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Effect of Cognitive Prehabilitation on the Incidence of Postoperative Delirium Among Older Adults Undergoing Major Noncardiac Surgery
The Neurobics Randomized Clinical Trial

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IMPORTANCE Postoperative delirium in older adults is a common and costly complication after surgery. Cognitive reserve affects the risk of postoperative delirium, and thus preoperative augmentation of reserve as a preventive technique is of vital interest.

OBJECTIVE To determine whether cognitive prehabilitation reduces the incidence of postoperative delirium among older adults.

DESIGN, SETTING, AND PARTICIPANTS This was a prospective, single-blinded randomized clinical trial conducted from March 2015 to August 2019 at the Ohio State University Wexner Medical Center in Columbus. Patients 60 years and older undergoing major, noncardiac, nonneurological surgery under general anesthesia, with an expected hospital stay of at least 72 hours, were eligible for trial inclusion. Patients were excluded for preoperative cognitive dysfunction and active depression.

INTERVENTIONS Participation in electronic, tablet-based preoperative cognitive exercise targeting memory, speed, attention, flexibility, and problem-solving functions.

MAIN OUTCOMES AND MEASURES The primary outcome was incidence of delirium between postoperative day 0 to day 7 or discharge, as measured by a brief Confusion Assessment Method, Memorial Delirium Assessment Scale, or a structured medical record review. Secondary outcomes compared delirium characteristics between patients in the intervention and control groups.

RESULTS Of the 699 patients approached for trial participation, 322 completed consent and 268 were randomized. Subsequently, 17 patients were excluded, leaving 251 patients in the primary outcome analysis. A total of 125 patients in the intervention group and 126 control patients were included in the final analysis (median [interquartile range] age, 67 [63-71] years; 163 women [64.9%]). Ninety-seven percent of the patients in the intervention group completed some brain exercise (median, 4.6 [interquartile range, 1.31-7.4] hours). The delirium rate among control participants was 23.0% (29 of 126). With intention-to-treat analysis, the delirium rate in the intervention group was 14.4% (18 of 125; $P = .08$). Post hoc analysis removed 4 patients who did not attempt any cognitive exercise from the intervention group, yielding a delirium rate of 13.2% (16 of 121; $P = .04$). Secondary analyses among patients with delirium showed no differences in postoperative delirium onset day or duration or total delirium-positive days across study groups.

CONCLUSIONS AND RELEVANCE The intervention lowered delirium risk in patients who were at least minimally compliant. The ideal activities, timing, and effective dosage for cognitive exercise–based interventions to decrease postoperative delirium risk and burden need further study.

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Supplemental content

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Postoperative delirium is a common complication after surgery, especially in older individuals, who now account for one-third of all surgical patients.[1] Hallmarked by acute onset of impaired cognitive function and inability to focus or sustain attention, postoperative delirium slows return to functional baseline, resulting in increased hospital length of stay and costs.[2,3] Morbidity and mortality risk also increases in patients with delirium,[3] and with incidence as high as 50% after some surgeries,[4] this postoperative complication is a major public health concern. The outcomes of postoperative delirium have persisted despite successful delivery of multidisciplinary, foundational care for decreasing delirium burden, such as the Hospital Elder Life Program,[5-7] and availability of expert guidelines on perioperative management of older patients undergoing surgery who are at risk for and develop delirium.[8] Considerable knowledge gaps exist in the pathophysiology of postoperative delirium, limiting targeted development of interventions for prevention and treatment.[9]

In perioperative medicine, emphasis is being directed toward improving baseline function in elderly patients to promote successful recovery after surgery. Current prehabilitation programs can target physical exercise, nutrition, behavioral techniques, and optimization of preexisting medical conditions as part of a plan to augment physiologic and emotional reserve to help patients tolerate the stresses of surgery.[10] There is evidence that up to 24% of older patients undergoing surgery present with some degree of baseline cognitive impairment, which increases the risk of delirium and postoperative complications.[11] Although cognitive activities have not been part of prehabilitation to date, interest is growing.[12]

