SHORT-TERM POSTOPERATIVE COGNITIVE FUNCTION
OF ELDERLY PATIENTS UNDERGOING
FIRST VERSUS REPEATED EXPOSURE
TO GENERAL ANESTHESIA

PETROS TZIMAS*, EFSTRATIOS ANDRITSOS**, ELENI ARNAOUTOGLOU***,
GEORGIOS PAPATHANAKOS**** AND GEORGIOS PAPADOPOULOS*****

Background: General anesthesia (GA) may affect cognitive functions and result in postoperative cognitive dysfunction. The aim of our prospective pilot study was to compare the short-term postoperative cognitive function of unimpaired elderly patients undergoing first versus repeated exposure to GA.

Methods: After approval from the Hospital Ethics Committee and informed consent of all participants, 46 patients, 70.1 ± 7.1 years of age, 20 men and 26 women were enrolled in the study. Twenty-five patients belonged to group A (never received GA before) and 21 patients belonged to group B (received at least once GA the last 5 years). Each patient was evaluated preoperatively and the 8th day postoperatively by a blinded examiner with a battery of neurocognitive tests.

Results: Group B patients performed preoperatively worse in Trail Making Test Part A, Stroop Color and Word Test and Three Words-Three Shapes Test. Postoperatively there were differences in almost every neurocognitive test, with group B patients again achieving the worse scores. This came along with increased Beck Depression Inventory Test score and increased incidence of delirium in Group B patients.

Conclusion: Our pilot study suggests that prior exposure of elderly patients to GA might lead to prolonged cognitive impairment and repeated GA exposure seems to be a potential risk factor for greater short-term postoperative cognitive impairment.

Keywords: Cognitive disorders, Anesthesia, Delirium, Dementia, Postoperative complications

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**Introduction**

Studies conducted on non-cardiac surgery have generally agreed that postoperative cognitive dysfunction (POCD) is quite common in the short-term period (up to several weeks after surgery) with no differences between regional and general anesthesia\textsuperscript{1-3}. General anesthesia has differential effects across cognitive domains and POCD in the elderly has been attributed to age-related neuronal changes exacerbated by pharmacotoxic effects\textsuperscript{4}. Although it is proposed that general anesthesia may demonstrate a cumulative long lasting detrimental effect on cognitive function of aged patients\textsuperscript{5}, it is also speculated that repeated exposure to anesthetics might adversely affect long-term performance in quantitative psychometric tests in the elderly\textsuperscript{1}. The effects of repeated exposure to anesthesia have been studied in experimental models\textsuperscript{6-11} and repeated anesthesia was recognized as a potential risk factor for the later development of learning disabilities in children\textsuperscript{12-14}. Unfortunately, the studies related to postoperative cognitive function of adult patients after repeated exposure to surgical anesthesia are very few and their results are questionable\textsuperscript{15-19}.

We hypothesized that elderly patients with a past history of general anesthesia present with a greater short-term cognitive impairment after a repeated anesthesia. For that reason we have conducted a pilot study in order to compare the short-term postoperative cognitive function of unimpaired elderly patients undergoing first versus repeated exposure to surgical anesthesia.

**Materials and Methods**

The Hospital Ethics Committee approved the study protocol for this prospective pilot study and all participants provided their informed consent. The study was conducted during an eighteen-month period, from January 2012 to June 2013. A total of 46 patients aged 60 to 80 years old, scheduled for elective general surgery or an intra-abdominal gynecologic operation under general anesthesia were categorized into two groups according to their past history, i.e. if they had never undergone a surgical procedure under general anesthesia before (Group A, 25 patients) or had received anesthesia at least once in the previous 2 to 5 years (Group B, 21 patients).

Inclusion criteria included patients aged 60 to 80 years old scheduled for elective general surgery or an intra-abdominal gynecologic operation under general anesthesia and scheduled to be admitted to the hospital as an inpatient for a minimum of 8 days after surgery. Participants were required to have Greek as their native language, to have at least an elementary level education and to be able to speak and read fluently in Greek.

We excluded patients if they had any severe visual or auditory disorder; had previously undergone neuropsychological testing; had a Mini Mental State Examination Score (MMSE) <22; had a disease of the central nervous system, e.g. Parkinson’s disease or a previous cerebral vascular event; had a mental disease, alcoholism, drug dependence or were taking tranquillizers or antidepressants; had chronic obstructive pulmonary disease (COPD) or congestive heart failure (CHF); were to undergo an emergency surgical procedure or had periprocedural desaturation (≥1 events of \(\text{SpO}_2 < 80\%\) for more than 2 minutes) or were hemodynamically unstable (≥1 events of mean arterial blood pressure ≤60 mmHg for more than 10 minutes).

