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Does mild cognitive impairment increase the risk of developing postoperative cognitive dysfunction?

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Abstract

BACKGROUND—Increasingly, postoperative cognitive dysfunction (POCD) is recognized as a complication after surgery in the elderly. We sought to determine whether patients with mild cognitive impairment (MCI) would have an accelerated progression of dementia postoperatively when compared with the patients without MCI.

METHODS—The Center for Brain Health at the New York University (NYU) Medical Center maintains records of volunteers who undergo a series of neurological assessments. We reviewed records of 670 patients who received at least 2 evaluations and whose surgery occurred before the second assessment. Longitudinal differences of several cognitive domains were examined.

RESULTS—Individuals with MCI and surgery had a greater decline in performance on the Digit Span Forward test compared with those with MCI without surgery on their postoperative evaluation ($F_{3,158} = 3.12$, P = .03). No performance changes were detected in the normal subjects.

CONCLUSION—These preliminary findings suggest that surgery negatively impacts attention/ concentration in patients with MCI but not in normal individuals. This is the first study that identified a specific subgroup of patients who are predisposed to POCD.

Keywords

Postoperative complications; Cognitive impairment; Working memory; Neurocognitive testing

Advances in surgical techniques and anesthetic care have resulted in a substantial reduction in perioperative mortality and morbidity in the elderly. Patients with multiple medical problems routinely undergo complex surgical procedures relatively late in life. Associated with these advances is the increased recognition that central nervous system (CNS) dysfunction is a complication after cardiac and noncardiac surgery in the elderly.^{1,2}

Postoperative cognitive dysfunction (POCD) is a deterioration of cognitive performance after surgery (and/or anesthesia) presenting as impaired memory or concentration. The condition is defined by assessing preoperative and postoperative intellectual performance. Although in most cases the impairment is transient (weeks to months), a cognitive decline is permanent in some elderly patients, leading to decrease in the activities of daily living (ADL) and loss of independence.³ Numerous studies have attempted to identify risk factors leading to POCD.^{1,2,4} Perioperative physiological derangements (ie, hypotension),

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anesthetics, duration of surgery, limited education, and respiratory complications have been suggested as possible causes, but only age has proven to be a consistent risk factor in most studies. Thus, it is unclear which subgroups of at risk patients are predisposed to develop CNS complications. An answer to this question is imperative if we are to consider instituting preventative measures to reduce the incidence of POCD. It would not be feasible from both the practical and economic points of view to treat every elderly surgical patient as though they were at risk for POCD.

Extensive research has identified an intermediate state between normal aging and dementia, which has been termed mild cognitive impairment (MCI).^{5,6} MCI is defined as impairment in 1 or more cognitive domains (typically various forms of memory) that are greater than would be expected for a person's age, that do not yet interfere with ADL. Individuals with MCI are known to have an increased risk of progressing to dementia compared with elderly age-matched persons with normal levels of cognitive functioning. Longitudinal studies of patients with MCI show conversion to dementia (mostly associated with Alzheimer's disease [AD]) at a rate of 10% and 15% per year. Elderly control subjects typically develop dementia at a rate of 1% to 2% annually.⁷ Patients with amnestic MCI (a subtype of MCI) are particularly known to progress to AD at a high rate.

A recent study probed the link between preoperative cognitive impairment (PCI) and POCD using the database of the International Study of Postoperative Cognitive Dysfunction (ISPOCD).^{8,9} PCI is a nonvalidated surrogate measure of MCI proposed by the authors. The study did not reveal an association between PCI and further memory deterioration. However, the authors cautioned that memory tests, which are a part of the neurocognitive battery used in the ISPCOD study (used to diagnose PCI), may not be adequately sensitive to diagnose MCI. They suggested that "future studies should be conducted to determine whether POCD occurs in MCI patients."⁹

