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Postoperative Cognitive Dysfunction in Middle-aged Patients

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Background: **Postoperative cognitive dysfunction (POCD) after noncardiac surgery is strongly associated with increasing age in elderly patients; middle-aged patients (aged 40–60 yr) may be expected to have a lower incidence, although subjective complaints are frequent.**

Methods: **The authors compared the changes in neuropsychological test results at 1 week and 3 months in patients aged 40–60 yr, using a battery of neuropsychological tests, with those of age-matched control subjects using Z-score analysis. They assessed risk factors and associations of POCD with measures of subjective cognitive function, depression, and activities of daily living.**

Results: **At 7 days, cognitive dysfunction as defined was present in 19.2% (confidence interval [CI], 15.7–23.1) of the patients and in 4.0% (CI, 1.6–8.0) of control subjects ($P < 0.001$). After 3 months, the incidence was 6.2% (CI, 4.1–8.9) in patients and 4.1% (CI, 1.7–8.4) in control subjects (not significant). POCD at 7 days was associated with supplementary epidural analgesia and reported avoidance of alcohol consumption. At 3 months, 29% of patients had subjective symptoms of POCD, and this finding was associated with depression. Early POCD was associated with reports of lower activity scores at 3 months.**

Conclusions: **Postoperative cognitive dysfunction occurs frequently but resolves by 3 months after surgery. It may be associated with decreased activity during this period. Subjective report overestimates the incidence of POCD. Patients may be helped by recognition that the problem is genuine and reassured that it is likely to be transient.**

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WE have shown that postoperative cognitive dysfunction (POCD) after noncardiac surgery occurs in the elderly population, but it is not associated with perioperative hypoxia and hypotension.[1] Incidence of POCD increases with age. There are many reported complaints of POCD after noncardiac surgery,[2] but it is also recognized that the relationship between subjective reports of POCD and objective measures may be poor.

Early cognitive dysfunction may complicate recovery in several ways. Delayed physical and emotional rehabilitation may postpone hospital discharge and return to work. It will interfere with accelerated care programs, which encourage early independence and a shorter hospital stay.[3] Such problems may be wrongly attributed to drugs or complications of surgery and anesthesia. There are obvious concerns about patients being in hazardous environments while cognitive function is impaired. Current advice regarding driving, for example, is vague and unhelpful, particularly as affected patients may have little insight into their impairment. Any long-term POCD would have catastrophic consequences for middle-aged patients, who may have to give up work and social activities. Identification of any preoperative risk factors predisposing to POCD would result in more informed decision making before proceeding with major surgery, and accurate information on the likely duration of any POCD would be useful to advise patients who are affected. Recent reports of a high incidence of long-term POCD after coronary artery bypass surgery[4] may be related to the surgical procedure, the cardiopulmonary bypass, or the underlying vascular disease process. Understanding any association between anesthesia or major surgery and POCD in the general noncardiac surgical population is important to further interpret these data.

In this multicenter study, we investigated the incidence of early and late POCD in middle-aged patients after major elective, noncardiac surgery. Objective measures and subjective reports of cognitive disturbance are assessed. We hypothesized that early POCD would be detected in middle-aged patients but at a lower incidence than in the elderly population.

Methods

Seven hospitals in five countries contributed patients to the study, each using the same protocol. All patients,

aged 40–59 yr, presenting primarily for major abdominal or orthopaedic surgery with general anesthesia and with an anticipated hospital stay of at least 4 days were eligible for the study. Within each hospital, we recruited an age-matched control group, consisting primarily of the patients' relatives. We enrolled subjects between October 1998 and October 1999. The study received ethics committee approval in all institutions, and each participant gave informed consent.

Exclusion criteria were diseases of the central nervous system, including dementia (defined as a Mini-Mental Score Examination[5] score below 24), consumption of tranquilizers (other than benzodiazepines as night sedation) or antidepressants, scheduled cardiac surgery or neurosurgery, previous neuropsychological testing, inability or unwillingness to abide by the protocol, inability to follow procedures, or poor comprehension of the language used in the study. Patients with severe visual or auditory handicap, illiteracy, alcoholism or drug dependence (alcoholism defined as intake more than 5 units of alcohol daily during the past 3 months), and those not expected to be discharged from hospital or able to complete the 3-month postoperative test were also excluded.