Proxies for cognitive reserve in the form of participation in activities such as playing computer games, reading books, singing, and emailing may have an association with postoperative delirium rates and severity. In an observational study of elderly patients undergoing orthopedic surgery, performance of these activities as part of a normal routine prior to surgery lowered postoperative delirium risk (with each activity lowering risk by 8%).[13] In studies of methods to augment cognitive reserve in older individuals, a range of interventions with different intensities, timing, and reliance on technology have been associated with positive outcomes on neuropsychological testing.[14-16] Video gaming with adaptive software to challenge participants leads to maintenance of independence in activities of daily living and sustained improvements in speed of processing, attention, and working memory in older people in as little as 10 hours.[17,18] Presumably through an increase in cognitive reserve, the goal of perioperative brain exercise is to provide protection against pathologic cognitive recovery after surgery.[19,20] Although mechanisms of postoperative delirium are multifactorial, cognitive exercise in the perioperative setting is a low-risk intervention that could potentially be used in a variety of patients.[21,22]

The Neurobics trial investigated the effect of preoperative cognitive exercise on postoperative cognitive recovery in aging patients undergoing surgery. It is (to our knowledge) the first large-scale application of cognitive prehabilitation in this population. We hypothesized that participation in a dynamic cognitive exercise program prior to surgery would decrease the incidence of postoperative delirium in patients having major noncardiac, nonneurological surgery.

Key Points

Question Does preoperative cognitive exercise reduce the incidence of postoperative delirium in older adults undergoing major noncardiac surgery?

Findings Results of this randomized clinical trial show patients who met at least minimum compliance with a preoperative cognitive exercise intervention had a significantly decreased incidence of postoperative delirium.

Meaning Modification of postoperative delirium risk with brain exercise remains a novel concept in the early stages of clinical study, and more investigation appears warranted based on this work, including investigation into the ideal activities, timing, and effective dosage.

Methods

Trial Design and Oversight

This was a prospective, single-blinded, parallel group, randomized clinical trial at the Ohio State University Wexner Medical Center in Columbus. Study procedures were conducted from March 2015 to August 2019. Institutional review board approval was obtained from The Ohio State University Office of Responsible Research Practices, and the study was registered on clinicaltrials.gov (NCT02230605). Details of the original study protocol are published,[23] and all study amendments are available as in the protocol in Supplement 2. Appointments scheduled at the outpatient preanesthesia clinic (OPAC) were screened for surgical patients 60 years and older undergoing major noncardiac, nonneurological surgery under general anesthesia with an anticipated hospital stay of at least 72 hours and immediate postoperative extubation. Potential trial candidates were contacted by telephone, provided with study details, and scheduled for follow-up with a researcher during their OPAC visit if they were interested in trial participation. Written informed consent and Health Insurance Portability and Accountability Act authorization was obtained from each participant at the OPAC visit prior to completion of study assessments.

Study Population

Patients were excluded if they demonstrated cognitive impairment on the modified Mini-Mental State Examination (score, <26 of 30 or <24 of 30 if the patient's education level was less than high school) or evidence of active depression (Geriatric Depression Scale; score >9 of 15) during their OPAC visit. Patient recruitment and randomization were performed by a specified researcher (J.-P.C.R., C.R., A.Z.-A., or A.O.). Patients who were cognitively normal and meeting inclusion criteria at least 8 days prior to their surgical procedure were randomized to either the cognitive exercise group (intervention) or the normal activity group (control) in a 1:1

ratio using a computer-generated randomized, permuted-block scheme. Sequentially numbered, opaque envelopes containing group assignment were used to ensure blinding until randomization. In the intervention group, patients were given an electronic tablet with preinstalled access to Lumosity (Lumos Labs), a dynamic cognitive exercise software application that does not require an internet connection to store patient activity and performance. Patients in the intervention group were trained to navigate the touchscreen tablet and guided through an introductory series of brain exercise games focused on 5 main categories: memory, speed, attention, flexibility, and problem-solving. Patients were asked to complete a cognitive exercise dosage of 10 total hours prior to their date of surgery, based on prior literature.[17,18] The timing of brain exercise activity in the days leading up to surgery was at the patient's discretion, although we suggested at least an hour a day. Control patients were instructed to continue their normal daily activities.