The preoperative evaluation was performed by an anesthesiologist and information about the patients’ demographic status, medical history, physical examination, type of surgery, ASA classification of physical status, and NYHA functional classification of heart disease were also recorded.

Each patient was evaluated preoperatively and the 8\textsuperscript{th} day postoperatively by a blinded examiner with a battery of neurocognitive tests: Mini Mental State Examination (for grading the cognitive state of patients), Beck Depression Inventory (for assessing the severity of depression), Trail Making Test Parts A and B (for assessing visual conceptual and visuomotor tracking skills), Stroop Color and Word Test (for assessing higher executive function), Controlled Oral-Word Association Test (for detecting changes in word association fluency) and Three Words-Three Shapes Test (for measuring different aspects of learning and memory, including incidental learning, trials to criterion, delayed retrieval and recognition) (Table
The examiner was trained in psychometric test administration and relevant interview techniques by a neuropsychologist. The tests were carried out in the morning, in quiet rooms and only the patient and the examiner were present. In case of reported opioid use due to postoperative pain the previous 24 hours, the psychometric evaluation of the patient was postponed. The patients were evaluated by the 0-10 Numeric Pain Rating Scale (for pain intensity evaluation).

Table 1
Battery of neurophysiological tests used in the study population

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mini Mental State Examination</td>
<td>Used to screen for cognitive impairment</td>
</tr>
<tr>
<td>Beck Depression Inventory</td>
<td>A multiple choice survey for assessing the severity of depression feelings</td>
</tr>
<tr>
<td>Trail Making Test (Parts A and B)</td>
<td>A test of visual conceptual and visuomotor tracking skills</td>
</tr>
<tr>
<td>Stroop Color and Word Test</td>
<td>Used for assessing higher executive function</td>
</tr>
<tr>
<td>Controlled Oral-Word Association Test</td>
<td>A measure of verbal fluency</td>
</tr>
<tr>
<td>Three Words-Three Shapes Test</td>
<td>Provides measures of different aspects of learning and memory</td>
</tr>
<tr>
<td>Confusion Assessment Method</td>
<td>Used for detection of postoperative delirium</td>
</tr>
</tbody>
</table>

Each patient was also evaluated the 2nd to 4th day postoperatively with Confusion Assessment Method for detecting postoperative delirium. The patient was considered delirious if the Confusion Assessment Method was positive on any one of these days.

The surgical operation in both patient groups was performed under general anesthesia. All patients received usual perioperative care, including routine anesthetic and safety monitoring: 5-lead electrocardiography (ECG), blood pressure (BP), oxygen saturation via pulse oximetry (SpO₂), end-tidal carbon dioxide and breathing oxygen. Propofol (2 mg/Kg), fentanyl (1-2 mcg/Kg) and a non-depolarizing muscle relaxant (rocuronium, 0.6 mg/Kg) were used for induction in general anesthesia and sevoflurane 1-2% in air/oxygen mixture together with remifentanil (0.2-0.4 mcg/Kg/min) were used for maintenance of anesthesia. Bispectral Index monitoring (BIS Quatro Sensor, Covidien-Medtronic, U.S.A) was used for estimating the depth of anesthesia and delivery of anesthesia was adjusted to maintain a BIS index of 40-60. Mechanical ventilation used was adjusted to tidal volumes of 6-8 ml/Kg, respiratory rate of 10-12/min, aiming at SpO₂ values >97% and end-tidal carbon dioxide values of about 35 mm Hg. Patients were treated for postoperative pain in order to keep Numeric Pain Rating Scale Score below 3 without any analgesic restriction.

Statistical Analysis

Data is presented as mean and standard deviation (SD). Categorical variables are expressed as number (%). The normality of data distribution was assessed using the Shapiro-Wilk test. Continuous data that was normally distributed was compared using the two-tailed Student’s t-test or, if not, by the Mann-Whitney U-test. Pairwise comparisons were performed using paired Student’s t-test or Wilcoxon test as appropriate. Analysis of categorical data was performed using the x² or Fisher’s exact tests. Significance was defined as a p value of less than 0.05. Analyses were performed using IBM® SPSS® Version 21.

