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Postoperative Cognitive Dysfunction in Patients with Preoperative Cognitive Impairment

Which Domains Are Most Vulnerable?

Jeffrey H. Silverstein, M.D., Jacob Steinmetz, M.D.,† Abraham Reichenberg, Ph.D.,‡ Philip D. Harvey, Ph.D.,§ Lars S. Rasmussen, M.D., Ph.D.‖*

Background: **The authors explored the database of the first International Study of Postoperative Cognitive Dysfunction study to specify the domains of cognitive function that were most vulnerable and to determine the pattern of deterioration in patients with preoperative cognitive impairment.**

Methods: **One thousand two hundred eighteen patients were included in the first International Study of Postoperative Cognitive Dysfunction, where neuropsychological testing was performed at entry to the study, at 1 week, and at 3 months after surgery. The authors' analyses determined the extent to which seven neuropsychological measures changed after surgery with focus on the relation with preoperative cognitive impairment, defined as a preoperative score 1.5 SD below healthy controls in the memory test.**

Results: **Preoperative cognitive impairment was found in 74 patients at baseline. At 1 week, cognitive deterioration was seen in all tests, but in particular in the Letter Digit Coding and the time of the Stroop interference test, with 14% and 16% of the total sample (n = 1,016) exceeding 2 SD, respectively. At 3 months, deterioration was more uniform. Significantly fewer in the preoperative cognitive impairment group had deterioration in the memory test, both at 1 week and at 3 months, with no patient displaying a deterioration exceeding 2 SD.**

Conclusions: **Postoperative cognitive deterioration was seen in all tests, although most commonly in attention and cognitive speed at 1 week. Deterioration in memory was difficult to detect after surgery in patients with preoperative cognitive impairment.**

IN recent years, the term *mild cognitive impairment* (MCI) has come to describe a potential transitional zone between the cognitive changes of normal aging and the earliest clinical features of Alzheimer disease.[1] These patients are identified on the basis of impairments in specific cognitive processes in the absence of global dementia, marked by the presence of multiple cognitive impairments and functional disability.[2] The presence of cognitive impairment short of dementia has been recognized with several different labels. Although not without controversy, MCI has been described in a comprehensive consensus statement of an international working group.[1] Petersen *et al.* [3] provided a formal assessment procedure for detection of amnestic MCI that combines clinical assessment with the systematic use of neuropsychological test data to reliably define the presence of MCI. *Postoperative cognitive dysfunction* (POCD) is a developing concept characterized by persistent deterioration of cognitive performance after surgery and anesthesia, defined by preoperative and postoperative cognitive testing.[4] Conceptually, patients with MCI would seem to be most at risk for the development of further cognitive impairment after surgery and anesthesia because of their already compromised status and their potential vulnerability to worsen into dementia due to a less cognitive reserve.[5] Although not strictly a new idea, in 1993 Satz[6] elucidated a theory of brain reserve capacity to explain threshold phenomenon in brain injury, *i.e.*, that a certain amount of brain damage can occur before clinical symptoms appear. In a recent review of the intellectual development of what has become known as *cognitive reserve,* Richards and Deary[5] indicate that there are aspects of brain structure and function that can buffer the effects of neuropathology such that the greater the reserve, the more severe the pathology must be to cause functional impairment. Cognitive reserve explains observations of a protective effect of education against the prevalence of Alzheimer disease,[7] a phenomenon also noted for POCD. Their pattern of deterioration could also be different from the general population of surgical patients.

The largest POCD studies for noncardiac surgery to date were undertaken by the International Study of Postoperative Cognitive Dysfunction (ISPOCD) group.[4] In those studies, the definition of POCD was based on a standardized score (Z score) reflecting a change to 1.96 SDs below normal after surgery. Patients with amnestic MCI might not be able to register that much deterioration with the instrumentation used because of baseline memory impairments. In addition, the deterioration across the different domains of cognitive functioning was not reported. Patients with a Mini-Mental State Examination score of 23 or lower were excluded. This eliminates some, although not all MCI patients, from these studies. Using the ISPOCD1 database, we sought to explore possible differences between tests in the pattern of deterioration after surgery with specific focus on

* Associate Professor, Departments of Anesthesiology, Surgery, and Geriatrics and Adult Development, ‡ Assistant Professor, § Professor, Department of Psychiatry, The Mount Sinai School of Medicine, New York, New York. † Staff Anesthesiologist, ‖ Associate Professor, Department of Anaesthesia, Centre of Head and Orthopaedics, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark.

