

Postoperative Cognitive Dysfunction in Older Patients with a History of Alcohol Abuse

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Background: Postoperative cognitive dysfunction (POCD) affects a significant number of patients and may have serious consequences for quality of life. Although POCD is most frequent after cardiac surgery, the prevalence of POCD after noncardiac surgery in older patients is also significant. The risk factors for POCD after noncardiac surgery include advanced age and preexisting cognitive impairment. Self-reported alcohol abuse is a risk factor for postoperative delirium, but its significance for long-term POCD has not been investigated. The goal of this study was to determine whether neurocognitive function is impaired after noncardiac surgery during general anesthesia in older patients with a history of alcohol abuse.

Methods: Subjects aged 55 yr and older with self-reported alcohol abuse (n = 28) and age-, sex-, education-matched non-alcoholic controls (n = 28) were tested using a neurocognitive battery before and 2 weeks after elective surgery (n = 28) or a corresponding time interval without surgery (n = 28). Verbal memory, visuospatial memory, and executive functions were assessed. A neurologic examination was performed to exclude subjects with potential cerebrovascular damage.

Results: Significant three-way interactions (analysis of variance) for Visual Immediate Recall, Visual Delayed Recall, Semantic Fluency, Phonemic Fluency, and the Color-Word Stroop Test implied that cognitive performance in the alcoholic group decreased after surgery more than it did in the other three groups.

Conclusions: The results suggest that a history of alcohol abuse in older patients presents a risk for postoperative cognitive impairment in the domains of visuospatial abilities and executive functions that may have important implications for quality of life and health risks.

IT has been recognized since the 1950s that some individuals emerge from general anesthesia with impairment of cognitive functions not present before surgery. Post-

operative cognitive dysfunction (POCD) affects a significant number of patients and, when prolonged, may have serious consequences for quality of life and health status. POCD is characterized by impairment of recent memory, concentration, language comprehension, and social integration.^{1,2} This syndrome may be detected days to weeks after surgery and may even be permanent.³ Although POCD is most frequent after cardiac surgery, the prevalence of POCD after noncardiac surgery in older patients is also significant (25% at 1 week, 10% at 3 months after surgery).⁴

Causes and consequences of long-term POCD after noncardiac surgery are not well established; however, major risk factors have been identified as advanced age, preexisting cognitive impairment, and severity of coexisting illness.⁴⁻⁹ Self-reported alcohol abuse has been identified as a risk factor for postoperative delirium¹⁰; however, its significance as a risk factor for long-term POCD has not been investigated. Chronic alcohol use causes atrophy of the frontal lobes^{11,12} and hypometabolism in the frontal cortex.¹³⁻¹⁵ It leads to a pattern of impaired executive functioning related to frontal lobe dysfunction and impaired memory that is detectable by neuropsychological testing.^{14,16,17} Alcohol use may have direct neurotoxic effects leading to the syndrome of alcohol-related dementia.^{18,19}

Whether surgery during general anesthesia may produce greater degrees of cognitive dysfunction in patients with a history of alcohol abuse has not been explored. To date, there is no evidence of neurocognitive dysfunction after surgery and general anesthesia in patients who have a history of alcohol abuse. The purpose of this investigation was to examine the extent of postoperative cognitive impairment in patients with a history of alcohol abuse. We focused on older patients (aged ≥ 55 yr) because of the greater likelihood of a longer period of alcohol abuse and cognitive deficit in this population. Early POCD may be superimposed on the temporary delirium that is common after major surgery in the elderly.^{20,21} The aged brain is more susceptible to anesthetic effects and more sensitive to nonanesthetic drugs.^{22,23} Age-related physiologic changes give rise to a decreased efficiency in the mobilization of homeostatic mechanisms²⁴ and the elimination of drugs.²⁵ Older persons are consumers of medications that produce cognitive deficits, such as antihypertensive agents, digitalis, antiparkinsonian drugs, antidepressants, and corticosteroids.^{26,27}

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We compared cognitive function in four groups: alcoholic and nonalcoholic patients undergoing surgery with general anesthesia as well as age-, education-, and sex-matched alcoholic and nonalcoholic nonsurgical controls. Four groups were necessary to differentiate between the effects of alcoholism and surgery. In each subject, cognitive tests were administered twice: before and after surgery or at equivalent time points in the nonsurgical controls. Because nonsurgical controls may perform better on the second testing due to a learning effect, the possible change in performance in surgical groups was evaluated in comparison to the change in performance in the nonsurgical groups. For example, if nonsurgical controls typically improve in performance, the absence of improvement in surgical patients would be indicative of cognitive deterioration.