The primary outcome measure for the study was the occurrence of cognitive dysfunction at approximately 7 days after surgery (definition given later in the article). The method requires neuropsychological testing preoperatively and 7 days and 3 months postoperatively; the changes from baseline are compared with those from the control group at the two postoperative testing sessions.

We estimated that a sample size of 600 (400 patients and 200 control subjects) would allow us to detect a difference in POCD at 1 week between 5% in control subjects and 15% in patients, with a power of 0.90 at the 0.05-significance level. In addition, a sample of that size would allow us to detect a difference of between approximately 25% in those aged more than 60 yr, from our previous study,[1] and 15% in the current group.

The method of data collection was based on our previous study. The major difference was the age of patients recruited. All surgery was performed with general anesthesia, and apart from ensuring normocapnia, there were no restrictions on the type or conduct of anesthesia or postoperative analgesia, which conformed to the usual practices of each institution. We recorded the patients' medical history and preoperative medication use. The patients were visited regularly during the immediate postoperative period, and the medical records were scrutinized for new medications or medical complications. The first postoperative testing session was performed at 7 days whenever possible, but earlier if discharge was before this time. If postoperative complications or therapy prevented testing at 7 days, the testing was delayed until it was possible. All data were immediately checked for compatibility and completeness on entry into a dedicated computer program.

We determined patients' mood preoperatively and after 3 months using the Geriatric Depression Scale (GDS), a measure validated for use in younger adults.[6] Subjective assessment of cognitive decline was evaluated after 3 months using the Subjective Cognitive Functioning questionnaire (SCF), which was given to patients and relatives. The questionnaire was designed specifically to detect change in subjective cognitive symptoms related to an intervention. It consists of four questions assessing memory, concentration, vitality, and ability to sustain mental burden. The score is from 0 to 7 for each component; 4 represents no change. A mean score was calculated from the four answers. There were two versions of the questionnaire, one for the patients and another for the relatives. Finally, the Instrumental Activity of Daily Living (IADL) score was assessed. This measure comprises seven questions related to shopping, domestic work, preparing meals, walking, handling money, handling medicine, and using a telephone. The IADL score was administered to patients and relatives preoperatively and 3 months postoperatively. For each of the seven questions, a score of 0 was given for no need of help, 1 was given for some need, and 2 was given in the case of inability to perform this activity. A summarized measure was calculated.

All neuropsychological tests used in the present study were also used in our previous study: cumulative number of words recalled in three trials and the number of words at delayed recall from the Visual Verbal Learning test;[7] the time and number of errors in part C of the Concept Shifting Test;[8] the time and error scores from the third part of the Stroop Color Word Interference Test;[9] and the number of correct answers from the Letter Coding Test, which is based on the Symbol Digit Modalities Test.[10] The tests have been translated into the relevant European languages and are culturally robust. Three parallel forms of the tests were used in a sequence using a full Latin square design for tests other than the Stroop test. Patient assignment to one of six possible sequences was random. Neuropsychological testing was performed in an undisturbed room. Staff training ensured consistency and reliability of data collection.

We compared the changes in performance for control subjects for each measure between baseline and subsequent tests 1 week and 3 months later. We calculated the mean and SD of these differences. These difference scores may denote individual changes and practice effects.[11] For patients, we compared baseline scores with the 1-week and 3-month postoperative 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 individual test outcome. Large positive Z scores indicate deterioration in cognitive function from baseline in patients suffering from cognitive dys-

Table 1. Psychometric Test Results at First Test Session for Seven Variables Used in the Evaluation of Cognitive Function

	Patients		Controls	
	Median	5–95% (Percentiles)	Median	5–95% (Percentiles)
Cumulative learning (No. of words)	30	21–39	31	23–40
Delayed verbal recall (No. of words)	11	6–15	11	6–15
Time in concept shifting task, part C (s)	33.0	20.1–63.0	30.6	20.7–49.4
Errors in concept shifting task, part C (No.)	0	0–3	0	0–3
Time for Stroop test, part 3 (s)	42.6	30.0–67.8	39.0	28.0–56.4
Errors for Stroop test, part 3, (No.)	0	0–3	0	0–2
Letter-digit coding (No. of correct answers)	34	20–44	36	27–45

function compared with control subjects. We defined a composite Z score from the total of the Z scores for the control subjects, the SD of which we used to normalize the patients' composite Z scores at 1 week and 3 months. Patients had cognitive dysfunction when two Z scores in individual tests or the combined Z score was 1.96 or more.