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Address correspondence to Dr. Silverstein: Department of Anesthesiology, Box 1010, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, New York 10027-6574. jeff.silverstein@mssm.edu.

patients with MCI. Because a determination of MCI requires the presence of a cognitive complaint and specific testing, it is not possible to make a retrospective diagnosis. Therefore, we have evaluated the ISPOCD data and established a surrogate measure that we call *preoperative cognitive impairment* (PCI). Within the limitations of the methodology, PCI is similar to amnestic MCI, the most common form of MCI.

We hypothesized that patients with PCI had a different pattern of deterioration in cognitive function, expressed as a difference in proportion of deterioration in single tests.

Materials and Methods

The data set was collected during the first ISPOCD. The ISPOCD was initially organized by Jakob Trier Moller, M.D., D.M.Sc. (Chair, Department of Anesthesia, Centre of Head and Orthopaedics, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark), Jan E.W. Beneken, Ph.D. (Eindhoven University of Technology, Eindhoven, The Netherlands), and Joachim Gravenstein, M.D. (Professor, Department of Anesthesiology, University of Florida, Gainesville, Florida). The goals of the first study (ISPOCD1) were to assess whether POCD could be detected after noncardiac surgery, the causative roles of hypoxemia and hypotension, and the role of age as a major risk factor for POCD.[4] Thirteen hospitals in nine countries recruited 1,218 patients between November 1, 1994, and May 31, 1996. Eligible patients were aged at least 60 yr, had presented for major abdominal, noncardiac thoracic or orthopedic surgery during general anesthesia, and had an expected duration of stay of 4 days or more. Patients who scored 23 or lower on the Mini-Mental State Examination were excluded. Patients completed a series of neuropsychological tests at entry to the study, at discharge from the hospital or 1 week after surgery, whichever was first, and 3 months after surgery. The psychometric tests were provided in seven languages and were tested for cultural sensitivity. In addition, 176 age-matched volunteers from the United Kingdom were recruited through advertisements as controls.

Neuropsychological Assessment

The tests used in the ISPOCD1 study included a Visual Verbal Learning Test, based on Rey's auditory recall of words[8]; the Concept Shifting Test, based on the Trail Making Test from Halstead and Reitan's neuropsychological test battery[9]; the Stroop Color Word Test[10]; the Paper and Pencil Memory Scanning Test[11]; the Letter Digit Coding Test, based on the Symbol-Digit Substitution Task from the Wechsler Adult Intelligence Scale[12]; and the Choice Reaction Time Test. The final primary outcome included the following: Visual Verbal Learning Test, cumulated learning and delayed recall; time on the Concept Shifting Test part C with error score, Stroop performance assessed as time during interference condition (part 3) with error score; score (correct items) on the Letter Digit Coding Test. In addition, two questionnaires were administered: the Cognitive Failures Questionnaire[13] and the Zung Depression scale.[14]

ISPOCD1 Criteria for POCD

To correct for learning effects, the ISPOCD1 investigators identified patients with postoperative cognitive dysfunction by comparison of changes in individual patients with the mean changes in test scores from baseline (first session) to 1 week and 3 months after the first test for the United Kingdom controls. For patients, they compared baseline scores with 1-week and 3-month test results, subtracted the average learning effect from these changes, and divided the result by the control group SD to obtain a Z score for each test. They further defined a composite Z score from the total of the Z scores for the United Kingdom controls, the SD of which we used to normalize the patients' composite Z scores at 1 week and 3 months. Patients were defined as having cognitive dysfunction when two out of seven Z scores in individual tests or the combined Z score were 1.96 or more. As noted above, such a definition of decline may not be suitable for use in a study with preexisting cognitive decline such as MCI patients.

In this article, we defined PCI as a preoperative score 1.5 SD below healthy controls in the Visual Verbal Learning Test. Therefore, patients were classified as having PCI if they had a preoperative score below 16 ($23.4 - 1.5 \times 5.3$) in cumulated learning or a preoperative score below 3 in delayed recall ($6.9 - 1.5 \times 2.8$) (table 1).

Data Analysis

Our analyses determined the extent to which the seven main neuropsychological summary measures changed after surgery. We wanted to determine whether the tests were differentially sensitive and whether the pattern of changes was different for patients with PCI as compared with patients without PCI.

