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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.

Discussion: 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

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