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A randomised pilot trial of combined cognitive and physical exercise prehabilitation to improve outcomes in surgical patients

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Editor—Millions of patients require surgery each year, and many experience a decline in their cognitive and functional status after the operation including perioperative neurocognitive disorders[1] and new disabilities in basic functions of self-care or more complex tasks necessary for independent living.[2,3] Changes may persist for months to years after an operation. Improving quality of life after surgery and preventing acquired cognitive impairment and disability is a public health problem that needs to be addressed. Functional decline after surgery is traditionally managed with rehabilitation programs. A newer approach focuses on increasing baseline reserve before major surgery to prevent significant decline in the postoperative period, termed prehabilitation. The benefits of resistance-based physical activity for community-dwelling older adults on health, quality of life, and physical and cognitive function have been established.[4] In the surgical population, nutritional and functional prehabilitation has demonstrated success in reducing time to recovery of baseline function, although data are mostly preliminary, the optimal dose and type of exercise remain unknown, and programs often require specialised equipment or frequent trips to exercise facilities.[5–7] Further, programs have started to include mindfulness techniques for stress reduction[8] but have not commonly incorporated activities for enhancing cognitive function. We, therefore, sought to investigate the feasibility of a novel, pragmatic combined cognitive and physical prehabilitation program that can be completed at home in the weeks before a major operation. We hypothesised that prehabilitation with both cognitive and physical exercises would be feasible and associated with improved postoperative outcomes when compared with an active attention control group.

This study was approved by the Institutional Review Board of Vanderbilt University Medical Center, Nashville, TN, USA (Study #161802) and registered (NCT03094988). Written informed consent was obtained from all participants. We conducted an open-label, randomised, controlled pilot feasibility trial in a convenience sample of patients ≥18 yr old awaiting major noncardiac surgery requiring ≥3 days hospitalisation. We enrolled participants during an appointment at our preoperative evaluation clinic where surgeons refer patients for evaluation and medical optimisation before surgery. The majority of patients at this clinic are older, have multiple comorbidities, and require major noncardiac surgery. Participants were excluded if <1 week remained before surgery, pre-existing conditions prevented

participation in resistance-based physical exercise, or they lacked access to the internet.

Baseline data collected included age, sex, years of education, ASA physical status, and Clinical Frailty Scale.[9] Baseline cognitive testing administered at enrolment included the following elements of the National Institute of Health (NIH) Cognitive Battery: Dimensional Change Card Sort (DCCS), a measure of executive function and shifting; Pattern Comparison Processing, a measure of processing speed; and Flanker Inhibitory Control, a measure of executive function and attention.[10] Elements of the NIH Cognitive Battery are independently validated, show comparable practice effect to gold standard testing, and use different sets or forms with repeated testing to minimise learning effect.[10] Baseline functional testing included the Pfeffer Functional Activities Questionnaire[11] to measure Instrumental Activities of Daily Living (IADLs); grip strength; and 2-minute walk test (2-MWT). This battery was repeated at a 1-month postoperative evaluation.

We randomised participants 2:1 to (1) a prehabilitation program with prescribed cognitive and physical exercises or (2) an active attention control group with generalised health information only. Participants in the intervention group received a tablet with a computerised cognitive training game from PositScience designed to improve aspects of cognition that decline after surgery. All activities are completely independent from the activities used to test cognitive function in the NIH Cognitive Battery. The game is adaptive, becoming progressively harder as the player's performance improves or less challenging when players have difficulty. An interactive demonstration at enrolment orientated participants to tablet features and the game. Participants also received a binder with generalised health information (e.g. sleep, nutrition habits), a prescribed resistance-based physical exercise plan, and resistance bands. A physical therapist called patients weekly to guide them through the resistance-based exercises and address questions. Participants were asked to complete prescribed cognitive and physical exercises daily.

Participants in the active attention control group also received a tablet with a trivia-based electronic game that lacked adaptive features or tasks targeted at improving cognition and were encouraged to play daily. The active control binder contained generalised health information *without* a prescribed physical exercise program or resistance bands. A physical therapist called participants weekly to answer questions and provide support.

The neuropsychiatric personnel who performed assessments were blinded to study group assignment. To assess feasibility, we monitored daily participation in computerised cognitive training using a log generated by each program that recorded days on which participants completed game activities. Physical exercise was recorded in a daily log that included exercises completed for the intervention group. Control participants logged any exercise including type and number of minutes spent exercising. Data collected during the hospitalisation included anaesthetic duration and length of hospital stay. As this study was not powered to detect significant differences in cognitive and physical function, we calculated the difference in raw scores on the physical and cognitive battery between baseline and 1-month postoperative evaluations to determine a trend towards worsening,