Materials and Methods

The protocol was approved by the Institutional Review Board of the Zablocki Veterans Administration Medical Center, Milwaukee, Wisconsin. All subjects provided written informed consent.

Participants

This investigation included 56 participants recruited from the Zablocki Veterans Administration Medical Center. Participants' ages ranged from 55 to 81; all were male, and 75% were white. There were four subject groups—surgical alcoholic, surgical nonalcoholic, nonsurgical alcoholic, and nonsurgical nonalcoholic—with 14 participants in each group. Eligible patients in the surgical groups were anesthetized with inhalational agents for noncardiac surgery. Patients undergoing regional analgesia, cardiac surgery, craniotomy, carotid endarterectomy, or major vascular surgery involving aortic cross clamping were not eligible. Alcohol abuse was defined as a history of self-reported admission to a detoxification treatment facility related to alcohol consumption. All alcoholic participants met the criteria for alcohol dependence, but not for either alcohol-induced persisting amnesic disorder or alcohol-induced persisting dementia according to *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition. Based on self-report, the alcoholic groups (both surgical and nonsurgical) were alcohol free for at least 5 weeks. Nonsurgical controls were recruited from various outpatient clinics by the recommendation of the head nurse who prescreened the patients for the study criteria. Five of the nonsurgical controls were recruited from service areas of the hospital. All participants were screened for physical health and psychological history and were excluded if there was evidence of organic brain syndrome, preexisting dementia, or use of psychotropic medications.

Procedure

Neurologic status and neurocognitive functions were assessed within 1 week of surgery. For premedication, patients received 1–2 $\mu\text{g}/\text{kg}$ fentanyl and 1–2 mg midazolam. Bispectral Index monitoring was started before induction. Patients received 3–5 $\mu\text{g}/\text{kg}$ fentanyl and 3–6 mg/kg thiopental for induction. Anesthesia was maintained with sevoflurane and nitrous oxide. Neuromuscular blockade was produced with rocuronium (1.0 mg/kg) and reversed with neostigmine (40–80 $\mu\text{g}/\text{kg}$) and glycopyrrolate (8–16 $\mu\text{g}/\text{kg}$). Morphine or other analgesics were administered postoperatively. Neurologic status and neurocognitive functions were reassessed 2 weeks after surgery (2 weeks after the first test in the nonsurgical groups).

For each participant, the primary investigator administered both the first and second neurocognitive tests. Neurologic examinations were performed by the coinvestigators. To ensure consistent ratings, the same neurologic examiner was used for each subject both before and after surgery. To avoid bias, all examiners were blinded to the participant's alcohol history.

Neurocognitive and Neurologic Testing

The test battery was comprised of standard clinical measures that were appropriate for use with subjects in the age group studied, making minimal sensory or motor demands. Total test administration time was less than 1 h. Alternate forms (A and B) were available to reduce practice effects across sessions. The order of presentation was counterbalanced with half of the subjects receiving form A at the first session and the other half receiving form B.

Repeatable Battery for the Assessment of Neuropsychological Status: The subtests of Story Memory, List Learning, and Semantic Fluency from the Repeatable Battery for the Assessment of Neuropsychological Status²⁸ are sensitive to cognitive deficits and early dementia. The level of difficulty is appropriate for the range from normal adult through moderately severe dementia. Story Memory measures the ability to learn and recall a narrative story in two trials immediately and after a brief delay. List Learning assesses the ability to learn and remember a list of 10 unrelated words across four sequential learning trials, delayed free recall, and a recognition task. Semantic Fluency requires executive functions related to language, *i.e.*, "Name all the fruits and vegetables (form A) or all the animals in the zoo (form B) that you can think of in one minute."