Trial Procedures

On the day of surgery, an unblinded researcher (J.-P.C.R., C.R., A.Z.-A., or A.O.) would collect the tablet device from patients randomized to the intervention group. The blinded anesthesia care team was instructed to collect data from a bispectral index monitor, avoid benzodiazepines if possible, and maintain anesthesia with sevoflurane. Other elements of the anesthetic plan were at the discretion of the clinicians. Patients were labeled in the electronic medical record as study participants, but all members of the clinical care team throughout the entire surgical admission were blinded to study group allocation, as were research team members (A.M.-M. and M.L.H.) interacting with the patients postoperatively. Stored data for the group receiving cognitive exercise was retrieved from the Lumosity application, and the dosage of cognitive exercise was calculated from the quantity of games a participant played, based on pooled usage data from Lumos Labs.[22] Trial recruitment stopped when a sufficient number of patients completed trial procedures for determination of the primary outcome.

Study Outcomes

The primary study outcome was incidence of delirium occurring between postoperative day 0 to discharge or day 7, whichever came first. Secondary outcomes included the day of postoperative delirium onset, duration (time from first to last delirium-positive day), and total delirium-positive days among patients who developed delirium in the control and intervention groups. Presence of postoperative delirium was assessed in the postanesthesia care unit and then twice daily (AM and PM) by blinded investigators (M.L.H. and A.M.-M.) using a brief Confusion Assessment Method[24] and Memorial Delirium Assessment Scale.[25] Because of the waxing and waning nature of delirium, researchers (A.M.-M. and E.S.) reviewed all progress notes and nursing documentation for delirium diagnoses, and a thorough medical record review process using the Chart-based Delirium Identification Instrument[26,27] with a blinded neuropsychologist (C.M.N.) was completed at the conclusion of the trial to detect any cases of delirium in patients that occurred outside of in-person delirium assessments. Identification of delirium by any study method yielded a patient being counted as having delirium on that postoperative day.

Statistical Analysis

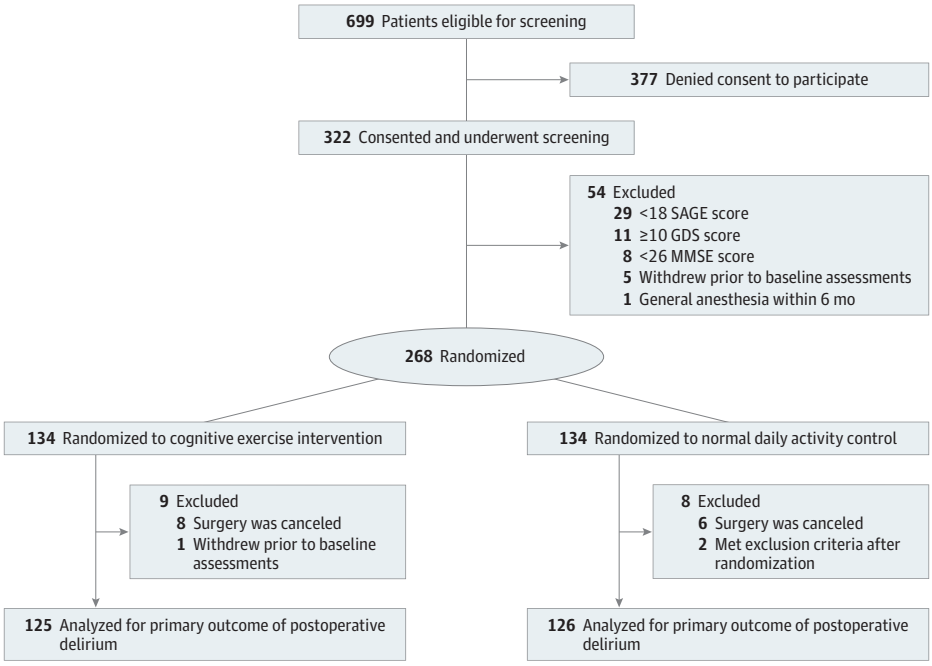
Assuming a 30% incidence of postoperative delirium in control patients based on a prior meta-analysis,[28] a total of 242 randomized patients completing study evaluation for the primary outcome (1:1 ratio, 121 in each group) was needed to achieve 80% power for detection of a 50% reduction in postoperative delirium using a χ^2 test. Continuous data were summarized (median and interquartile range [IQR]) and compared between randomization groups using Wilcoxon rank sum tests. Categorical data were summarized as frequencies (percentages) and compared between study groups using χ^2 tests or Fisher exact tests, as appropriate. The primary outcome, incidence of postoperative delirium, was compared between study groups using a χ^2 test with an intention-to-treat analysis. Minimum compliance with the intervention was defined as a patient having participated in some brain exercise, and a post hoc analysis compared postoperative delirium incidence in control participants with only the intervention patients who met minimum compliance. A multivariable generalized linear regression analysis modeled the effect of baseline variables on the incidence relative risk of delirium. Secondary outcomes in patients with delirium compared delirium characteristics using Fisher exact testing between the intervention and control groups. Additional analysis in patients in the intervention group assessed for a potential dose-response association between total hours of cognitive exercise completed and incidence of delirium using a Mantel-Haenszel χ^2 test. We used SAS version 9.4 (SAS Institute) for all analyses. Hypothesis testing was conducted at an overall 5% type I error rate.

