Intradialytic Cognitive and Exercise Training May Preserve Cognitive Function

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Introduction: Cognitive decline is common and increases mortality risk in hemodialysis patients. Intradialytic interventions like cognitive training (CT) and exercise training (ET) may preserve cognitive function.

Methods: We conducted a pilot randomized controlled trial of 20 hemodialysis patients to study the impact of 3 months of intradialytic CT (tablet-based brain games) (n = 7), ET (foot peddlers) (n = 6), or standard of care (SC) (n = 7) on cognitive function. Global cognitive function was measured by the Modified Mini Mental Status Exam (3MS), psychomotor speed was measured by Trail Making Tests A and B (TMTA and TMTB), and executive function was assessed by subtracting (TMTB − TMTA). Lower 3MS scores and slower TMTA and TMTB times reflected worse cognitive function. *P* values for differences were generated using analysis of variance, and 95% confidence intervals (CIs) and *P* values were generated from linear regression.

Results: Patients with SC experienced a decrease in psychomotor speed and executive function by 3 months (TMTA: 15 seconds; $P = 0.055$; TMTB: 47.4 seconds; $P = 0.006$; TMTB − TMTA; 31.7 seconds; $P = 0.052$); this decline was not seen among those with CT or ET (all $P > 0.05$). Compared with SC, the difference in the mean change in 3MS score was −3.29 points (95% CI: −11.70 to 5.12; $P = 0.42$) for CT and 4.48 points (95% CI: −4.27 to 13.22; $P = 0.30$) for ET. Compared with SC, the difference in mean change for TMTA was −15.13 seconds (95% CI: −37.64 to 7.39; $P = 0.17$) for CT and −17.48 seconds (95% CI: −41.18 to 6.22; $P = 0.14$) for ET, for TMTB, the difference was −46.72 seconds (95% CI: −91.12 to −2.31; $P = 0.04$) for CT and −56.21 seconds (95% CI: −105.86 to −6.56; $P = 0.03$) for ET, and for TMTB – TMTA, the difference was −30.88 seconds (95% CI: −76.05 to 14.28; $P = 0.16$) for CT and −34.93 seconds (95% CI: −85.43 to 15.56; $P = 0.16$) for ET.

Conclusion: Preliminary findings of our pilot study suggested that cognitive decline in psychomotor speed and executive function is possibly prevented by intradialytic CT and ET. These preliminary pilot findings should be replicated.

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Cognitive impairment is a well-recognized complication of end-stage renal disease (ESRD),[1,2] and only 13% of hemodialysis (HD) patients have normal cognitive function.[3] Cognitive decline often starts early in the progression of kidney disease even before HD initiation,[4–6] and continues to decline while undergoing HD[7] at a rate much faster than the general population.[8] Specifically, HD patients have worse executive function, which is a higher order cognitive ability that regulates goal-directed behavior and problem solving.[9] Executive function is the domain of cognition that is most affected by HD initiation.[10] At dialysis initiation, 7.5% of patients have impairment of psychomotor speed, a component of executive function. By 1 year, the prevalence of this impairment rises to 10.7%,[11] and among all patients on HD, regardless of their duration on dialysis, the prevalence of impairment is 38%.[12]

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This cognitive decline of patients with ESRD has a significant effect on other adverse health outcomes. HD patients with cognitive impairment are at a 2.5-fold increased risk of mortality;[13] in particular, worse executive function is associated with an increased mortality risk.[14] Mortality rates for those with the worst executive function are comparable to those with dementia,[14] making this a highly vulnerable group of HD patients.[15] In addition, in patients undergoing HD, cognitive impairment is associated with other poor outcomes, including an increased number of hospitalizations.[16] Unfortunately, interventions have not been tested in this population, and there are currently no proven methods for mitigating cognitive decline and impairment in HD patients.

In an attempt to reduce cognitive decline in patients on HD, we tested 2 novel, convenient interventions: intradialytic cognitive training (CT) and exercise training (ET).[17] CT prevents age-related declines in key areas of executive function, including abstraction, working memory, verbal reasoning, and inhibition[18–24] by improving the neural structures that mediate executive function.[25–27] Even before improving physical function and strength,[28] ET in older adults reduces inflammatory markers (C-reactive protein, tumor necrosis factor-α, and interleukin-6), improves brain plasticity and executive function,[29,30] and also improves executive function[31] through increased (i) cerebral blood flow,[32] (ii) brain volume in the prefrontal cortex and hippocampus[33–35] and (iii) brain-derived neurotrophic factor.[29,36–39] Although CT and ET have been shown to slow decline in cognitive function, including declines in psychomotor speed and executive function, for community-dwelling older adults,[40–44] they have never been tested in adults with ESRD of any age. HD presents a unique window of opportunity for these interventions. They could replace the common, passive activities that occur during the HD session, namely, like sleeping and watching TV. To better understand the impact of these interventions, we conducted a preliminary analysis of our pilot randomized controlled trial of 20 patients who underwent HD to study the impact of 3 months of intradialytic CT or ET on cognitive function relative to a controlled standard of care (SC) group.