This definition considered general deterioration (in all tests) or substantial deterioration in only some tests. Risk factors for POCD were initially assessed in univariate analysis using chi-square tests. For secondary data analysis, we used multiple logistic regression to investigate associations between risk factors and subsequent cognitive dysfunction.

Despite the use of a standard protocol and training procedures, we included a term for study centers to correct for variations between countries and data collection centers with regard to patient population, data collection variations, and anesthetic and surgical practices. We assessed the relation between activity of daily living score and postoperative cognitive dysfunction by Spearman rank test on the composite Z score. All data are reported with the 5–95% range or 95% confidence interval (CI) where appropriate.

Results

Five hundred eight patients (375 women and 133 men) and 183 control subjects (133 women and 50 men) for the normal control population were recruited. Their median age was 50.5 (range, 41.0–58.9) yr and 48.7 (range, 40.9–58.9) yr, respectively. Eighty-six patients (16.9%) did not complete the 3-month assessment. Stated reasons for dropout included patient refusal, 30 (5.9%); violation of testing protocol (*i.e.*, testing performed outside the permissible time period, *e.g.*, second postoperative test performed less than 2 months after surgery), 21 (4.1%); follow-up testing not possible–other than refusal, 15 (3%); change in surgery or anesthesia (*e.g.*, major to minor procedure or general to regional technique), 13 (2.6%); psychosis, 1 (0.2%); data lost, 1 (0.2%); and death, 5 (1%). We report the available data from 463 patients at 1 week and 422 at 3 months.

The first postoperative test was performed a median of 6 days (range, 2–18) after surgery, and cognitive dysfunction was found in 89 of 463 (19.2%; CI, 15.7–23.1) patients. At the second postoperative test, a median of 102 days (range, 71–184) after the operation, cognitive dysfunction was identified in 26 of 422 (6.2%; CI, 4.1–8.9]) patients. In the control population, the criteria for cognitive dysfunction were fulfilled in 7 of 176 (4.0%; CI, 1.6–8.0]) subjects at 1 week and in 7 of 169 (4.1%; CI, 1.7–8.4) at 3 months. The difference in cognitive dysfunction between patients and control subjects is significant ($P = 0.001$) after 1 week but not at 3 months ($P = 0.33$). Of 420 patients completing both postoperative test sessions with valid data, cognitive dysfunction was noted in 80 after 1 week and in 26 after 3 months. Nine fulfilled criteria for POCD at both sessions (35% of the 26), whereas the remaining 17 declined between the first and second test sessions. Accordingly, in those 80 patients having early POCD, the risk of having POCD

Table 2. Changes in Psychometric Test Results in Patients (Postoperative-Preoperative) for Seven Variables Used in the Evaluation of Cognitive Function

	Change to First Postoperative Test		Change to Second Postoperative Test	
	Median	5–95% (Percentiles)	Median	5–95% (Percentiles)
Cumulative learning (No. of words)	−1	−10–8	2	−6–10
Delayed verbal recall (No. of words)	−1	−6–3	0	−4–4
Time in concept shifting task, part C (s)	0.94	−15.2–22.7	−2.0	−19.7–13.4
Errors in concept shifting task, part C (No.)	0	−2–3	0	−2–2
Time for Stroop test, part 3 (s)	−1.1	−11.6–16.0	−3.0	−13.1–5.8
Errors for Stroop test, part 3 (No.)	0	−3–2	0	−3–1
Letter-digit coding (No. of correct answers)	−1	−9–5	2	−5–8