Results

Patient Characteristics

Six hundred and ninety-nine patients were approached about study participation, 322 provided consent, and 268 were randomized equally between the control and intervention groups. Subsequently, 17 patients were excluded, leaving 125 patients in the intervention group and 126 control patients in the primary outcome analysis (median [IQR] age, 67 [63-71] years; 163 women [64.9%]; **Figure 1**). Randomization was effective, and no differences were observed between the 2 study groups with respect to demographic data; comorbidity burden; years of education; highest level of education completed; baseline performance on Mini-Mental State Examination testing; presence of depression indicators; and presurgery use of antidepressants, benzodiazepines, and narcotic pain medications (**Table 1**). Frailty indicators[29] were similar between groups, with exception to walking several hundred yards (those answering "a lot" to the question "does your health limit you in walking several hundred yards?": intervention group, 33 of 121 [27.3%] vs control group, 49 of 125 [39.2%]; P = .05; eTable 1

Figure 1. CONSORT Diagram



Of the 699 patients eligible for screening, 322 patients provided consent and underwent screening. At this point, 54 patients were deemed ineligible, and 268 were randomized, 134 to cognitive exercise intervention and 134 to normal daily activity control (protocol in Supplement 2 includes discussion of Self-Administered Gerocognitive Evaluation [SAGE] exclusion process). Prior to surgery, 9 patients were excluded from the intervention group and 8 from the normal daily activity control group. Overall, 125 patients were analyzed for postoperative delirium in the cognitive exercise intervention group and 126 patients in the normal daily activity control. GDS indicates the Geriatric Depression Scale; MMSE, Mini-Mental State Examination.

in Supplement 1). Most patients underwent general (94 of 251 [37.5%]) or orthopedic (118 of 251 [47.0%]) surgeries, with more patients in the control group having orthopedic procedures compared with the intervention group (intervention group: 52 of 125 [41.6%] vs 66 of 126 [52.4%]; $P = .03$). However, none of the intraoperative variables or medications were significantly different between study groups (eTable 2 in Supplement 1), including length of surgery (overall: median, 217 [IQR, 151-317] minutes; $P = .57$; Table 1). Patients were generally extubated in the operating room (245 of 251 [97.7%]) and brought to the postanesthesia care unit, where recovery times were similar between groups (overall: median, 125 [IQR, 99-183] minutes; $P = .57$). Rates of postoperative intubation were low (intervention, 2 patients [1.6%]; control, 4 patients [3.2%]; $P = .68$) (eTable 2 in Supplement 1). Compared with the intervention group, more patients in the control group were admitted to the intensive care unit postoperatively (9 patients [7.2%] vs 19 patients [15.1%]; $P = .047$) (eTable 2 in Supplement 1). Twenty-three of 28 patients who were in the intensive care unit had undergone orthopedic surgery. However, the intervention and control groups had similar overall hospital length of stay (median, 4 [IQR, 3-6] days; $P = .55$) (Table 1).