METHODS

Patient Eligibility and Enrollment

We enrolled HD patients at a single dialysis center in Baltimore, Maryland (February 2016) into a randomized controlled trial that sought to determine whether intradialytic CT or ET could preserve cognitive function. Patients at the dialysis center who were deemed medically fit to participate were identified by the center nephrologists and nurse practitioners. The study inclusion criteria consisted of currently undergoing maintenance HD, aged 18 years and older, English speaking, and able to provide informed consent. Exclusion criteria included angina pectoris, chronic lung disease, cerebral vascular disease, musculoskeletal or orthopedic conditions limiting physical activity, lower or upper extremity amputation, decreased mental capacity, or diagnosed dementia, consistent with previous exercise intervention studies of HD patients.[45–51] We approached 27 HD patients, and 1 was not eligible. Of the 26 patients identified as eligible, 23 agreed to participate, and 20 were available for follow-up at 3 months (the other 3 changed dialysis centers during the study and were excluded) (Figure 1). Informed consent was obtained from all individual participants included in the study.

Baseline and Follow-up Assessments

After participants provided informed consent, they underwent a baseline assessment at the dialysis center, which included measurement of cognitive function (see the following). Participants were randomized (1:1:1) to 3 months of intradialytic CT ($n = 7$), 3 months of intradialytic ET ($n = 6$), or 3 months of SC ($n = 7$). Follow-up assessments were conducted 3 months after the baseline assessment in the dialysis center, and cognitive function was measured (see the following). Participants were compensated $25 after completion of the follow-up assessment.

Interventions

Research assistants conducted 20-minute training sessions with the participants randomized to CT or ET. Participants were encouraged to engage in the assigned CT or ET for as long as they were able and willing during their HD session. Participants initiated the intervention 15 to 30 minutes after the start of the HD session and were able to stop the intervention or take breaks at any time. At each dialysis session, research assistants helped set up the interventions for the participants.

Participants randomized to CT were given tablets at each dialysis session, with connection to Lumosity, a web-based CT program. They had 10 different brain games to play at each session; the games varied at each dialysis session. Tablets were configured ahead of enrollment so that all other features of the tablet were disabled, and participants only had access to the "brain games" feature. Lumosity is available for research purposes and has been used for CT interventions across a variety of research settings.[41,52–54] The cognitive games trained different executive and global cognitive