The pattern of deterioration was assessed by calculating the proportion of patients showing a Z score above 1.96 in the individual seven test variables. In addition, we calculated the proportion of patients showing a Z score above 1 in the test variables as less deterioration seemed especially relevant in patients with MCI.

Continuous data were reported as mean with SD and compared with the Mann–Whitney test. Proportions were reported with 95% confidence intervals and compared with the chi-square test (SAS version 9.1; Cary, NC).

Table 1. Neuropsychological Test Results

	Patients			Controls		
	Baseline	1 Week	3 Months	Baseline	1 Week	3 Months
n	1,185	998	940	176	175	170
Visual Verbal Learning, cumulated recall, number of words	24.4 (5.6)	23.3 (6.0)	25.9 (5.6)	23.4 (5.3)	23.9 (5.8)	25.9 (6.0)
Visual Verbal Learning, delayed recall, number of words	7.8* (2.9)	6.9 (3.0)	8.3 (3.0)	6.9 (2.8)	6.6 (3.0)	8.1 (3.1)
Concept Shifting Test, time for part C, s	50.5† (22.4)	52.7 (23.2)	46.5 (19.2)	36.2 (14.1)	34.2 (14.3)	33.8 (12.6)
Concept Shifting Test, number of errors in part C	1.0 (1.8)	1.2 (1.9)	0.8 (1.4)	0.6 (0.9)	0.5 (1.0)	0.4 (0.7)
Stroop Color Word Test, time for part 3, s	60.1† (22.0)	61.8 (27.3)	54.6 (19.2)	50.6 (13.4)	48.2 (13.6)	46.3 (11.6)
Stroop Color Word Test, number of errors in part 3	1.7† (3.5)	1.8 (3.5)	1.1 (2.6)	1.0 (2.0)	0.8 (1.5)	0.5 (1.6)
Letter-Digit Coding, score	23.9† (7.7)	22.6 (7.6)	25.6 (7.7)	30.4 (7.6)	31.5 (7.4)	32.4 (7.4)

Patients (median age, 68 yr; 5–95% range, 60–79 yr) and controls (median age, 67 yr; 5–95% range, 61–81 yr). Data are mean (SD).

* Patients significantly better than controls at first test. † Controls significantly better than patients at first test (Mann–Whitney rank sum test).

Results

Of the 1,218 patients in the ISPOCD1 study, 1,185 had a reliable and complete preoperative Visual Verbal Learning Test and 74 had PCI, defined as a performance below 1.5 SD the mean value in the age-corresponding control group (table 1). Patients with PCI were significantly older, and significantly fewer females were in that group, but there was no significant difference in duration of education, cognitive complaints, or depression (table 2). As expected, the preoperative test performance in these patients was lower in these patients (no statistical analysis performed).

After surgery, neuropsychological testing could be performed at 1 week in 1,016 of the 1,185 patients and at 3 months in 933. Deterioration was seen in all test variables, but at 1 week especially in the Letter Digit Coding Test and the time of the Stroop Test, where 139 and 158 out of 1,016 exceeded a 2-SD deterioration (14% and 16%, respectively) (table 3). At 3 months, deterioration was more uniformly distributed in the test variables. Patients with PCI had less decline in the memory test, and no patient with PCI had a deterioration exceeding 2 SD at 1 week or at 3 months after surgery (table 3). This was only statistically significant for one of the tests, but the pattern was the same for deterioration of 1 SD where deterioration was significantly less common in the memory tests both at 1 week and 3 months (table 4). Based on the definitions from the original publications, POCD was noted at 1 week in 12 of 63 (19%) of patients defined as PCI as compared with 252 of 953 (26.4%) of patients not classified as PCI ($P = 0.19$). At 3 months, POCD was seen in 8 of 55 (15%) of patients with PCI *versus* 84 of 878 (9.5%) of patients not classified as having PCI ($P = 0.23$).

Discussion

In a further analysis of data from the ISPOCD1 study, we found that postoperative cognitive deterioration was seen in all seven test variables used for assessing cognitive dysfunction. The highest proportion of deterioration at 1 week after surgery was seen in tests thought to assess attention and cognitive speed. In patients with PCI, deterioration was significantly less common in memory function.

This analysis was undertaken to elucidate whether the pattern of cognitive deterioration was different for patients with preexisting impairment in cognitive function.