The Alzheimer's Disease Center (ADC) at the New York University (NYU) School of Medicine is 1 of 30 AD research centers in the United States supported by the National Institutes on Aging. The center focuses on the longitudinal characterization of cognitive and functional status of nondemented aging, MCI, and mild AD patients. Standardized cognitive assessments and histories of participating volunteers are obtained during the visit and, as one would expect, subjects at times have surgery between assessments. The effect of surgery and anesthesia in a MCI population is not known and explored in this paper. We hypothesized that surgery accelerates cognitive deterioration in patients with MCI but that it is not associated with decreased future performance in normal functioning elderly. Therefore, in a retrospective longitudinal study we compared the results of cognitive tests in patients with and without surgery from the ADC database.

Methods

Participants

We retrospectively examined data from community-dwelling study volunteers drawn from a pool of individuals participating in brain aging studies at the NYU ADC and the affiliated NYU Center for Brain Health (CBH). Subjects were selected from the pre-existing database, provided that they fit the inclusion and exclusion criteria. Informed consent, approved by the NYU School of Medicine institutional review board, was obtained from all participants at each evaluation. Most subjects had at least 12 years of education (88%), were of middle to upper socioeconomic status, and were predominately Caucasian (89%). Subjects received an extensive diagnostic evaluation that included medical, neurological, psychiatric, and neuropsychological examinations, as well as brain computerized tomographic (CT) or magnetic resonance (MR) imaging.

Patients were divided into MCI and normal groups. MCI was diagnosed using the clinical assessment in accordance with the recommendations of the Clinical Task Force from the ADC.¹⁰ The Global Deterioration Scale (GDS) was used as a basis for the diagnosis of MCI.¹¹ All data were obtained from chart review. We did not interview the patients for this study but relied on data in research charts.

Study inclusion/exclusion criteria

Participants whose data were included in the current analyses were between the ages of 60 and 90 with at least 9 years of education, and had at least 2 cognitive evaluations. Subjects who were not native English speakers (17 of 169) were included if they achieved a scaled score of at least 11 on a Wechsler Adult Intelligence Scale (WAIS) Vocabulary subtest, which is considered an average score in a general population.¹² Both normal and MCI subjects were included if their GDS⁹ score was ≤ 3 (see diagnostic procedures below). Individuals with evidence of any diagnosable neurological or psychiatric disorder (eg, any brain disorder affecting cognition other than AD, including intracranial surgery, cortical stroke, normal pressure hydrocephalus [defined clinically and by imaging], or depression as defined by a Hamilton Depression Scale¹³ score >9) were excluded.

Diagnostic procedures

A semi-structured clinical interview using the Brief Cognitive Rating Scale (BCRS)¹⁴ assessed the magnitude of cognitive impairment in concentration, recent and past memory, orientation, and functioning/self-care providing a numerical score for each domain. Information obtained from the BCRS was used to determine the GDS. The GDS,¹¹ a 7-point rating scale, uses validated descriptors assess the global cognitive and level of functional capacity as follows: normal (NL) (GDS = 1 or 2 characterized as cognitively and functionally normal; differentiated by the absence vs presence of subjective memory complaints, respectively), MCI (GDS = 3), mild to moderate AD (GDS = 4 or 5), and severe AD (GDS ≥ 6).¹⁵ The GDS scoring system is based on clinical assessment (a subject interview). The GDS score was assigned independently of neuropsychological testing. Furthermore, the clinicians performing the GDS assignment were in all cases blind to the findings from the neuropsychological testing procedures.

All diagnoses were made at a consensus meeting. Patients with dementia noted at presurgical evaluation were excluded. The NL and MCI diagnoses for the remaining cohort were based only on the GDS and relevant medical data obtained at the evaluation.^{16–18} Criteria for the diagnosis of MCI were memory complaints documented by the patient and a collateral informant, normal general cognition, normal ADL, no dementia, and a GDS score of 3. Subjects were included in either the normal or MCI groups as described below, with all groups being mutually exclusive. Subjects were divided into 4 groups: (1) MCI without surgery; (2) MCI with surgery, (3) NL without surgery; (4) NL with surgery. Individuals who underwent a surgical procedure requiring general anesthesia and at least 1 day of hospitalization were defined as part of a surgery group. Subjects received surgical procedures between the 2 clinical evaluations of note.