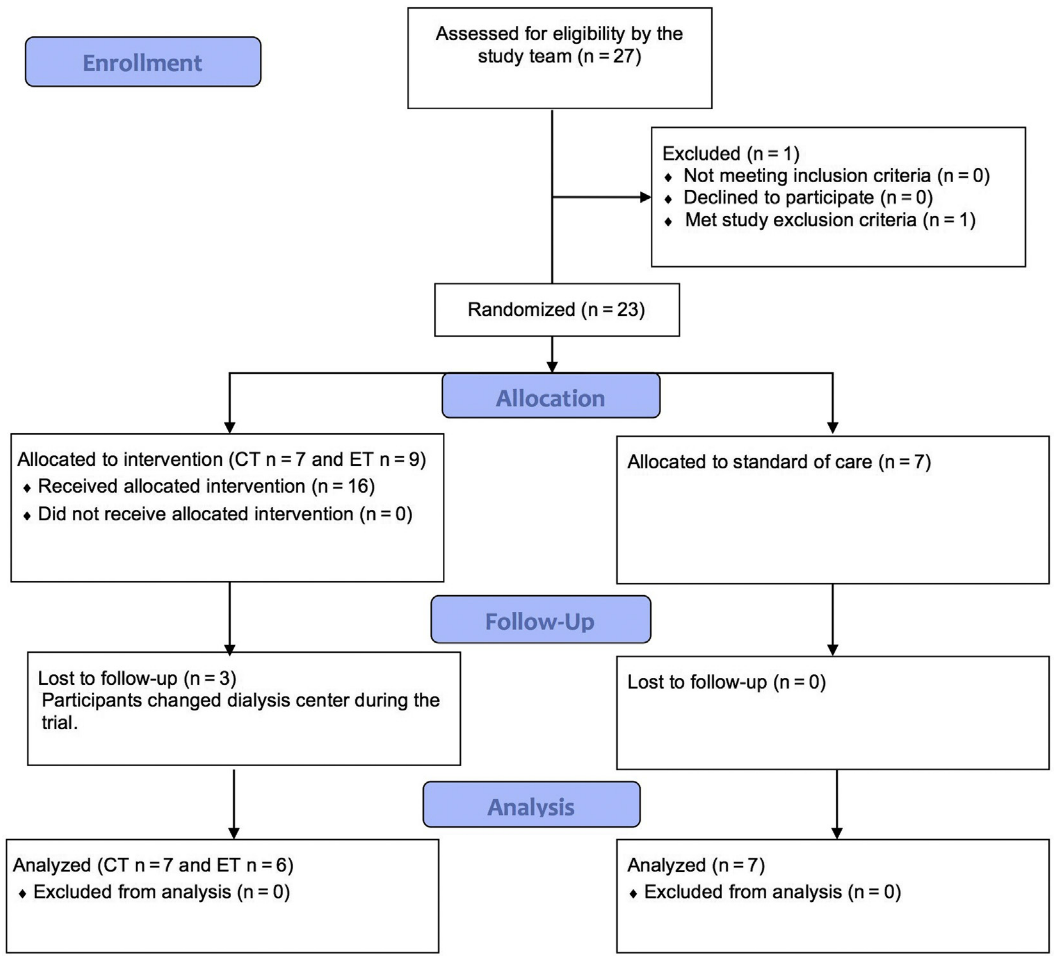

Figure 1. Consort flow diagram for the pilot study of intradialytic exercise training (ET) and cognitive training (CT).

tests than those used to measure changes in these outcomes to avoid training to the test.

Participants randomized to ET were asked to use a stationary foot pedal exerciser at each dialysis session. The pedals were placed at a distance from the dialysis chair that was comfortable for the patient.

Cognitive Function Measures

Cognitive function was measured by the Modified Mini Mental Status (3MS) examination and the Trail Making Tests A and B (TMTA and TMTB) before the start of HD. The 3MS is a measure of global cognitive function (range: 0−100), with higher scores representing better cognitive function.[55] The TMT consists of 2 timed tests that measure psychomotor speed and executive function.[56] Part A assesses visual search, attention, and psychomotor speed, and Part B further assesses executive set shifting and complex sequencing function. Both parts measure the time required to connect a series of numbered (TMTA) and numbered and lettered (TMTB) circles in an ascending alphanumeric sequence as quickly and accurately as possible. Psychomotor speed was assessed by TMTA and TMTB, and executive function was assessed by subtracting the time to complete TMTA from TMTB (TMTB − TMTA). Longer times represented worse cognitive function.

Statistical Analyses

The characteristics of the participants were summarized using descriptive statistics: (i) means and SDs for normally distributed characteristics, and (ii) percentages for categorical characteristics. We tested whether participant characteristics differed among the groups using a Fisher's exact test for categorical variables, and analysis of variance tests were used to estimate the P value for categorical variables.

We estimated the means and SDs of the cognitive function tests among patients randomized to CT, ET, and SC. The within-group differences in cognitive function between baseline and the 3-month follow-up were estimated using repeated-measures analysis of variance. Finally, we used unadjusted linear regression to test the between-group differences in mean change of the cognitive function tests from baseline to 3-month follow-up, comparing those randomized to CT and to

ET with SC, separately. All tests were prespecified, and all analyses were intention to treat.

This study was approved by the institutional review board of the Johns Hopkins Bloomberg School of Public Health and registered with ClinicalTrials.gov (NCT02697942; February 9, 2016). All procedures adhered to the Declaration of Helsinki. All participants provided written consent. All analyses were performed using Stata 14.0 (Stata Corp, College Station, Texas).

RESULTS

Study Population

Among the study participants, mean ± SD age was 50.8 ± 10 years (range: 31−65 years), 35.0% were women, and 90.0% were African American. None of the participants had a history of myocardial infarction, diagnosed dementia, cerebrovascular disease, or peripheral vascular disease. Thirty percent had a history of diabetes, and 25% were HIV positive. Seven participants were randomized to CT, 6 to ET, and 7 to SC. There were no statistically significant differences in the 3 arms (Table 1), except that there were more women randomized to CT ($P = 0.02$). On average, those with ET participated for 30.3 min/session over an average of 27 sessions; those with CT participated for 35.4 min/session over an average of 45 sessions.

