al.*[42] The TMT scores in the present study also provide further evidence for a cognitive decline in the HD patient population. Our participants had worse TMT scores than an age matched healthy population. This is indicative for reduced cognitive skills, which can lead to reduced mobility, and it once more stresses the importance of this study and the consequent need for future studies.

In the current study, the TUG test was used to assess the functional mobility of the patients. Moreover, 1 of the diagnostic tests used in the present study was the TUG-dual, a dual task test. This test was selected specifically because the dual task paradigm is a recent trend that represents the ability to simultaneously perform 2 tasks, usually a cognitive and a motor one, and in this way evaluating the cognitive motor interaction.[43] In a study by Singh *et al.*,[44] patients with HD experienced more pronounced interference between walking and talking in contrast to the healthy age matched control group. The challenge of simultaneously walking and engaging in cognitive tasks carries meaningful consequences for daily activities and could potentially contribute to an elevated risk of experiencing falls.[45,46]

One of the strengths of this study is avoiding low sensitivity of cognitive test regularly used (such as the Mini-Mental State Examination and the Montreal Cognitive Assessment) by using tests that have shown higher sensitivity and that minimize practice effects.[47,48] Unlike some previous studies,[49-51] we chose to perform baseline and posttest assessments on nondialysis days. This approach was taken to avoid potential confounding factors associated with predialysis or postdialysis fatigue effects. In our study, patients achieved a high level of compliance with training sessions. One potential explanation for the strong compliance could be attributed to the nature of the intervention delivered during dialysis. Patients are usually motivated for intradialytic activities because they feel like the dialysis procedure passes faster. In addition, our study is the first to combine intradialytic physical and cognitive training sessions in patients on HD in a randomized controlled design with sufficient statistical power. This approach is novel, practical, and readily feasible to administer.

One of the limitations is the lack of different active control groups. The lack of an active control group limits our ability to determine the subjective and objective aspects of cognitive abilities as well as the possible placebo effect. Indeed, it cannot be definitively determined whether the results can be attributed to the synergistic effect of cognitive and physical training, or if separate interventions would yield similar outcomes. Therefore, future research should additionally include 2 separate groups, 1 participating solely in intradialytic cycling and the other in cognitive training. Another limitation stems from the language used in the CogniFit platform, which was often not the patients' native language. To address this issue, we ensured the presence of research assistants who translated the instructions before each "brain game" session. Given the nature of the intervention, it was not feasible to blind investigators and patients. Nonetheless, the outcome assessors remained blinded to the group allocation.

In conclusion, the present study demonstrated that a 12 week combined physical and cognitive intradialytic training intervention led to improvements in executive function, psychomotor speed, cognitive flexibility, mobility, and cognitive motor performance in comparison to the control group. The current study concept, with sequential physical and cognitive training was well tolerated because no exercise related adverse events were recorded. This confirms both the safety and feasibility of the study protocol. The outcomes of the present study provide strong evidence that this type of intervention is an effective tool to mitigate cognitive and physical decline in this HD patient population.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Prelaboratory and postlaboratory parameters and body composition values.

CONSORT checklist.

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