Cognitive tests

The cognitive test battery administered in this study included the Guild Memory Test¹⁹ to assess several components of memory function, including paragraph immediate and delayed recall (PARI, PARD), immediate and delayed recall of verbal paired associates (VPAI, VPAD), and visual paired associates design (DESN). The test battery also included several subtests from the WAIS which assess working memory, concentration, processing speed, and attention, specifically, Digits Span Forward (DS-F) and Backward (DS-B), and the Digit Symbol Substitution Test (DSST). Cognitive measures were converted into *z* scores based

on the NYU longitudinal normative database.¹⁴ Table 1 describes the cognitive domain that is measured by each of these tests.

Statistical analyses

We examined group differences in continuous demographic variables (eg, age) using analysis of variance (ANOVA) with post hoc Tukey tests. Group differences for categorical demographic variables (eg, gender) were compared using Pearson χ^2 analyses. Repeated measures analysis of covariance (ANCOVA) was used to evaluate change in z scores for cognitive tests at evaluations before and after surgery. Since this was a retrospective study, the time between cognitive evaluations (visits) varied between subjects and, while the mean follow-up time was not significantly different for the study groups, one might expect some correlation between follow-up time and change in cognitive scores, particularly for tests that are correlated with age. By adding the follow-up time as a covariate in our repeated measures ANCOVA models, we are able to factor out (account for) these differences and evaluate changes beyond those associated with the time differences. For tests that showed significant group changes between visits, the baseline scores were examined with ANOVA with *post hoc* Tukey tests, to rule out regression towards the mean. Random coefficients regression analyses were also used to examine cognitive change accounting for time differences between cognitive evaluations We were primarily interested in decreases in performance that were different between groups which is the within subjects group by visit interaction in the repeated measures ANCOVA. Therefore, we have reported only the results for the group by visit effects both in the text and the table. Statistical significance was defined as P values $\leq .05$ on all analyses except for *post hoc* analyses for the repeated measures ANCOVA where, to account for multiple comparisons, P values $\leq .02$ where considered significant. SPSS (version 12.0; Chicago, IL) was used for data analyses.

Results

We identified 169 patients who met the inclusion criteria. There were 48 patients with MCI who had 2 assessments, 14 of whom had a surgery between evaluations. We also identified 121 NL who had 2 assessments, 50 of whom had a surgery between evaluations. Table 2 shows subjects' demographic characteristics. There were no statistically significant differences between groups for age, gender, or years of education. The information regarding surgery was taken from the patients' research evaluation charts which were completed during a nonstructured interview as a part of an overall medical assessment. We do not know the exact dates of surgery. Times between cognitive visits were as follows (mean \pm SD): NL, no surgery: 2.17 \pm .95; NL, surgery: 2.14 \pm 1.19; MCI, no surgery: 1.87 \pm .37; and MCI, surgery: 1.92 \pm .4 (Table 3).

Table 4 shows the neuropsychological test results for the NL and MCI patients with and without surgery. There was a significant interaction between group and visit for the DS-F test ($F_{3,158} = 3.12$, P < .05). There were no significant differences in the baseline scores for any of the groups on this test. *Post hoc* test of the longitudinal data showed that the MCI with surgery group had a significantly greater decline in performance on the DS-F test compared with the NL group (P < .01) and to the MCI with no surgery group (P = .01), which indicates decreased attention and working memory performance. We did not find statistically significant different longitudinal decline in other cognitive domains after surgery in individuals with or without MCI.