Cognitive Exercise Compliance

A total of 121 of 125 patients (96.8%) in the intervention group met our definition of minimum compliance. Four patients (3.2%) randomized to the intervention group completed no brain exercise. The time of cognitive exercise performance was widely variable (range, 0-32.5 hours), with only 11 of 125 patients (8.8%) completing the goal of 10 hours per study protocol. Overall, the median preoperative exercise time was 4.6 (IQR, 1.3-7.4) hours (**Figure 2**).

Primary Outcome

A total of 1679 of a possible 2268 in-person delirium assessments by researchers were completed for study patients (74.0%). Twenty-three patients (intervention group, 13; control group, 10) did not receive any in-person delirium assessments (medical record review only). The overall delirium rate for the trial was 18.7% (47 of 251 patients). The control group delirium rate was 23.0% (29 of 126 patients). With intention-to-treat analysis, delirium was identified in 18 of 125 patients in the intervention group (14.4%; $P = .08$; **Table 2**). Post hoc analysis removed 4 patients from the intervention group who did not meet minimum compliance (2 patients with delirium and 2 who did not develop delirium). This yielded a delirium rate of 13.2% (16 of 121 patients; $P = .04$).

Multivariable Regression Analysis

In multivariable regression modeling, the relative risk of delirium was lower in the intervention group compared with control patients, after adjusting for surgical procedure and response to frailty indicators. In an intention-to-treat analysis, the incidence relative risk was 0.58 (95% CI, 0.33-0.99; $P = .047$; Table 2).

Secondary Outcomes

Delirium onset, duration, and total delirium-positive days are represented in **Figure 3** and summarized in Table 2. Secondary analyses showed no statistical differences in postoperative delirium onset day, duration (overall: median, 2 [IQR, 1-4] days; $P = .91$), or total delirium-positive days (overall: median, 2 [IQR, 1-4] days; $P = .84$) among patients with any delirium across the intervention and control groups (18 patients and 29 patients, respectively). In the intervention group,

Table 1. Characteristics of Patients at Baseline

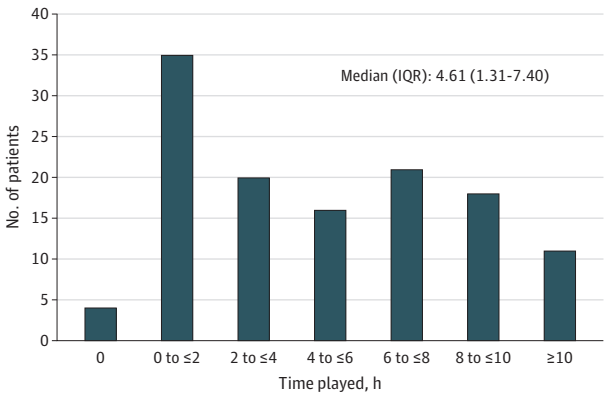
Characteristic	No. (%) Overall (n = 251)	Intervention (n = 125)	Control (n = 126)	*P* value
Age, median (IQR), y	67 (63-71)	67 (64-70)	67.5 (63-72)	.61
BMI, median (IQR)	31.4 (27-37.2)	31.5 (28-37.1)	31.2 (27-37.8)	.92
Female	163 (64.9)	77 (61.6)	86 (68.3)	.27
Education level, median (IQR), y	14 (12-16)	14 (12-16)	14 (12-16)	.47
No.	246	123	123	
Mini-Mental State Examination, median (IQR)	29 (28-30)	29 (28-30)	29 (28-30)	.55
Self-Administered Gerocognitive Evaluation, median (IQR)[a]	20 (18-21)	20 (18-21)	19.5 (18-21)	.11
No.	232	112	120	
Geriatric Depression Scale, median (IQR)	2 (1-4)	2 (1-4)	2 (1-4)	.72
Charlson Comorbidity Index score, median (IQR)	2 (1-3)	2 (1-3)	1 (1-2)	.67
Preoperative medications				
Narcotics	78 (31.1)	34 (27.2)	44 (34.9)	.19
Antidepressants	79 (31.5)	42 (33.6)	37 (29.4)	.47
Benzodiazepines	47 (18.7)	23 (18.4)	24 (19.0)	.90
American Society of Anesthesiologists physical status level				
I-II	36 (14.3)	14 (11.2)	22 (17.5)	.22
III	204 (81.3)	107 (85.6)	97 (77)	
IV	11 (4.4)	4 (3.2)	7 (5.6)	
Surgical procedure				
General	94 (37.5)	48 (38.4)	46 (36.5)	.03
Orthopedic	118 (47.0)	52 (41.6)	66 (52.4)	
Gynecologic	10 (4.0)	4 (3.2)	6 (4.8)	
Thoracic	6 (2.4)	2 (1.6)	4 (3.2)	
Urology	9 (3.6)	8 (6.4)	1 (0.8)	
Plastic	11 (4.4)	8 (6.4)	3 (2.4)	
Other[b]	3 (1.2)	3 (2.4)	0 (0)	
Length of surgery, median (IQR), min	217 (151-317)	221 (161-317)	215 (138-300)	.57
Length of stay, median (IQR), d	4 (3-6)	4 (3-6)	4 (3-6)	.55