Results

Forty-six patients, 70.1 ± 7.1 years of age, 20 men and 26 women were enrolled in the study. Twenty-five patients belonged to group A (never received general anesthesia before) and 21 patients belonged to group B (received at least once general anesthesia the last 2 to 5 years). No one patient presented surgical complications and there was no need for any patient to be admitted in the intensive care unit postoperatively.

There were no significant differences between two groups considering demographics, American Society of Anesthesiologists (ASA) classification of physical status, New York Heart Association (NYHA) functional classification of heart disease, duration of anesthesia and postoperative value of hemoglobin. However, a significant difference was observed.
Table 2
Demographics, clinical characteristics and operative data. Values are expressed as mean ± standard deviation or number of patients (%).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A N = 25</th>
<th>Group B N = 21</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>68.96 ± 7.05</td>
<td>71.43 ± 7.09</td>
<td>0.174</td>
</tr>
<tr>
<td>ASA</td>
<td>1.32 ± 0.48</td>
<td>1.48 ± 0.51</td>
<td>0.285</td>
</tr>
<tr>
<td>NYHA</td>
<td>1.08 ± 0.28</td>
<td>1.19 ± 0.40</td>
<td>0.273</td>
</tr>
<tr>
<td>Preoperative Hb (mg/dL)</td>
<td>12.21 ± 1.44</td>
<td>13.44 ± 1.06</td>
<td>0.006</td>
</tr>
<tr>
<td>Postoperative Hb (mg/dL)</td>
<td>12.42 ± 1.29</td>
<td>13.20 ± 0.91</td>
<td>0.056</td>
</tr>
<tr>
<td>Duration of anaesthesia (min)</td>
<td>158.40 ± 39.23</td>
<td>162.86 ± 36.21</td>
<td>0.688</td>
</tr>
<tr>
<td>Hypertension</td>
<td>n = 10 (40.0%)</td>
<td>n = 8 (38.1%)</td>
<td>0.896</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>n = 4 (16.0%)</td>
<td>n = 2 (9.5%)</td>
<td>0.521</td>
</tr>
</tbody>
</table>

Table 3
Comparison of scores of cognitive and pain intensity tests between group A and group B patients, preoperatively and the 8th day postoperatively (mean values ± standard deviation or number of patients (%)).

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Mini Mental State Examination</td>
<td>28.24 ± 1.17</td>
<td>27.71 ± 1.45</td>
<td>0.181</td>
<td>28.20 ± 1.38</td>
<td>25.48 ± 1.08</td>
<td>0.000</td>
</tr>
<tr>
<td>Numeric Pain Rating Scale</td>
<td>0.12 ± 0.33</td>
<td>0.19 ± 0.40</td>
<td>0.512</td>
<td>3.68 ± 0.48</td>
<td>3.62 ± 0.50</td>
<td>0.669</td>
</tr>
<tr>
<td>Trail Making Test A</td>
<td>78.20 ± 41.37</td>
<td>116.24 ± 73.06</td>
<td>0.029</td>
<td>84.32 ± 47.04</td>
<td>120.48 ± 79.91</td>
<td>0.069</td>
</tr>
<tr>
<td>Trail Making Test B</td>
<td>202.76 ± 96.70</td>
<td>253.95 ± 97.07</td>
<td>0.081</td>
<td>197.04 ± 106.76</td>
<td>286.05 ± 154.11</td>
<td>0.032</td>
</tr>
<tr>
<td>Stroop Color and Word Test</td>
<td>77.24 ± 19.87</td>
<td>57.81 ± 18.59</td>
<td>0.001</td>
<td>80.28 ± 21.64</td>
<td>59.76 ± 20.45</td>
<td>0.002</td>
</tr>
<tr>
<td>Controlled Oral-Word Association Test</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Words starting with C</td>
<td>6.68 ± 2.90</td>
<td>7.14 ± 2.39</td>
<td>0.947</td>
<td>6.20 ± 2.75</td>
<td>6.76 ± 3.00</td>
<td>0.671</td>
</tr>
<tr>
<td>Words starting with S</td>
<td>7.12 ± 2.83</td>
<td>6.10 ± 3.45</td>
<td>0.277</td>
<td>6.52 ± 3.19</td>
<td>5.52 ± 3.44</td>
<td>0.122</td>
</tr>
<tr>
<td>Words starting with A</td>
<td>7.12 ± 3.70</td>
<td>5.67 ± 3.38</td>
<td>0.175</td>
<td>6.04 ± 3.54</td>
<td>4.67 ± 4.26</td>
<td>0.140</td>
</tr>
<tr>
<td>Three Words-Three Shapes Test</td>
<td>24.40 ± 6.01</td>
<td>20.48 ± 6.88</td>
<td>0.045</td>
<td>28.20 ± 2.83</td>
<td>22.14 ± 7.68</td>
<td>0.002</td>
</tr>
<tr>
<td>Incidental recall</td>
<td>22.40 ± 3.85</td>
<td>20.71 ± 4.82</td>
<td>0.345</td>
<td>24.60 ± 4.55</td>
<td>22.38 ± 3.40</td>
<td>0.082</td>
</tr>
<tr>
<td>Beck Depression Inventory Test</td>
<td>n = 3 (12%)</td>
<td>n = 1 (4.8%)</td>
<td>0.391</td>
<td>n = 3 (12%)</td>
<td>n = 8 (38%)</td>
<td>0.041</td>
</tr>
</tbody>
</table>