In addition, we compared change in *z* scores from the first to the second visit for the group. In a logistic regression with MCI surgery and no surgery, we have a sensitivity of 78.6% (ie, 11 of the 14 MCI surgery subjects can be correctly classified as different from nonsurgery subjects based on the change in the *z* score for DS-F) and specificity of 67.6% (23 of 34

MCI nonsurgery subjects can be correctly classified as different from the MCI surgery group based on the change in the *z* score for this test).

Comments

This retrospective cohort analysis of patients enrolled at the ADC and the affiliated NYU CBH at the NYU School of Medicine suggests that surgery may negatively impact auditory working memory, attention, and concentration (as measured by the DS-F) in patients with MCI but not in normal individuals. There were no statistically significant differences in performance on other cognitive tests. Our analysis suggests that surgery may differentially affect specific cognitive domains in a particular subset of patients. Considering that decline of executive function may lead to functional limitation more readily than decline in memory,²⁰ the results are intriguing and clinically relevant (eg, assessing risk factors for postoperative complications in some patients scheduled for an elective surgery). Although long-term postoperative changes in mental function are well documented, this is the first study that has identified decline in a particular cognitive domain in patients who are predisposed to this complication.

MCI is a term that describes a level of cognitive functioning that reflects an intermediate state between normal aging and dementia.²¹ The diagnosis of MCI includes the following criteria: (1) memory complaints, preferably corroborated by an informant; (2) objective memory impairment for age and education; (3) largely intact general cognitive function; (4) essentially pre-served ADL; and (5) no evidence of dementia.⁷ It is expected that patient with MCI will have inferior performance on neuropsychological assessments that measure memory and learning, but will be intact in the concentration/attention/processing speed domain. Accordingly, we have chosen to assess subjects' longitudinal performance using a battery of tests that assess these 2 cognitive domains reasonably independently.

As expected, MCI patients in our study had significantly lower baseline scores than normal subjects on neurocognitive tests measuring various *memory* performances. It is expected, because memory problems are one of the hallmarks of the MCI diagnosis. There were no significant differences in the baseline performance on DS-F and DS-B, which measure attention/concentration and processing speed (ie, executive function). It is less likely that surgery will significantly affect learning/memory in MCI patients because it is already compromised (eg, "flooring effect"). The negative effect of surgery (if any) will be more pronounced in executive/attention (also referred as a "working memory" by some authors²²) area where patients are not impaired yet. Our findings corroborate this assertion.

We observed a significant decline in DS-F performance, which is a predictor of attention and concentration.²³ However, the performance on the DS-B measure was not affected. Working memory refers to an individual's ability to hold relevant information in mind for the purpose of completing a task; it is that functional system that provides for temporary storage and manipulation of information.^{22,23} It made up of 3 subsystems: the phonological loop, the visuospatial sketchpad, and the central executive. The phonological loop is comprised of a temporary storage system and subvocal rehearsal system that preserves information in short-term auditory memory.²⁴ The visuospatial sketchpad serves as a means of integrating visual and spatial information that may be stored and manipulated temporarily²⁵; the attentional control of working memory in maintained by the central executive system. DS-F tasks rely on either the articulatory loop or visual sketchpad with little need for a central executive system. By contrast, DS-B tasks require some resources of the executive system due to the increase in attentional demands and control processes needed. Our results suggest that surgery may impair 1 cognitive domain without significantly affecting other areas of cognition.