Digit Span measures attention span, concentration, and working memory. This subtest of the Wechsler Adult Intelligence Scale, Third Edition,²⁹ combines reciting digits forward and digits backward. The original test does not include an alternate form, so alternate forms were constructed by using only one string of numbers for each digit length, rather than two. The maximum attainable score for this version of the test was 15.

*Geriatric Depression Scale 15-item version*³⁰ is a brief yes/no questionnaire assessing symptoms of depression.

*The Color-Word Stroop Test, Interference Trial*³¹ is a test of the executive functions of inhibition, selective attention, mental speed and interference susceptibility. This test presents a list of color words printed in an incongruous color and requires that the examinee name the color while ignoring the word. The obtained score is the number of words correctly named in the color of printed ink in 60 s.

*Brief Visual Memory Test-Revised*³² measures visuospatial recent memory using a nonverbal construction task. Participants are exposed to a card showing six simple geometric designs for 10 s on three sequential trials. When the card is removed, the examinee draws the designs in the locations remembered. A delayed free recall trial is administered 20–25 min later. Full credit (12 points per trial) is given if all designs are correct and in the appropriate locations. Partial credit is given for incorrect but recognizable designs or correct designs in the wrong location. For recognition, 12 items are presented serially, including the six original designs and six distracters. Three measures are obtained from this test: Visual Immediate Recall, Visual Delayed Recall, and Visual Recognition.

*Visual Learning and Retention Test*³³ measures learning for visually presented information (pictures of landscapes, clocks, and other common and abstract images) in a slideshow format. This test is sensitive to learning, retention, and ventral/dorsal visual functioning. Exposure is controlled using a continuous response procedure. Thirty-six images are shown at the rate of 3 s per image. The maximum attainable score is 36. The advantage of this test compared with the Brief Visual Memory Test is that it eliminates motor response demands.

Orientation to time was elucidated by asking two questions: “How many years have passed since the first Gulf War and the Vietnam War?” Maximum score is 2.

Phonemic Fluency measures executive speed of word generation using phonetic cues, e.g., “Name all the words that you can think of that start with the letter S (form A) and P (form B) in one minute.” The obtained score is the number of appropriate words generated in 1 min.

The neurologic examination focused on detection of significant visual and auditory impairment, level of consciousness, cranial nerve function, motor strength, cerebellar ataxia, intention tremor, sensation, frontal lobe release signs, deep tendon and plantar reflexes, and gait ataxia. The Hachinski Ischemia Score³⁴ was calculated using the Hachinski Ischemia Scale. A score greater than 4 is typical for multi-infarct dementia.

Demographic data including age, ethnicity, handedness, current marital status, highest grade of education, and current occupational status were gathered. Also, data on smoking history, alcohol consumption history, treatment for

alcohol use, medical conditions, current medications, and sleep history were collected.

Statistical Analyses

Repeated-measures analysis of variance was used with three factors: alcoholism and anesthesia/surgery as between factors and the test session as the within factor. With this design, the main study hypothesis, that performance of alcoholic patients decreases after anesthesia/surgery more than that of the control subjects, would be supported by a significant three-way interaction. Multiple linear regression was performed to examine the possible effects of clinical and perioperative conditions on the cognitive test results. The chi-square test was used to determine significant between-group differences in demographic and medical data. An *a priori* statistical significance level of $P < 0.05$ was established for all statistical comparisons.

Results

Demographic, Medical, and Perioperative Data

Table 1 contains a summary of demographic and medical data. The frequency of grossly abnormal values of blood glucose, sodium, and potassium was low. Hypertension was frequent in all patient groups. Heart disease was less frequent. Depression was the most common in the nonsurgical alcoholic group ($P < 0.05$). This was likely related to the higher prevalence of depression in alcoholic *versus* nonalcoholic subjects ($P < 0.05$). Sleep disorder was the most frequent in the surgical alcoholic patients ($P < 0.05$) relative to the other three groups. Marital status was also the lowest in the surgical alcoholic group ($P < 0.05$). Neurologic abnormalities were rare. Hachinski scores were less than 4. Therefore, no multi-infarct dementia was indicated in any of the subjects.