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); IQR, interquartile range.

[a] Missing data attributable to a protocol amendment removing the Self-Administered Gerocognitive Evaluation as an exclusion criterion.

[b] Other surgical procedures include vascular, transplant, and otolaryngology surgeries.

Figure 2. Lumosity Gameplay Distribution



Preoperative cognitive exercise times for the 125 patients randomized to intervention. Median and interquartile ranges (IQRs) for brain exercise time are 4.61 (1.31-7.40) hours. Four patients did not participate in any cognitive training, while 11 patients completed the recommended 10 hours of training.

incidence of delirium among those who played less than 5 hours was 18.4% (12 of 65 patients). For patients who completed 5 to 10 hours of cognitive exercise, the delirium rate was only 10.2% (5 of 49 patients) and 9% (1 of 11 patients) for those completing more than 10 hours (Mantel-Haenszel $P = .20$). Baseline characteristics were similar between patients who played more than vs less than 5 hours of brain exercise (eTable 3 in Supplement 1).

Discussion

Despite having a lower than anticipated delirium rate in the control group, our intervention resulted in a decreased incidence of delirium in patients that were at least minimally compliant. This effect was present despite wide variability in the amount of cognitive exercise completed by patients in the intervention group. Our interpretation of the secondary outcomes is limited by the number of patients included in the analyses, although it appears that cognitive exercise did not affect the

Table 2. Postoperative Delirium Characteristics and Incidence Relative Risk (IRR) Models

Characteristic	No. (%) Overall (n = 251)	Intervention (n = 125)	Control (n = 126)	*P* value
Primary outcome				
Postoperative delirium	47 (18.7)	18 (14.4)	29 (23.0)	.08
Secondary outcomes[a]				
No.	47	18	29	NA
Delirium onset, postoperative d				
0	13 (27.7)	5 (27.8)	8 (27.6)	.84
1	11 (23.4)	3 (16.7)	8 (27.6)	
2	12 (25.5)	6 (33.3)	6 (20.7)	
3	6 (12.8)	2 (11.1)	4 (13.8)	
4	3 (6.4)	1 (5.6)	2 (6.9)	
5	1 (2.2)	0 (0)	1 (2.2)	
6	1 (2.2)	1 (5.6)	0	
7	0	0	0	
Delirium duration, median (IQR), d	2 (1-4)	2 (1-4)	2 (1-4)	.91
Delirium-positive days, median (IQR)	2 (1-4)	2 (1-4)	2 (1-3)	.84
Model results, IRR (95% CI)[b]				
Unadjusted	0.63 (0.37-1.07)	NA	NA	.08
Adjusted[c]	0.58 (0.33-0.99)	NA	NA	.047

Abbreviations: IQR, interquartile range; NA, not applicable.

[a] Secondary outcomes were calculated only for patients diagnosed with postoperative delirium.

[b] Both results compare the intervention group vs the control group.