Table 3. Changes in Psychometric Test Results in Controls (Second Test Session—First Session, and Third Test Session—First Session) for Seven Variables Used in the Evaluation of Cognitive Function

	Change from First to Second Session		Change from First to Third Session	
	Median	5–95% (Percentiles)	Median	5–95% (Percentiles)
Cumulative learning (No. of words)	−1	−8–7	2	−6–10
Delayed verbal recall (No. of words)	0	−4–3	0	−3–4
Time in concept shifting task, part C (s)	−1.0	−15.4–11.8	−1.4	−12.6–12.6
Errors in concept shifting task, part C (No.)	0	−2–3	0	−2–2
Time for Stroop test, part 3 (s)	−3.0	−10.2–5.1	−2.6	−10.8–6.2
Errors for Stroop test, part 3 (No.)	0	−2–1	0	−1–1
Letter-digit coding (No. of correct answers)	1	−5–7	1	−4–7

after 3 months was 9 of 80 = 11.3% compared with 17 of 340 = 5.0% in those not having POCD at 7 days ($P = 0.07$).

The baseline data for the patient and control groups are shown in table 1. Tables 2 and 3 show the changes in cognitive performance in the tests at the first and second postoperative test sessions, respectively.

Of 89 patients defined as having POCD at the first postoperative test session, 46 fulfilled both criteria (combined Z score > 1.96 and two individual Z scores > 1.96), 26 fulfilled only the former, and 17 only the latter. At 3 months, the distribution of criteria among 26 patients was: 7 (both), 7 (combined), and 12 (two individual).

Compared with our previous results in patients aged more than 60 yr,[1] the incidence of POCD is significantly less in middle-aged patients after 7 days and also after 3 months (89/463 *vs.* 266/1,031, $P = 0.0064$ and 26/422 *vs.* 94/947, $P = 0.026$).

The interval between surgery and testing and the value of the Z score at this first test was assessed with Spearman rank test. This showed R = −0.06, $P = 0.19$.

Sedative medication was received by 71 patients within 24 h of the first postoperative test, but the incidence of POCD (25%) in these patients was not significantly different from those who received no sedatives.

The proportions of patients with postulated risk factors and the incidence of POCD at 7 days for these groups are shown in table 4. The univariate analyses revealed the following as significant risk factors: center code, duration of anesthesia, epidural analgesia, omission of nitrous oxide, type of surgery, heart disease, no preoperative alcohol intake, administration of opioids within 24 h of testing, education, and American Society of Anesthesiologists (ASA) physical status. Age was not important within the age group studied. In the multiple logistic regression analysis, we found only a significant relationship between early POCD and center, reported avoidance of alcohol intake, and supplementary epidural analgesia (table 5). The incidence of POCD was significantly higher in patients receiving epidural analgesia (odds ratio, 2.47; 95% CI, 1.43–4.27) and in patients who reported no preoperative alcohol consumption (odds ratio, 1.81; 95% CI, 1.02–3.2).

Of 92 patients who had postoperative epidural anesthesia, 79 received bupivacaine as the local anesthetic agent. We did not specifically record epidural medications administered during the 24 h before testing, but our impression is that most epidural infusions were discontinued at least 24 h before the first postoperative tests were performed.

There was a significant correlation between POCD measured at 1 week and a decline in the IADL-score reported by the relatives at 3 months ($P < 0.02$). No correlation was found between the GDS scores and POCD.

Table 4. Proportion of Patients with Postoperative Cognitive Dysfunction (POCD) at 1 Week by Risk Factor (N = 463)