Surgical and anesthesia data (table 2) were similar in the two groups. Two significant differences were present. Alcoholic patients received opioid pain medication within 24 h before the first test more often than did nonalcoholic patients. There was no difference between groups with respect to opioid medication within 24 h before the second test. Postoperative admission to intensive care unit (ICU) or ward was significantly more frequent in the alcoholic patients. Two patients in the alcoholic group had postoperative complications in the ICU, including pulmonary edema and confusion for one patient, and anemia and infection in the other. One patient in the nonalcoholic group had postoperative anemia.

Neurocognitive Test Scores at Baseline

Alcoholic subjects had lower baseline scores than did nonalcoholic subjects on Digit Span ($P < 0.005$) and

Table 1. Demographic and Medical Data in Four Patient Groups

	Nonsurgical Alcoholic (n = 14)	Nonsurgical Nonalcoholic (n = 14)	Surgical Alcoholic (n = 14)	Surgical Nonalcoholic (n = 14)
Age, yr	62.3 ± 6.7	62.4 ± 7.1	62.3 ± 7.9	63.7 ± 7.6
Education, yr	12.0 ± 1.8	12.6 ± 2.6	13 ± 2.2	12.8 ± 1.4
Glucose < 60 or > 300 mg/dl, frequency	1	0	1	0
Sodium < 130 or > 150 mm, frequency	1	0	1	1
Potassium < 3 or > 6 mm, frequency	0	0	0	0
Hypertension, frequency	10	8	7	8
Heart disease, frequency	4	3	4	3
Post-traumatic stress disorder, frequency	5	1	2	2
Anxiety disorder, frequency	3	0	1	1
Depression, frequency	10*†	2	7†	3
Sleep disorder, frequency	6	6	10*	4
Diabetes, frequency	4	4	6	2
Neurologic abnormality—test 1, frequency	1	0	1	2
Neurologic abnormality—test 2, frequency	1	0	2	2
Hatchinski score ≥ 4—test 1, frequency	0	0	0	0
Hatchinski score ≥ 4—test 2, frequency	0	0	0	0
White	8	11	10	13
Married	8†	9	2*†	10
History of smoking, frequency	14	14	14	14
Current smoker, frequency	7	3	6	6
Employment, frequency	3	2	2	6
Right handedness	14	12	10	13

* $P < 0.05$ vs. all others. † $P < 0.05$ vs. nonalcoholic.

Semantic Fluency ($P < 0.05$). Alcoholics also had significantly higher depression scores than did nonalcoholics ($P < 0.001$). Surgical patients performed worse than nonsurgical subjects on three tests at baseline: Visual Immediate Recall ($P < 0.01$), Visual Delayed Recall ($P < 0.01$), and the Visual Learning and Retention Test ($P < 0.05$).

Table 2. Surgical, Anesthesia, and Postoperative Care Data in Two Patient Groups

	Alcoholic (n = 28)	Nonalcoholic (n = 28)
Ear, nose, and throat surgery, frequency	3	2
Urologic surgery, frequency	1	2
Gastrointestinal surgery, frequency	3	0
Orthopedic surgery, frequency	7	9
Lung surgery, frequency	0	1
Intraoperative hypotension, frequency	1	3
Intraoperative hypertension, frequency	3	1
Estimated blood loss > 500 ml, frequency	2	2
Anemia, frequency	1	0
ASA physical status, frequency, II/III	6/8	9/5
Anesthesia duration, min	195 ± 97	186 ± 92
Bispectral Index value	44 ± 7	46 ± 8
Sevoflurane dose, %	1.6 ± 0.4	1.4 ± 0.3
Nitrous oxide dose, %	54.1 ± 7.5	50.0 ± 6.7
Rocuronium dose, mg	103 ± 46	114 ± 107
ICU or ward after surgery, frequency	9*	3
Postoperative complications, frequency	2	1
Opioid before surgery, frequency	6*	1
Opioid after surgery, frequency	8	5

* $P < 0.05$ vs. nonalcoholic.