Several recent analyses have addressed the selective vulnerability of various cognitive domains in response to surgery. Silverstein et al have used the ISPOCD database to explore patterns of deterioration in patients with PCI.9 The diagnosis of PCI may or may not include patients with MCI. The most notable decline was found in tests assessing attention and cognitive speed (1 week after surgery). Deterioration was less common in memory function. Considering the limitations of both studies our findings are remarkably similar. Price et al examined the type and severity of cognitive impairment in elderly surgical patients enrolled in a recently completed POCD investigation.²⁶ They reported that more subjects were impaired on the memory indexes (54%) relative to executive functions (34%). Lower educational level predicted the incidence of POCD. This result seems contradictory to our findings. However, the subjects recruited for this study were not tested for the diagnosis of MCI. MCI assumes rather uniform memory assessment, which is based on a clearly defined criteria (see above) and there is a very little "room" for further decline. The baseline performance of the subjects on memory tests was variable. Thus, it is not surprising that the authors observed a higher proportion of patients with memory deterioration. Contrary to Price's study, our patients had already reached the limits of their "cognitive reserve." Cognitive reserve is believed to mediate the relationship between a degree of brain damage and the onset of clinical dementia. The significance of this concept is that subjects with greater cognitive reserve can sustain more neuronal loss or pathological changes before exhibiting signs of clinically significant cognitive impairment.

Individuals in our sample had 15.9 years of education. It is higher than in most studies on POCD. Only 25.3% of patients in the ISPOCD study more than high school education.⁸ Monk et al reported 13.43 ± 2.79 years of education in their patients.²⁷ Level of education is one of the most consistent predictors of POCD. Thus, it is reasonable to expect that less educated patients with MCI would have a higher incidence of progressive dementia than in our sample after surgery/anesthesia.

There several limitations to our study. The major one is related to our inability to control for the time interval between pre- and postoperative testing due to the retrospective nature of the study. In addition, only 1 of 8 assessments suggested a statistically significant deterioration. Thus, type II error cannot be excluded. However, it appears that our observation (the differential effect of surgery on a specific cognitive domain) is in agreement with the conclusion of a recent analysis,²⁶ thus emphasizing the potential impact of surgery/ anesthesia in patients with MCI. Second, the surgical diagnoses as well as the extent of the surgery were not matched (and unknown in some cases). Third, it was difficult to establish connections between cognitive impairment and ADL. Not all medical records contained this information. Preservation of ADL is an ultimate goal of any research designed to study POCD. Fourth, we had no information in regards to a perioperative management of the subjects, such as a type of anesthesia, incidence of hypotension, hypoxia, length of surgery, etc.

In conclusion, we have demonstrated that surgery may negatively affect the domain of attention/concentration in patients with a preoperative diagnosis of MCI. However, surgery did not result in impairment of long-term memory, most likely due to "flooring" effect. Our study was exploratory in nature. Hence, the results should be interpreted as hypothesis-generating rather than hypothesis-testing. The prospective study investigating the association between surgery and accelerated progression to dementia in patients with MCI is warranted.

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Bekker et al.

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Bekker et al.

Table 1

Description of neuropsychological tests

Psychometric test	Description
Wechsler Digit Forward	A participant is required to repeat 3–9 digits forward. Test measures short-term auditory memory, sequencing, and concentration.
Wechsler Digit Backward	A participant is required to repeat 2-9 digits backwards. Measures working memory and concentration.
Digits Symbol Substitution Tests	A subject learns a code in which each digit is represented by a symbol and then tries to substitute the correct symbol for a series of digit as quickly and accurately as possible. It measures attention and speed of information processing
Paragraph Recall Immediate	The test is used in assessing a short-term memory and features a serial-position effect with participants recalling beginning and end of the paragraph.
Delayed Paragraph Recall	Tests delayed memory. Delayed paragraph recall can help predict short-term risk for decline to mild cognitive impairment and Alzheimer's disease.
Paired Associates Immediate Recall	Test is used in assessing explicit episodic memory performance. There is a positive correlation between decline in memory acquisition and older age.
Paired Associates Delayed Recall	Test is used in assessing explicit episodic memory performance. There is a positive correlation between decline in memory acquisition, and older age. Performance on the PARD is related to education and verbal IQ.
Visual Paired Associates Design	The test is a part of the Wechsler Memory Scale battery; it measures both visual immediate memory and visual delayed memory.