regarding the preoperative value of hemoglobin between two patient groups, with Group A patients having lower values of hemoglobin preoperatively (p = 0.006) (Table 2).

Between the two patient groups, there were significant differences preoperatively in Part A of the Trail Making Test, the Stroop Color and Word Test, and the Three Words-Three Shapes Test (incidental recall), with Group B patients achieving worse scores (Table 3). In contrast, postoperatively there were significant differences in almost every neurocognitive test (Mini Mental State Examination, Trail Making Test Part B, Stroop Color and Word Test and Three Words-Three Shapes Test, incidental recall), with Group B patients again achieving the worse scores (Table 3).

Three patients in Group A (12%) and 8 patients in
Group B (36.1%) had postoperatively increased Beck Depression Inventory Test scores \( p = 0.041 \).

Delirium, as evaluated using the Confusion Assessment Method, was identified in 5 Group A subjects (20%) and in 9 Group B subjects (42.8%), although not reaching a statistical significance \( p = 0.097 \).

**Discussion**

Based on current medical literature on POCD\(^1\) and on experimental and clinical observations of cumulative adverse effects of anesthesia\(^6\)-\(^19\), we hypothesized that multiple exposures compared with first exposure to general anesthesia would be associated with greater short-term postoperative cognitive impairment. It was difficult to predict specifically which domains would be affected at most. For that reason we have used pre-and postoperatively a number of different neurocognitive tests in order to examine a broad range of neurocognitive domains.

In our study, preoperatively scores of the Mini Mental State Examination, Trail Making Test Part B, Controlled Oral-Word Association Test and Beck Depression Inventory Test between the two patient groups were statistically non-significant. This finding is consistent with the study of Abildstrom et al found that in non-cardiac surgery patients, POCD if present, has a gradual resolution with cognitive decline being indistinguishable from matched controls at 1 year\(^28\). In the retrospective study of Avidan et al\(^29\), it was found that long-term cognitive decline in older subjects was not attributable to non-cardiac surgery, with the median years of annual follow-up after surgery being 3.1 (1.6-5.5). Furthermore, Ancelin et al\(^4\) showed that 13 months after non-cardiac anesthesia no significant changes in attention, implicit memory, delayed visual memory, verbal fluency and logical series were present.

The unexpected finding of our study was the significantly worse performance of patients with a past history of general anesthesia in Trail Making Test Part A, Stroop Color and Word Test and Three Words-Three Shapes Test at baseline. The Trail Making Test evaluates visual conceptual and visuomotor tracking skills. Stroop Color and Word Test is an instrument for the examination of mental activity variables, concentration effectiveness, cognitive flexibility and executive function, while the Three Words-Three Shapes test (incidental recall) has been proved to be a relatively quick and cost effective way to differentiate between normal and abnormal memory function with aging. This finding strengthens the controversial hypothesis that anesthesia initiates or accelerates subtle lesions leading to more permanent effects and contributes to the development of long-term cognitive decline\(^5\).

Between the two groups there were significant differences in almost every neurocognitive test postoperatively: Mini Mental State Examination, Trial Making Test Part B, Stroop Color and Word Test and Three Words-Three Shapes Test (incidental recall), with group B patients achieving again worse scores. The high rate of delirium recorded in our study is in agreement with previous studies\(^30\). This came along with slightly increased Beck Depression Inventory Test score in Group B patients (Table III).

Mini Mental State Examination tests global cognitive functions, including orientation, recall, attention, calculation, language manipulation, and constructional praxis. Trail Making Test Part B is a well validated test to differentiate between normal and pathological aging and requires cognitive flexibility, working memory, set-shifting abilities, the ability to maintain two response sets as well as inhibitory functions\(^31\). This test focuses on not just cognitive processing speed but also considers attention switching difficulties\(^32\).