Adverse Events

There were no safety concerns or deaths in the SC, CT, or ET arms of the study.

Table 1. Characteristics of hemodialysis patients randomized to standard of care, intradialytic cognitive training, and intradialytic exercise training

Characteristic	All participants $N = 20$	Standard of care $n = 7$	Cognitive training $n = 7$	Exercise training $n = 6$	*P* value
Age (yr)	50.8 ± 10.0	55.0 ± 9.7	48.9 ± 12.2	48.0 ± 7.0	0.39
Female	35.0	0	71.4	33.3	0.02
African American race	90.0	85.7	85.7	100	0.99
Body mass index (kg/m^2)	29.1 ± 7.9	30.4 ± 6.9	25.5 ± 6.2	32.0 ± 10.1	0.30
Less than high school education	20.0	28.6	16.7	14.3	0.99
Diabetes	30.0	28.6	14.3	50.0	0.41
HIV	25.0	28.6	28.6	16.7	0.99
Dialysis duration (yr)					0.96
<2	27.8	33.3	20.0	28.6	
2−5	33.3	16.7	40.0	42.9	
≥5	38.9	50.0	40.0	28.6	

Values are presented as percentages and mean ± SD.
To estimate the *P* values, Fisher's exact tests were used for categorical characteristics and analysis of variance was used for age and body mass index (continuous, normally distributed characteristics).

Global Cognitive Function

At baseline, the mean ± SD 3MS score was 84.1 ± 6.6; there was no difference in the baseline 3MS scores ($P = 0.44$) and no difference in change in 3MS score between baseline and 3 months for those on CT, ET, or SC (Table 2). Compared with the mean change in 3MS score among those who received SC, the difference in the mean change in the 3MS score was −3.29 (95% confidence interval [CI]: −11.70 to 5.12; $P = 0.42$) for CT and 4.48 points (95% CI: −4.27 to 13.22; $P = 0.30$) for ET (Table 3).

Psychomotor Speed and Executive Function

At baseline, there were no differences in baseline TMTA, TMTB, or TMTB − TMTA times for those with CT, ET, or SC (TMTA: $P = 0.45$; TMTB: $P = 0.45$; TMTB − TMTA: $P = 0.30$).

By 3 months, HD patients on SC experienced declines in both psychomotor speed and executive function (longer times) (TMTA difference: 15 seconds; $P = 0.055$; TMTB difference: 47.4 seconds; $P = 0.006$; TMTB − TMTA difference: 31.7 seconds; $P = 0.052$); however, those who underwent CT or ET did not experience these declines (all $P > 0.05$) (Table 2 and Figure 2). Compared with those with SC, the difference in the mean change in the TMTA time was −15.13 seconds (95% CI: −37.64 to 7.39; $P = 0.17$) for CT and −17.48 seconds (95% CI: −41.18 to 6.22; $P = 0.14$) for ET. This was even more pronounced for TMTB, in which CT and ET patients did not experience the profound decline in psychomotor speed seen with SC; the difference in the mean change in the TMTB score was −46.72 seconds (95% CI: −91.12 to −2.31; $P = 0.04$) for CT and −56.21

Table 2. Cognitive function at baseline and after 3-months of intradialytic cognitive and exercise training

Measure of cognitive function	Baseline	3-Month	Mean change	*P* value for mean change
3MS score				
Standard of care ($n = 7$)	84.1 (6.8)	84.0 (8.1)	−0.1 (7.0)	0.96
Cognitive training ($n = 7$)	88.3 (5.9)	84.9 (12.0)	−3.4 (9.2)	0.24
Exercise training ($n = 6$)	84.2 (7.4)	88.5 (4.5)	4.3 (5.4)	0.17
TMTA time (s)				
Standard of care ($n = 7$)	43.0 (10.0)	58.0 (26.1)	15.0 (25.8)	0.055
Cognitive training ($n = 6$)	44.1 (7.4)	43.9 (20.5)	−0.2 (14.7)	0.98
Exercise training ($n = 5$)	49.9 (12.9)	47.3 (20.5)	−2.5 (9.3)	0.77
TMTB time (s)				
Standard of care ($n = 6$)	119.3 (33.4)	166.6 (50.6)	47.4 (45.7)	0.006
Cognitive training ($n = 6$)	114.1 (26.4)	114.9 (46.9)	0.6 (29.1)	0.97
Exercise training ($n = 4$)	108.9 (23.3)	100.0 (13.8)	−8.9 (24.4)	0.63
TMTB − TMTA time (s)				
Standard of care ($n = 6$)	77.3 (32.1)	109.0 (32.7)	31.7 (47.8)	0.052
Cognitive training ($n = 6$)	70.0 (29.0)	70.8 (42.5)	0.8 (23.3)	0.96
Exercise training ($n = 4$)	59.0 (12.0)	55.7 (19.9)	−3.2 (31.2)	0.86