Table 2

Demographics

Characteristics	No surgery	Surgery
No. of subjects		
Normal aging	71	50
MCI	34	14
Age		
Normal aging	61.9 ± 15.2	63.3 ± 14.0
MCI	76.1 ± 8.8	73.8 ± 6.9
Education in years		
Normal aging	16 ±2	17 ± 2
MCI	14 ±3	16±3
Percent of women in a sample		
Normal aging	65	70
MCI	56	57

MCI = mild cognitive impairment.

Table 3

Surgical procedures

Surgical procedure	Patients without MCI	Patients with MCI
Orthopedic	16	7
Breast/skin	7	0
Abdominal	6	0
Gynecologic	5	2
Urological	5	2
Thoracic (excluding procedures that required by-pass)	4	2
ENT	2	0
Vascular	1	1
Ophthalmologic (excluding cataracts)	2	0
Unknowns	2	

ENT = ear, nose, throat.

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Table 4

Summary statistics of the effect of surgery on the performance of patients with and without MCI in various tests of cognitive function

			G	dno.		
Cognitive tests	Visit point	NL no surgery	NL surgery	MCI no surgery	MCI surgery	$F_{(df)}$, P value
Paragraphs Recall Immediate	Baseline	7.73 ± 2.72	7.62 ± 2.66	5.87 ± 2.35	5.89 ± 1.93	$F_{3,158} = 1.09,$
	Follow-up	7.86 ± 2.62	8.14 ± 3.04	5.45 ± 2.08	5.43 ± 2.18	P = .35
Paragraphs Recall Delayed	Baseline	9.65 ± 3.20	9.32 ± 2.89	6.78 ± 3.44	6.79 ± 3.18	$F_{3,158} = 1.67,$
	Follow-up	9.74 ± 3.23	9.32 ± 3.38	5.92 ± 3.06	5.71 ± 3.7	P = .18
Paired Associates Immediate	Baseline	5.61 ± 2.59	5.64 ± 2.72	3.50 ± 2.57	3.43 ± 2.17	$F_{3,158} = 1.48,$
Recall	Follow-up	5.35 ± 3.12	5.65 ± 2.73	2.58 ± 2.25	2.14 ± 2.32	P = .22
Paired Associates Delayed Recall	Baseline	6.14 ± 2.83	6.20 ± 2.82	3.68 ± 2.46	4.36 ± 2.59	$F_{3,158} = 1.94,$
	Follow-up	6.10 ± 3.35	6.39 ± 3.09	3.29 ± 2.88	2.79 ± 3.21	P = .13
Visual Paired Associates Designs	Baseline	6.62 ± 2.73	6.46 ± 2.62	4.06 ± 2.70	4.00 ± 2.6	$F_{3,158} = 1.22,$
	Follow-up	7.06 ± 2.54	6.37 ± 2.62	3.94 ± 2.31	4.14 ± 2.48	P = .30
Digit Symbol Substitution Test	Baseline	57.41 ± 13.16	57.50 ± 10.84	43.38 ± 11.81	46.43 ± 9.28	$F_{3,158} = 1.40,$
	Follow-up	57.03 ± 14.82	58.42 ± 12.54	41.28 ± 12.91	44.31 ± 8.13	P = .25
Digit Span Forward	Baseline	7.22 ± 1.26	7.14 ± 1.07	6.85 ± 1.25	7.07 ± 1.07	$F_{3,158} = 3.12,$
	Follow-up	7.08 ± 1.11	7.00 ± 1.18	6.97 ± 1.22	6.00 ± 1.15	$P = .03^{*}$
Digit Span Backward	Baseline	$\textbf{5.58} \pm \textbf{1.33}$	5.78 ± 1.59	4.97 ± 1.45	4.93 ± 1.38	$F_{3,158} = .74,$
	Follow-up	5.47 ± 1.47	5.32 ± 1.32	4.74 ± 1.48	4.85 ± 1.07	P = .53

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* Significant at P < .05.