Although the difference noticed preoperatively in Trail Making Test Part A was not confirmed postoperatively, Trail Making Test Part B is a more reliable tool to identify brain damage and disease and evaluate the status of the brain, regardless of whether the damage is focal or diffuse or the type of pathological involvement\(^33\).

An increased Beck Depression Inventory Test score in group B patients lies in agreement with studies reporting that greater levels of depressive symptoms are associated with greater postoperative cognitive impairment after non-cardiac surgery\(^34\).

The different performance between groups suggests that patients with a past history of general anesthesia present greater short-term cognitive
impairment after repeated anesthesia. The patients with a past history of general anesthesia also presented a greater incidence (almost twice) of postoperative delirium. This difference never reached statistical significance, possibly due to the small number of patients enrolled in our study. Overall, it seems that elderly patients having previously undergone anesthesia at least once prove to be more vulnerable to adverse cognitive effects of general anesthesia.

The higher occurrence of postoperative delirium in cognitively unimpaired elderly subjects may be associated with a worse cognitive outcome and an increased risk of dementia35. It is important to note that Trial Making Test Part B is a very common tool used to assess cognitive function in people with possible dementia36 and executive function in neurodegenerative disorders31.

Human studies which examined the link between anesthesia, surgery, and Alzheimer’s disease had conflicting results37. An early case-control study showed that neither exposure to six or more episodes of general anesthesia, nor cumulative exposure to 600 min or more of general anesthesia, was associated with an increased risk of Alzheimer’s disease18. In another retrospective study, there was no association between the number of procedures or cumulative exposure to anesthesia and development of dementia16. A meta-analysis examining the association between general anesthesia and Alzheimer’s disease, showed no significant association between cumulative exposure to general anesthesia and development of Alzheimer’s disease17. However, two more recent studies both found an increased incidence of dementia after anesthesia and surgery15,19. It is worth mentioning the existence of a study which concluded that exposure to general anesthesia is inversely associated with dementia; this effect was consistent as a trend with increasing exposure to anesthesia (never general anesthesia: OR = 1.7, 95% CI = 1.1-2.7; one general anesthesia: OR = 1.4, 95% CI = 0.9-2.0; two-five general anesthesias: referent 1.0; more than five general anesthesias: OR = 0.7, 95% CI = 0.3-1.5, Pr et. al trend = 0.003)18.

Our study should be considered in light of certain limitations. The small sample size of our pilot study cannot detect the precise effect of repeated anesthesia on short-term postoperative cognitive outcome and the clinical evaluation of postoperative short-term cognitive function is biased by the multiple variables that can complicate or characterize the perioperative period. Despite these limitations, this study has several strengths, namely a neuropsychological battery which aimed at detecting changes in the full range of information processing functions. The included patients represent a group of cognitively healthy aged subjects without brain disease and we were able to adjust for a large range of confounding factors (age, gender, depressive symptomatology, cerebrovascular, and cardiac pathology) and perioperative factors (such as pain or depression) which could have led to an underestimation of postoperative cognitive decline. The homogeneity of anesthetic technique and the absence of patients undergoing an emergency procedure is another advantage of our study.

The results of our pilot study support the hypothesis that prior exposure of unimpaired elderly patients to general anesthesia might lead to prolonged cognitive impairment and that repeated exposure to general anesthesia seems to be a potential risk factor for a greater short-term postoperative cognitive impairment. Longitudinal studies will be necessary to clarify the long-term impact of multiple exposures to general anesthesia and surgery on patients’ cognitive status.
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5.avidan MS and Evers AS: Review of clinical evidence for persistent cognitive decline or incident dementia attributable to surgery or general anesthesia. *J Alzheimers Dis*; 24(2):201-16, 2011.


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\textsuperscript{1} Train-of-four
\textsuperscript{2} Post-tetanic count
\textsuperscript{3} Second twitch

**REFERENCES:**
1. BRIDION Summary of Product Characteristics (SPC)

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JULY 1, 2016

KEYNOTE SPEAKERS

J.R. MARTINEZ
BEST-SELLING AUTHOR
Survival, Strength and Spirit

STEVEN SHAFER, MD
PROFESSOR OF ANESTHESIOLOGY
Michael Jackson, Murder, Mayhem and Mystery: The Propofol Quandary

STEWARD L. COHEN, ESQ.
A Lawyers Review of Critical Sedation Related Medical Malpractice Cases

www.PediatricSedationConference.com