Table 2. Baseline Neuropsychological Test Results and Demographic Data

	Preoperative Cognitive Impairment (n = 74)	No Preoperative Cognitive Impairment (n = 1,111)
Age, yr	72.4 (5.8)	68.6 (5.8)
Female sex (%)	20 (27)	530 (48)
Years of education	9.3 (3.5)	10.0 (3.8)
Cognitive Failures Questionnaire score	36.9 (17.4)	36.4 (17.9)
Zung depression scale score	37.9 (8.8)	35.8 (7.6)
Visual Verbal Learning, cumulated recall, number of words	14.7 (3.6)	25.0 (5.1)
Visual Verbal Learning, delayed recall, number of words	3.1 (2.2)	8.1 (2.7)
Concept Shifting Test, time for part C, s	68.9 (34.8)	49.7 (23.0)
Concept Shifting Test, number of errors in part C	1.8 (2.5)	1.0 (1.8)
Stroop Color Word Test, time for part 3, s	73.8 (35.9)	60.0 (22.8)
Stroop Color Word Test, number of errors in part 3	3.1 (5.1)	1.8 (3.7)
Letter-Digit Coding, score	18.0 (6.5)	24.3 (7.7)

Data are mean (SD). Patients with preoperative cognitive impairment were significantly older, and female sex was significantly less common (Mann–Whitney rank sum test and chi-square test).

Table 3. Postoperative Deterioration in Individual Neuropsychological Scores: Two Standard Deviations

	1 Week		3 Months	
	PCI (n = 63)	No PCI (n = 953)	PCI (n = 55)	No PCI (n = 878)
Visual Verbal Learning, delayed recall, number of words	0 (0–6.9)	47, 4.9% (3.7–6.5)	0 (0–7.8)	47, 5.4% (4.0–7.1)
Visual Verbal Learning, cumulated recall, number of words	0 (0–6.9)	84,* 8.8% (7.2–10.8)	0 (0–7.8)	48, 5.5% (4.1–7.2)
Concept Shifting Test, time for part C	4, 6.4% (2.1–15.7)	70, 7.4% (5.9–9.2)	4, 7.3% (2.4–17.8)	26, 3.0% (2.0–4.3)
Concept Shifting Test, errors in part C	8, 12.7% (6.3–23.4)	92, 9.7% (7.9–11.7)	9, 16.4% (8.6–28.5)	71, 8.1% (6.5–10.1)
Stroop Color Word Test, time for part 3	12, 19.1% (11.1–30.6)	146, 15.3% (13.2–17.8)	5, 9.1% (3.5–20.0)	53, 6.0% (4.6–7.8)
Stroop Color Word Test, errors in part 3	8, 12.7% (6.3–23.4)	96, 10.1% (8.3–12.2)	5, 9.1% (3.5–20.0)	40, 4.6% (3.4–6.2)
Letter-Digit Coding Score	8, 12.7% (6.3–23.4)	131, 13.8% (11.7–16.1)	2, 3.6% (0.3–13.0)	30, 3.4% (2.4–4.9)

Deterioration was defined as a Z score above 2. Data are numbers and percentage for patients with and without preoperative cognitive impairment (PCI) with (95% confidence interval).

* $P < 0.05$ between PCI and no PCI (chi-square test).

The previous analyses of the entire ISPOCD1 data set were based on a binary endpoint—POCD—that was a combined measure of seven variables. Accordingly, it was not assessed whether certain domains of function were more vulnerable, nor was it considered whether there was a relation between poor preoperative cognitive status and subsequent deterioration. In this article, we considered all seven endpoints individually to calculate the proportions of patients who exceeded 1 or 2 SD deterioration after surgery with a specific focus on patients with PCI.

There are several limitations in this analysis. First, our construct of PCI is a retrospective attempt to simulate MCI. In the absence of a prospective determination, PCI might include some patients who would not be diagnosed as MCI. We excluded patients with a Mini-Mental State Examination score below 24 to avoid the inclusion of demented patients who would probably not be able to comprehend the test instructions. Still, poor preoperative performance could result in an inability to detect cognitive decline as a result of floor effects in tests based on scores such as the Visual Verbal Learning test or the Letter Digit Coding Test. The tests may not allow assessment of highly different cognitive domains. Therefore, it is questionable to ascribe functions to particular regions and lesions seldom conform to functionally homogenous systems. Furthermore, cognitive deficits may be complicated because of interactions with compensatory measures and preexisting decline.[15] In other analyses of ISPOCD1 data, the Concept Shifting Test, part C, has been considered as a measure of cognitive flexibility, whereas the Stroop test, part 3, was considered a measure of interference susceptibility. Speed of information processing was thought to be assessed in the Letter Digit Coding Test.[16] All these tests are, however, highly dependent on attention, and all are timed tests where the patient is asked to work as fast as possible. Therefore, it would probably be appropriate to classify them as assessing attention and cognitive speed. POCD seems to affect most aspects of cognitive function, and it is therefore difficult to suggest a specific deficit or brain lesion.