P values were estimated using analysis of variance. Values are mean ± SD.
3MS, Modified Mini Mental Status Exam; TMTA and TMTB, Trails Making Test A and B.

Table 3. Three-month mean change in cognitive function for hemodialysis patients who underwent intradialytic cognitive and intradialytic exercise training compared with standard of care

	3-Month change in cognitive function			
Intervention	3MS (score)	TMTA (s)	TMTB (s)	TMTB − TMTA (s)
Standard of care	Reference	Reference	Reference	Reference
Cognitive training	−3.29 (−11.70 to 5.12)	−15.13 (−37.64 to 7.39)	−46.72 (−91.12 to −2.31)	−30.88 (−76.05 to 14.28)
P value	0.42	0.17	0.04	0.16
Exercise training	4.48 (−4.27 to 13.22)	−17.48 (−41.18 to 6.22)	−56.21 (−105.86 to −6.56)	−34.93 (−85.43 to 15.56)
P value	0.30	0.14	0.03	0.16

Lower Modified Mini Mental Status Exam (3MS) scores reflect worse cognitive function and slower times on Trail Making Test A (TMTA) and Trail Making Test B (TMTB), and TMTB − TMTA reflects worse cognitive function. The estimates presented in the table are mean changes (and 95% confidence intervals and *P* values) in 3MS score, TMTA time, TMTB time, and TMTB − TMTA time between baseline and 3 months of cognitive training and exercise training using linear regression. Hemodialysis patients participating in intradialytic cognitive training had statistically significant better preserved psychomotor speed and executive function than those with standard of care.

seconds (95% CI: −105.86 to −6.56; $P = 0.03$) for ET, compared with SC. When TMTA and TMTB were combined to test change in executive function, the difference in the mean change of TMTB − TMTA was −30.88 seconds (95% CI: −76.05 to 14.28; $P = 0.16$) for CT and −34.93 seconds (95% CI: −85.43 to 15.56, 6.22; $P = 0.16$) for ET compared with SC.

DISCUSSION

In this pilot randomized controlled trial of HD patients, our preliminary findings suggested that the cognitive decline in psychomotor speed and executive function seen with SC was possibly prevented by CT and ET. The difference in the mean change in psychomotor speed measured by TMTB was nearly 1 minute for those with CT and ET compared with those with SC. To our knowledge, neither intradialytic CT nor ET have been tested as a means to prevent cognitive decline in HD patients.

The trial participants had similar 3MS scores to incident HD and ESRD patients, but better TMTA and TMTB times than this population.[11,12] As expected, the trial participants had worse 3MS scores and worse TMTB times than published norms.[12]

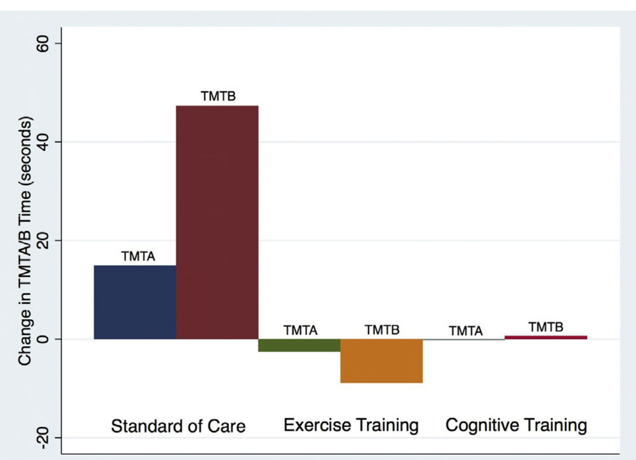

Figure 2. Mean change in psychomotor speed (Trail Making Tests A and B [TMTA and TMTB]) at 3 months for those with cognitive training, exercise training, and standard of care.