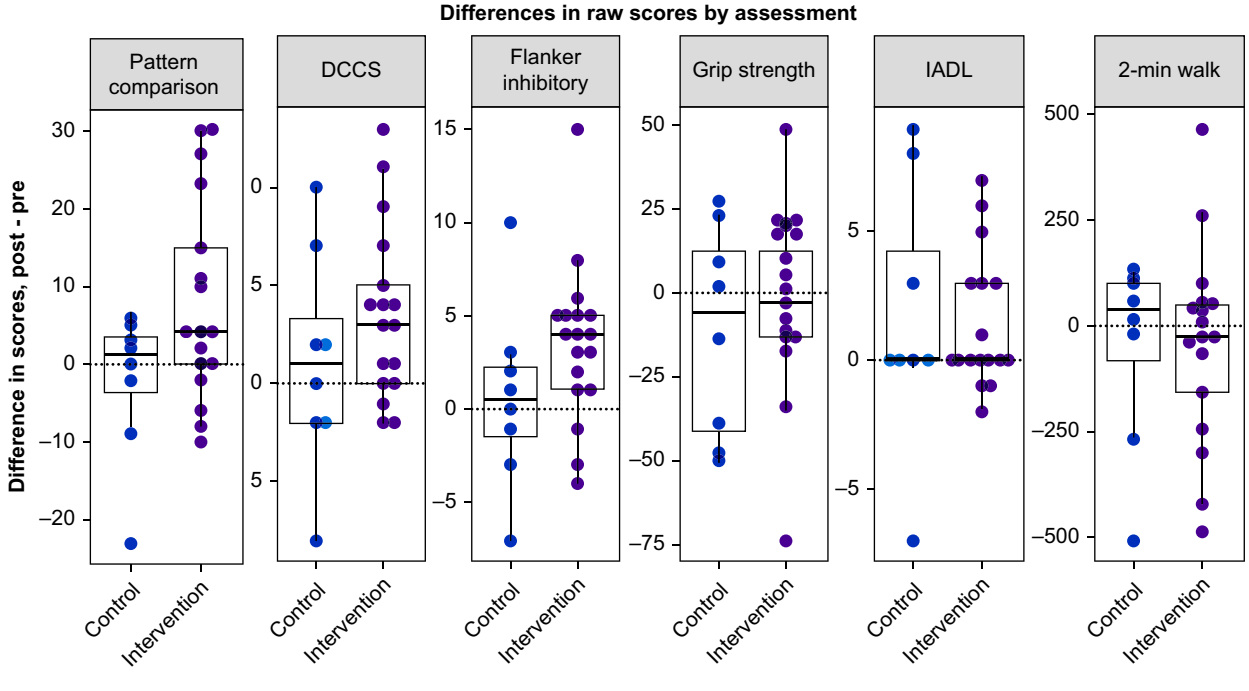

Fig 1. Graphic representation of the change in raw scores on each assessment from baseline. A positive change on the graph from baseline on the Pattern Comparison, Dimensional Change Card Sort (DCCS), and Flanker tests indicate an *improvement* in cognitive function, whereas zero would be no change from baseline, and a negative change would be a *decrease* in cognition. Positive changes in grip strength and 2-MWT indicate *improvement* in physical function. Conversely, a positive change in Instrumental Activities of Daily Living (IADLs) correlates to *more* disability and worse functional status.

preservation, or improvement of function. We used linear regression based on intention-to-treat to estimate the difference in scores between groups, adjusted for age.

We enrolled 32 patients in this pilot feasibility trial, four of whom withdrew from the study and three whose surgeries were cancelled, with a median of 14 (inter-quartile range [IQR]: 10–21) days before surgery for prehabilitation. Reasons for withdrawal included inability to find time to participate in the intervention and pain from the presenting illness preventing participation in physical activity. The intervention group (n=17) had a median age of 62 (IQR: 50–69) yr and ASA physical status of 3 (IQR: 2–3) compared with 56 (IQR: 44–66.5) yr and 3 (IQR: 3–3) in the control group (n=8). Baseline Clinical Frailty Scale[9] scores were similar in both groups with a median of 3 (IQR: 3–4) in the intervention group and 3 (IQR: 3–3) in the control group, representing an overall population with co-morbid diseases that were well controlled.

The intervention group completed computerised cognitive training on 40% of days compared with 45% of days of game play in the control group. The intervention group reported completing the prescribed resistance training program on 62% of days compared with 83% for any exercise (most commonly light walking) reported in the control group. Overall, 88% of participants in the intervention group and 87% in the control group performed at least one of the assigned activities during the preoperative period.

The difference in raw scores from baseline to 1-month follow-up are shown in Figure 1 for each test, with the target difference being at minimum zero or no change from baseline. Overall, patients in the intervention group tended toward *improvement* in cognitive scores (DCCS, Flanker, Pattern Comparison) with no difference in physical scores (2-MWT, grip strength, IADLs) compared with control. With limited cohort size and power, the intervention was not significantly associated with less decline in cognitive and functional scores despite trends towards positive results (all P>0.05).

Our study shows that in-home combined cognitive and physical training before surgery is feasible. Although daily compliance with a prehabilitation program was not high, we found that patients will participate in cognitive or physical activities 3 to 5 days per week, which is consistent with previous successful trials of physical exercise alone.[5] Participation in cognitive training was comparable between the two groups despite the more challenging experience in the intervention group, whereas participation in physical activity was slightly higher in the control group. Factors contributing to this difference may be the younger age of the control cohort or the lack of prescriptive exercise activity. Patient compliance with regimens will be an important challenge to overcome in future studies and in clinical implementation, lending importance to targeted training programs that optimise impact during the sessions completed. A prescribed cognitive and physical exercise prehabilitation program is a potential method to reduce the burden of postoperative cognitive and physical dysfunction. Designing programs that may be completed at home using telehealth technology will enable expansion of the availability of such programs to most surgical patients. In the future, larger RCTs to determine the true impact and mechanism of prehabilitation on cognitive and physical recovery, and optimal dose and duration, are needed.

Declaration of interest

The authors declare that they have no conflicts of interest.

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