[c] Multivariable generalized linear models were adjusted for surgical procedure (orthopedic vs nonorthopedic) and baseline frailty-associated questions (listed in eTable 1 in the Supplement).

temporal onset of delirium or overall delirium burden (duration and total delirium-positive days) in patients positive for delirium. Based on our trial, a dose of less than 10 hours of cognitive exercise appears protective against postoperative delirium, although a minimal effective dosage remains to be determined, and an appropriately powered study is needed to make conclusions about the effect of cognitive exercise on delirium course.

From this trial, it is clear that roughly an hour a day of preoperative cognitive exercise in the several consecutive days leading up to major surgery is not achievable for a significant portion of older patients undergoing surgery. Two perioperative brain exercise feasibility trials have also reported difficulty with patient compliance,[21,22] although prescribed interventions may have better compliance than voluntary research activities. This trial was not designed to examine dosage effects, but acknowledging that patients who completed less than 5 hours of cognitive exercise in our trial had almost twice the incidence of delirium of those who completed more than 5 hours highlights that future studies should consider comparing patients assigned to different cognitive exercise time goals. We captured patients in a somewhat brief window prior to surgery (a minimum of 8 days), but it is not clear from our work if future trials should consider longer study durations with less daily exercise burden or shorter durations with more daily exercise to improve patient compliance with the intervention.

We chose the Lumosity application for the cognitive exercise in this trial because of its user-friendliness, adaptive format, lack of requirement for home internet access, and ability to allow us to verify patient participation. Although there are logistical benefits of tablet-based exercise, the older patients undergoing cardiac surgery in the Prevention of Early Postoperative Decline trial[22] reported use of a tablet device, in addition to lack of desire to participate in research and time constraints, as factors limiting their participation. Even if non-technology-based brain exercise, such as crossword puzzles, would be better adhered to, it is difficult to truly know compliance and therefore difficult to research efficacy. As younger adults who are comfortable with technology at baseline become older adults, some of the current barriers to electronic brain exercise may resolve, although we identified no baseline differences in patients playing less brain exercise compared with those playing more, including age. Vlisides et al[12] suggest a need for supervision of preoperative brain exercise. This may be especially important in patients with preexisting cognitive impairment, who are at increased risk of postoperative delirium and have yet to be specifically targeted in a preoperative brain exercise study, to our knowledge. In the future, investment in devices with cellular capability for patients prescribed home-based cognitive exercise could provide the additional capability of allowing a research or clinical team member to monitor patient participation and performance, intervening or supervising as needed for patient support. There was no evidence in our trial that patients experienced harm or unintended effects of the brain exercise intervention.