Our findings were consistent with the gerontology literature, in which CT and ET were associated with preservation or improvement in some, but not all domains, of cognition.[40–44] Among older adults, CT using Lumosity showed a trend toward improving executive control and other domains of cognition.[41] In addition, with a 6-month ET intervention, older adults without ET had a decline in cognitive function, whereas those patients with ET had preserved cognitive function over 18 months.[42] This study extended these findings of the cognitive decline of aging to the cognitive decline associated with ESRD and HD, and to adults of all ages.

There is a general consensus that intradialytic ET is safe,[57,58] and our study supported the safety of intradialytic ET and intradialytic CT. As might be expected, previous studies demonstrated an impact of intradialytic ET (i.e., physical exercise) on physical findings, including physical function,[45,46,50] treatment-related symptoms,[59] dialysis efficacy,[60] inflammation,[45] bone mineral density,[45,47] quality of life,[48] peak oxygen consumption,[49,50] anxiety,[51] and exercise capacity.[61] We extended these studies to test the impact of physical exercise on cognitive findings (i.e., intradialytic ET preserves cognitive function). Furthermore, we also included a previously untested novel intradialytic intervention in this pilot study, namely, CT, and demonstrated that either physical or cognitive intervention was able to preserve psychomotor speed and executive function compared with SC.

Impairments in executive function are common in patients who receive maintenance HD[9] and are likely not the direct result of residual uremia. Instead, executive function impairment has been found to be associated with aging, depression, and cerebrovascular disease.[62,63] CT and ET may be the most effective way for preventing executive function decline because this decline results from factors other than residual uremia.[62,63] Physical activity has been shown to have a significant impact on executive function in aging adults.[64] Our study was the first to demonstrate that intradialytic CT and ET prevented decline in psychomotor speed and executive function over the short-term. Results might be greater with longer term follow-up.

This study had some notable limitations. First, this pilot study, which was designed to assess feasibility, showed low statistical power; thus, results should be interpreted cautiously because of the potential for bias. Second, only 20 of the 23 randomized participants completed the 3-month assessment. However, the 3 participants who did not complete the 3-month assessment were not different from those who did complete the study. Furthermore, they were not able to complete this follow-up assessment because they switched dialysis centers mid-study. Third, because this was a small preliminary pilot study, there was a potential imbalance in the characteristics by study arm, which potentially limited generalizability and the ability to adjust for imbalances. For example, by chance alone, no women were randomized to SC, and the distribution of the duration of dialysis might have differed among the groups. However, among ESRD patients, women and those with longer dialysis durations are more likely to have cognitive impairment, so it was unlikely that this imbalance affected the observed associations. In other words, any bias introduced by this imbalance would drive our inferences toward the null.[65] There might still be potential biases that arise from imbalances in measured and unmeasured confounders, and the results should be interpreted with caution. Fourth, we focused on 3 months of intradialytic CT and ET, but a longer intervention might be needed to demonstrate differences in global cognitive function. Finally, by design, our study only recruited patients who underwent HD who were able to participate in intradialytic interventions; our findings were generalizable to this population and not all patients treated with HD.

The main strengths of this pilot study were its randomized controlled trial design, homogeneity of dialysis environment across the 3 arms, representation of non-white patients, extension of interventions from gerontology to a more age-diverse HD population, and use of novel, yet practical, intradialytic interventions to preserve cognitive function. High participation and follow-up rates bode well for the conduct of a larger and longer trial with sufficient power and rigor to influence clinical practice and guidelines.

In conclusion, the findings from this preliminary pilot study suggested that intradialytic CT and ET are not only safe but might also aid in preventing psychomotor speed and executive function decline. Future studies should replicate these findings and test whether longer durations of CT and ET preserve global cognitive function. Pragmatic trials could explore environments most suited to providing these interventions and subgroups of HD patients who might experience the greatest benefit from them. These interventions, once better understood, are likely easily integrated into dialysis center practices and implementable at dialysis centers nationally.

DISCLOSURE

All the authors declared no competing interests.

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All authors participated in the design of the work, acquiring data, or played an important role in interpreting the results. All authors have revised the manuscript and approved the final version. The corresponding author had full access to the data in the study and takes final responsibility for the decision to submit for publication.

Lumosity provided the brain games for the intervention arm through the Human Cognition Project but did not participate in the study design, conduct of the study, statistical analysis, or drafting of the paper.

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