ASA = American Society of Anesthesiologists; ICU = intensive care unit.

Effects of Anesthesia/Surgery and Alcohol Use on Neurocognitive Test Scores

Significant three-way interactions from analysis of variance were found for five of the neurocognitive tests: Visual Immediate Recall ($P < 0.05$), Visual Delayed Recall ($P < 0.05$), Semantic Fluency ($P < 0.01$), Phonemic Fluency ($P < 0.05$), and the Color-Word Stroop Test ($P < 0.01$) (fig. 1). These results were unaffected if the depression score was included in the analysis of variance model as a covariate. These data indicate not only that the alcoholic group displayed greater neurocognitive impairment than other groups before anesthesia/surgery, but that the level of impairment increased significantly after anesthesia/surgery. The level of functioning for other groups did not change significantly.

To clarify the importance of the observed changes, effect sizes were calculated for the five neurocognitive variables that showed three-way interaction. The mean differences in performance between presurgical and postsurgical test scores of alcoholics for all five measures were between 0.5 and 0.8 SDs. In addition, mean postsurgical performance scores of the alcoholic group for Visual Immediate Recall and Visual Delayed Recall were more than 2 SDs below those of nonalcoholic nonsurgical controls. The magnitude of this difference would be sufficient to confer a diagnosis of impaired cognitive function in most alcoholic surgical participants.

Of those tests that did not show three-way interaction, some still showed a two-way interaction. A significant