Risk factor	No. of Patients	POCD	*P* Value
Age (yr)			
40–49	193	36 (18.7%)	0.79
50–59	270	53 (19.6%)	
Duration of anesthesia (min)			
≤120	155	13 (8.4%)	0.001
121–240	208	47 (22.6%)	
≥241	100	29 (29.0%)	
Epidural analgesia			
Yes	92	31 (33.7%)	0.001
No	371	58 (15.6%)	
Nitrous oxide			
Yes	325	51 (15.7%)	0.003
No	138	38 (27.5%)	
Type of surgery			
Upper abdominal	111	37 (33.3%)	0.001
Lower abdominal	181	20 (11.1%)	
Orthopaedic	95	19 (20.0%)	
Other	76	13 (17.1%)	
Heart disease			
Yes	26	9 (34.6%)	0.04
No	437	80 (18.3%)	
Alcohol			
No	235	63 (26.8%)	0.001
Yes	228	26 (11.4%)	
Opioid <24 hours before test			
Yes	146	40 (27.4%)	0.003
No	316	49 (15.5%)	
Education			
Less than high school	189	25 (13.2%)	0.009
High school	105	29 (27.6%)	
More than high school	169	35 (20.7%)	
ASA class			
1 to 2	384	64 (16.7%)	0.002
3 to 4	79	25 (31.7%)	

ASA = American Society of Anesthesiologists.

Table 5. Risk Factor Analysis Odds Ratio (95% CI) for the Major Risk Factors in Relation to the First (7 day) Postoperative Test

	First Test (N = 463)	
Possible Risk Factor	*P*	Odds ratio (CI)
Epidural analgesia	0.0012	2.47 (1.43–4.27)
Nitrous oxide	0.92	1.03 (0.57–1.88)
ASA class		
1–2		
3–4	0.60	1.19 (0.62–2.27)
Type of surgery		
Upper abdominal	0.60	1.24 (0.56–2.76)
Lower abdominal	0.98	0.99 (0.43–2.29)
Orthopaedic	0.93	0.96 (0.40–2.31)
Other		
Duration of anesthesia		
<120 min	0.13	0.52 (0.22–1.22)
121–240 min	0.86	1.06 (0.57–1.95)
>240 min		
History of heart disease	0.25	1.72 (0.68–4.34)
No alcohol intake	0.04	1.81 (1.02–3.20)
Opioid <24 h before test	0.96	0.98 (0.55–1.77)
Level of education		
Less than high school	0.97	1.01 (0.51–2.03)
High school	0.20	1.52 (0.80–2.89)
More than high school		
Center	0.0001	—

CI = confidence interval.

Subjective reports of cognitive problems by patients were common at 3 months; 29% of patients had SCF scores greater than 16. The patients' and relatives' subjective reports of POCD correlate significantly with measured POCD after 3 months ($P < 0.003$ and $P < 0.04$, respectively). Fourteen of 26 patients with measured POCD at 3 months had an increased SCF score (> 16); however, only 7% of patients with an increased SCF had measurable POCD.

Postoperative complications recorded in the patients are as follows. In 508 patients, there were no major cerebral complications such as stroke, but 3 patients (0.6%) developed delirium. Four patients (0.8%) had respiratory failure, two patients (0.4%) had cardiac failure, and nine patients (1.8%) had infective episodes. Twenty-eight patients (5.5%) required an intensive care unit stay of longer than 24 h, and 1 patient (0.2%) needed a second operation.

Discussion

The study demonstrates that our patients had an incidence of POCD at 1 week of 19.2% compared with a background level in the control subjects of 4.0%. This problem is temporary but nevertheless associated with decreased levels of daily activity at 3 months, according to relatives' report. The incidence of cognitive dysfunction after 3 months of 6.2% is not significantly greater than in the control group (4.1%). These findings are in accord with our previous study of older adults, where patients in their seventh decade had an incidence of POCD of 23% at 7 days and 7% at 3 months.[1]

We have demonstrated lack of objective evidence of POCD in our patients on formal testing at 3 months, although subjective complaints are common. Depression was associated with subjective but not objective measures of cognitive dysfunction, and this finding is consistent with a previous study in cardiac patients.[12] Medications taken in the 24 h before testing do not appear to contribute to POCD.

Patients tested earlier in the postoperative period may have a higher incidence of POCD than those tested later, possibly related to the persistent effects of anesthetic agents, but we found no significant correlation between POCD and the time of testing after surgery.

Patients with poor general health or who prefer to avoid the sedative effects of alcohol for other reasons may be more vulnerable to the effects of sedative medications given perioperatively, which may explain the observed association between alcohol avoidance and early POCD.