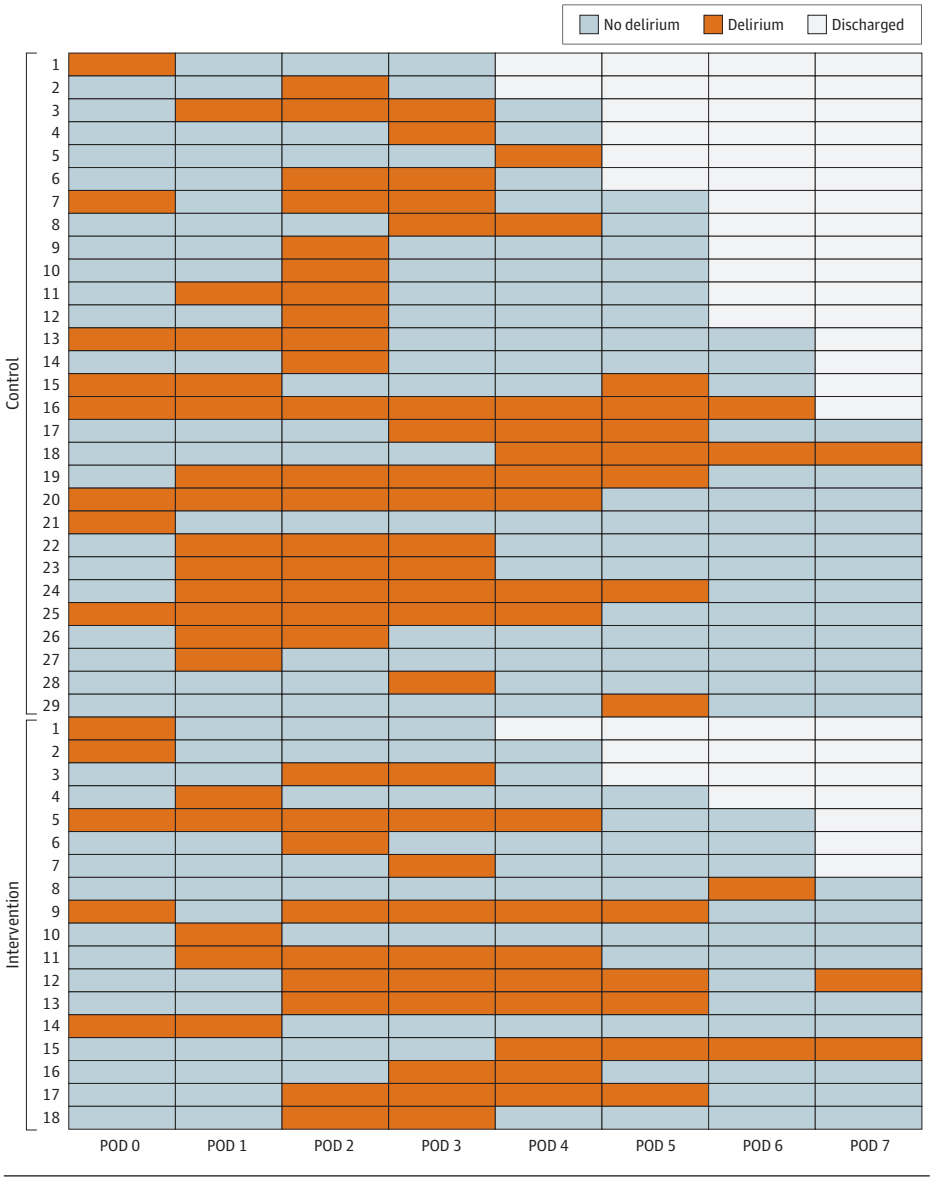
Strengths

Our study has several important strengths. Although postoperative delirium typically occurs in the first 72 hours after surgery, we followed up patients to discharge or postoperative day 7 to evaluate the entire postoperative period in which delirium is diagnosed.[30] We had a high rate of in-person delirium assessment completion, which is challenging, with a rigorous protocol evaluating for delirium twice daily to capture the waxing and waning nature of the disorder.

Limitations

Important limitations include patient compliance and the need to estimate completed hours of brain exercise from

Figure 3. Postoperative Delirium Onset and Duration



Postoperative delirium course of the 47 patients with delirium (29 in the control group and 18 in the intervention group) as diagnosed by Confusion Assessment Method, Memorial Delirium Assessment Scale, or medical record review from postoperative days (PODs) 0 through 7.

the number of games played. Multivariable analysis, adjusted for baseline factors, supported that risk of delirium was decreased in patients in the intervention group compared with control patients. However, other unquantifiable influences may have affected the study over its duration of more than 4 years, including study personnel changes, growing awareness about postoperative delirium, and implementation of surgical recovery quality improvement programs at our institution. We focused on patients having major noncardiac, nonneurological surgery, so generalizability to populations with potentially different mechanisms of postoperative delirium, such as patients undergoing cardiac surgery, is limited.

At the start of this trial, we were not yet aware of the considerable percentage of geriatric patients who present for surgery with evidence of at least mild cognitive impairment.[31] The implications of brain exercise in patients with preexisting cognitive impairment may be very different from patients who are cognitively normal, and this warrants specific study. For elderly patients undergoing nonelective surgery, which is high risk for postoperative delirium, the postoperative period is most of the possible therapeutic window. Although we focused on the preoperative period for brain exercise, the notion of using cognitive exercise postoperatively to promote successful cognitive recovery merits study as well.

Conclusions

Our brain exercise intervention resulted in a decreased delirium incidence in patients who were at least minimally compliant. The ideal activities, timing, and effective dosage

for cognitive exercise-based interventions to decrease postoperative delirium risk and burden need further study. Modification of postoperative delirium risk with brain exercise remains a novel concept in the early stages of clinical study, and more investigation appears warranted, based on our work.

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