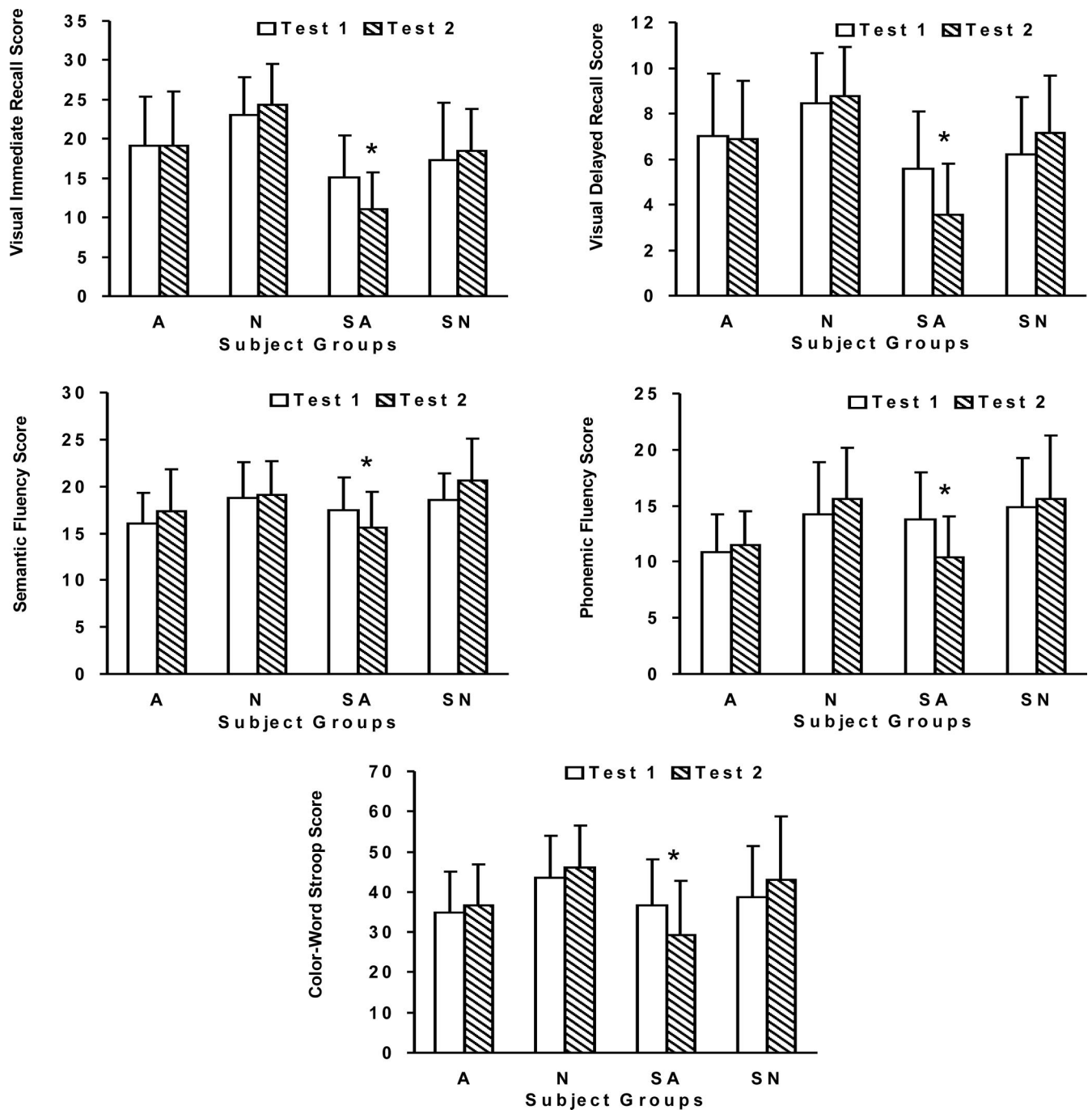


Fig. 1. Neurocognitive test scores (mean ± SD) from two sessions in four subject groups for which significant 3-way interaction from analysis of variance was found. These effects indicate surgery/anesthesia-related neurocognitive impairment specifically in subjects with prior alcohol abuse. A: Nonsurgical Alcoholic group, N: Nonsurgical Nonalcoholic group, SA: Surgical Alcoholic group, SN: Surgical Nonalcoholic group. * indicates the patient group for which the change in test scores between test 1 and test 2 was significantly different from that in the other three groups.

two-way interaction between anesthesia/surgery and testing session was present for List Learning recognition ($P < 0.05$), indicating that patients after anesthesia/surgery performed worse on this test regardless of alcohol abuse history. Significant two-way interactions between alcohol abuse and testing session were also found for List Learning immediate memory ($P < 0.005$), List Learning delayed memory ($P < 0.01$), and List Learning

recognition ($P < 0.01$), indicating that subjects with a history of alcohol abuse performed worse in these tests regardless of whether they underwent surgery.

Effect of Medical and Surgical Variables on Neurocognitive Difference Scores

Finally, we examined whether the changes in the neurocognitive scores before surgery to after surgery could

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be predicted by medical or surgical variables irrespective of group membership for alcoholism. We only considered those neurocognitive tests that showed a significant change postsurgery either in the alcoholic or in both groups of patients. Stepwise linear regression analysis revealed that the change in Visual Delayed Recall correlated with diabetes ($P < 0.05$, $R^2 = 0.44$), ICU or ward admission ($P < 0.005$, $R^2 = 0.30$), and estimated blood loss of greater than 500 ml ($P < 0.005$, $R^2 = 0.15$). The change in List Learning immediate memory correlated with ICU or ward admission ($P < 0.05$, $R^2 = 0.19$). The change in List Learning delayed memory correlated with depression ($P < 0.01$, $R^2 = 0.25$). The correlation coefficients were low, indicating that a relatively small portion of variance of the neurocognitive data were predictable by the available data. Because of the low number of subjects in the current study, these results should be considered exploratory until confirmed.

Discussion

The purpose of this study was to determine whether a history of alcohol abuse in older patients undergoing anesthesia/surgery increased the risk of POCD. POCD has been identified as an important issue because it affects a significant number of patients² and may have serious consequences for quality of life and health risks.³⁵ POCD in patients with history of alcohol abuse has not been previously investigated. We hypothesized that general anesthesia/surgery may provoke or accelerate neurocognitive impairment in alcoholic patients.