It is difficult to interpret the strong association of early POCD with epidural analgesia. We included this treatment as a risk factor anticipating either no effect or otherwise an improvement in cognitive function at 1 week because of reduced exposure to systemic sedative analgesics and improved overall recovery from surgery.[13] The results may be because patients receiving epidurals may have had more extensive surgery, but we included all factors that were available to us, which may have confirmed this explanation for our findings. We were not able to include a single term that described the "majorness" of the procedure. An alternative explanation is an adverse effect of an infusion of local anesthetic continued for several days on neuropsychological testing. The epidural subgroup was relatively small (20% of the study population), and because the epidural treatment was not randomly allocated, this group may have had characteristics for which we were unable to control in the multiple logistic regression analysis but which, nevertheless, contributed to increased POCD. Plasma concentrations of bupivacaine, which was the principal local anesthetic used in the study, found in long-term analgesic nerve block studies[14] may overlap with those shown to be associated with neurologic symptoms during acute toxicity studies.[15] We have included this finding because it was pronounced and unexpected. It raises the hypothesis that infusion of local anesthetics at clinically relevant doses for several days may cause cognitive dysfunction, and we note that this finding has not previously been formally assessed.

This multicenter study has enabled us to include many patients in a range of surgical settings. Despite attempted uniformity of testing and training procedures,

there is still a significant difference in the incidence of POCD between individual centers. This difference probably represents the total of many minor factors in patient and staff characteristics, resources, and practices for which we are unable to control and which are inherent in such a study. A similar center effect was also noted in the 1-week results from our earlier study in the elderly population.[1]

We have used a robust study method in line with recent guidance.[11] The age-matched control group has allowed us to control for learning effect and patient variability, including educational level, background, and culture. The particular importance of including a control group is demonstrated by this study. Without a control group, we might have overemphasized the incidence of POCD at 3 months of 6.2%, even using our definition that has been described as conservative.[16] However, when compared with our control group, no difference can be demonstrated at the conventional level.

The study size was determined to investigate only early (7-day) POCD. Testing at 3 months was included to demonstrate resolution of any early POCD seen. We have chosen to define POCD as deterioration beyond the normal variation in cognitive function observed in a control population. Of the 26 patients (6.2%) who had abnormal testing for POCD at 3 months, 17 patients (4.1%) who appeared to develop POCD between the 7-day and 3-month testing sessions are likely to represent the normal variation in cognitive function and are comparable with the 4.0% in the control group. This background variation has been shown previously in other long-term follow-up studies.[17] The additional nine patients (2.1%) do not represent a statistically significant incidence of POCD when compared with the control group, but low statistical power at this time point should be considered. A study to detect a 2% difference between 4–6% in the incidence of POCD with a power of 0.8 and significance of 0.05 would require 4,000 patients. This study cannot therefore exclude a small incidence of long-term POCD in middle-aged patients.

Despite a statistically significant correlation between the POCD and SCF, only one half of the patients with abnormal testing at 3 months had an increased SCF score. It is therefore unlikely that this simple subjective measure will be a specific or sensitive screening tool for objective POCD.

These results complement the results from our previous study in elderly patients. Middle-aged patients are prone to early POCD, but the association of this with duration of anesthesia and educational level that we observed in the elderly population was not observed in the younger age group. Postoperative infection and respiratory complications occurred infrequently in middle-aged patients and therefore could not be included in analysis. We can confirm that POCD at 3 months after noncardiac surgery is related primarily to older age. Inclusion of objective and subjective measures in this study has demonstrated a substantial overestimation of POCD by the latter. Nevertheless, early POCD is a problem for 15% of patients, and it may affect rehabilitation. Management of early POCD that in the absence of cognitive testing is likely to present as a subjective complaint should include acknowledgment of the problem together with strong reassurance that it is likely to resolve. Only 11% of patients with objective POCD at 7 days still had abnormal test results at 3 months.

We do not know the exact duration of the early POCD that we have demonstrated; a further study with more frequent testing in the first month after surgery would be helpful to establish this. The strong association with epidural analgesia may possibly be related to local anesthetic toxicity, and this relation should be evaluated specifically in future studies.

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