We defined PCI as a low performance in memory, which is analogous to the current definition of amnestic MCI. Much like the definition of POCD, there is considerable discussion among researchers as to a precise definition of MCI.[2] A recent consensus conference agreed that all definitions "refer to non demented persons with cognitive deficits measurable in some form or another,

Table 4. Postoperative Deterioration in Individual Neuropsychological Scores: One Standard Deviation

	1 Week		3 Months	
	PCI (n = 63)	No PCI (n = 953)	PCI (n = 55)	No PCI (n = 878)
Visual Verbal Learning, delayed recall, number of words	5, 7.9% (3.1–17.7)	267,* 28.0% (25.3–31.0)	2, 3.6% (0.3–13.0)	189,* 21.5% (18.9–24.4)
Visual Verbal Learning, cumulated recall, number of words	3, 4.8% (1.1–13.6)	253,* 26.6% (23.8–29.4)	2, 3.6% (0.3–13.0)	167,* 19.0% (16.6–21.8)
Concept Shifting Test, time for part C	14, 22.2% (13.6–34.0)	239, 25.1% (22.4–27.9)	11, 20.0% (11.4–32.5)	129, 14.7% (12.5–17.2)
Concept Shifting Test, errors in part C	14, 22.2% (13.6–34.0)	261, 27.4% (24.7–30.3)	13, 23.6% (14.2–36.5)	153, 17.4% (15.1–20.1)
Stroop Color Word Test, time for part 3	18, 28.6% (18.8–40.8)	295, 31.0% (28.1–34.0)	10, 18.2% (10.0–30.5)	159, 18.1% (15.7–20.8)
Stroop Color Word Test, errors in part 3	11, 17.5% (9.9–28.8)	160, 16.8% (14.6–19.3)	6, 10.9% (4.7–22.2)	77, 8.8% (7.1–10.8)
Letter-Digit Coding Score	20, 31.8% (21.5–44.1)	353, 37.0% (34.0–40.2)	12, 21.8% (12.8–34.5)	192, 21.9% (19.3–24.7)

Deterioration was defined as a Z score above 1. Data are numbers and percentage for patients with and without preoperative cognitive impairment (PCI) with (95% confidence interval).

* $P < 0.05$ between PCI and no PCI (chi-square test).

and (ii) represent a clinical syndrome that can be utilized to classify persons who do not fulfill a diagnosis of dementia, but who have a high risk of progressing to a dementia disorder."[1] MCI has been classified into amnestic MCI, nonamnestic MCI, and multiple domain. Our purpose in undertaking this analysis was to determine whether we would be able to detect levels of subsequent impairment in MCI patients undergoing anesthesia and surgery using the ISPOCD test battery. The ability to reliably detect a change in attention and speed suggests that testing batteries that include these domains will be capable of detecting change in patients with MCI. In contrast, this analysis suggests that a memory test like the Visual Verbal Learning Test is not particularly susceptible to change after surgery and anesthesia in patients with PCI. Other cognitive measures not included in this study may be sensitive to POCD, and these measures may detect POCD changes that do not overlap with each other. Future research will need to identify the array of cognitive outcomes that are influenced by surgery and anesthesia.

The neurobiology of cognition has been shown to be increasingly complex as improved imaging techniques provide increased opportunities to explore connections between different areas of the brain. Future studies should be conducted to determine whether postoperative cognitive deterioration occurs in MCI patients and whether there are specific cognitive domains that are particularly vulnerable as investigators seek to define POCD. The current analysis suggests that memory tests are not adequately sensitive.

In conclusion, postoperative cognitive deterioration was seen in all tests, although most commonly in attention and cognitive speed at 1 week. In patients with PCI, deterioration in memory is difficult to detect after surgery.

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