We chose to study alcoholic subjects aged 55 yr and older because they demonstrate at least two risk factors for POCD: older age^{36,37} and preexisting cognitive impairment.^{7,14,36,38-47} The participants in this study reportedly did not consume alcohol in the 5 weeks before testing. However, it is known that long-term deficits in the learning of novel associations are usually present even after prolonged periods of abstinence.³⁷ An impairment of visuospatial recent memory³⁶ and of the ability to learn new verbal material was described in abstinent alcoholics not undergoing surgery.^{38,39} Executive dysfunction is another characteristic sign of chronic heavy drinking according to previous studies.^{14,43}

Consistently, we found that the baseline performance of subjects with previous alcohol abuse was lower on Digit Span and Semantic Fluency. After surgery/anesthesia, neurocognitive differences were more pronounced, involving visuospatial recent memory and executive functions. The impairment was greater in visuospatial than executive functions, similar to a recent finding by others.⁴⁸ Executive functions may have decreased less because patients were already impaired in this modality presurgically. Nevertheless, further worsening of executive functions after surgery was indicated by three tests:

Semantic Fluency, Phonemic Fluency, and the Color-Word Stroop Test. Previous neuropsychological and imaging studies demonstrated dysfunction in mediofrontal and in the left dorsolateral prefrontal cortex in chronic alcoholic subjects in the absence of explicit neurologic symptoms.^{13,14,49} Similarly, in our investigation, executive (frontal lobe) functions were impaired in alcoholic patients despite an absence of neurologic abnormalities.

Alcoholic patients more often received opioids for pain before the first neurocognitive test *versus* nonalcoholic patients. This difference tended to diminish after surgery. Even with the low baseline scores, possibly related to opioid use, a significant decrease in neurocognitive performance postsurgery was found. One would expect that in the absence of opioid administration, the changes in test scores from baseline might have been even greater.

There were differences in some baseline scores between the surgical and nonsurgical groups. Surgical patients may have had previous surgeries and medical conditions not identified in this investigation. The psychological effect of impending surgery could also have been a factor. Pain and stress are common in older patients and are likely to be exacerbated by the fear of surgery and its outcome, and an unfamiliar environment.^{50,51}

Factors contributing to POCD in alcoholic subjects include preexisting diseases. In this investigation, postoperative impairment of certain memory tests was associated with the following: diabetes, depression, ICU or ward admission, and estimated blood loss greater than 500 ml, although the degree of correlation was relatively low. Other investigators have reported that poor cognitive performance is associated with diabetes, postoperative delirium, and greater intraoperative blood loss.⁵² Diabetes and mood disorders are frequently observed in alcoholics and influence cognitive performance.^{3,53-57} It is known that depression influences specific areas of cognition, notably attention,⁵⁸ and it seems to be partly involved in the decline of cognitive performance after anesthesia.⁵⁹ The fact that alcoholic patients were more likely to need postoperative admission to the ICU or ward than the nonalcoholic patients may be indicative of a compromise in the general health of alcoholics. Postoperative sleep deprivation could also have had a negative impact on cognitive performance.⁶⁰ Whether these differences contributed to POCD in the alcoholic group at the 2-week postoperative testing session merits further investigation.

Whether general anesthesia itself contributed to POCD in the older alcoholic patients is unclear. Specific surgical procedures or factors secondary to systemic changes and other drug effects could have been involved. General anesthesia affects brain function at all levels, including neuronal membranes, receptors, ion channels, neurotransmitters, cerebral blood flow, and metabolism.^{61,62}

General anesthesia may be a vulnerability factor for age-related cognitive decline.^{61,63,64} It is possible that perioperative cerebral damage, even when its clinical effects are reversible, involves some neuronal loss that makes an individual more vulnerable to deficits from age-dependent cell loss in the future.

In conclusion, the current results support the hypothesis that a history of alcohol abuse in patients aged 55 yr and older contributes to postoperative cognitive dysfunction after noncardiac surgery with general anesthesia. Additional studies are required to determine the effect of different anesthetics or anesthetic techniques on POCD, the duration of cognitive changes, and their impact on rehabilitation and quality of life.

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