Accepted Manuscript

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PII: S0020-1383(18)30527-8
DOI: https://doi.org/10.1016/j.injury.2018.09.023
Reference: JINJ 7830

To appear in: Injury, Int. J. Care Injured

Accepted date: 9-9-2018


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The influence of anesthetic techniques on postoperative cognitive function in elderly patients undergoing hip fracture surgery: General vs Spinal Anesthesia

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Abstract

Background
Hip fracture is common and morbid in elderly patients. Postoperative cognitive dysfunction (POCD) is also very common in these subjects undergoing surgery with an incidence which exceeds 40% in some reports. To date, the evidence is ambiguous as to whether anesthetic technique may affect the patients’ outcome as far as postoperative cognitive function is concerned.

Objective
The aim of this study was to compare the effect of general and subarachnoid (spinal) anesthesia on the development of POCD up to 30 days after surgery in elderly patients undergoing hip fracture surgery.

Methods
Subjects over 65 years with hip fracture undergoing surgery were recruited for this study. They were enrolled and randomized to receive either general anesthesia (GA group) or subarachnoid (spinal) anesthesia (S group). Cognitive function was assessed using a battery of neuropsychological tests undertaken preoperatively and at 30 days postoperatively. The incidence of delirium was examined during the same period and their functional status, in terms of activities of daily living was also recorded.

Results
A total of seventy patients, 33 men and 37 females, mean age of 76 years were analyzed. Thirty-three patients received general anesthesia (GA group) and 37
subarachnoid (spinal) anesthesia (S group). The two groups of patients were similar with respect to baseline characteristics, comorbidities and perioperative data. The results of neuropsychological testing showed that there were no significant differences between the groups in eight out of ten neurocognitive tests at baseline and 30 days after surgery. There was a statistically significant decline of the Instrumental Activities of Daily Living Scale score in S group compared with group GA on the 30th postoperative day (p=0.043). A significant decline was also present in Color-Word Task test in S group compared with group GA at baseline (p=0.014) and 30 days postoperatively (p=0.003). Postoperative delirium was present in four patients (12%) for the GA group, and in 10 patients (27%) for the group receiving subarachnoid anesthesia.

**Conclusion**

We concluded that the choice of anesthesia modality does not appear to influence the emergence of postoperative cognitive dysfunction in elderly patients undergoing hip fracture surgery.

**Keywords:** Anesthesia, Hip Fracture, General Anesthesia, Regional Anesthesia, Spinal, Postoperative Cognitive Dysfunction, Cognitive Function, Postoperative Delirium, Aged, Anesthetic Modalities.
Introduction

Postoperative cognitive dysfunction (POCD) is a functional mental disorder which affects isolated cognitive processes such as the verbal memory and visual memory, and leads to defective concentration, distracted attention and impediments in language comprehension and visuospatial abstraction [1]. POCD and delirium, which are separate entities, increase morbidity and mortality and prevent rapid rehabilitation and recovery among elderly surgical patients [2]. To date, the pathogenesis of POCD is not sufficiently clarified in spite of investigation [2, 3].

Despite its temporal fluctuations that typically reach a nadir in the early postoperative period, this cognitive disorder is reversible for most of the patients and recovers to preoperative levels within one week after surgery. Type of surgery, coexisting medical diseases, preexisting cognitive dysfunction and advanced age are predisposing factors that increase the risk of POCD and affect a significant number of patients [4]. For example, patients undergoing joint arthroplasty are vulnerable to develop postoperative cognitive decline and delirium ranging from 7% to 75% depending on the definition, patient population, time of postoperative assessment and the instruments used to identify cognitive dysfunction [1, 5].

Even though many anesthetists encourage the use of regional anesthesia techniques in the elderly [6], studies conducted on non-cardiac surgery have generally showed that POCD is quite common up to several weeks after surgery with no differences between regional and general anesthesia [3, 7-9].
Although anesthetic agents exert their effects on diverse central nervous system targets it is difficult to ascribe cognitive changes to anesthetic drugs per se. [2]. Whether anesthesia itself can lead to postoperative cognitive complications remains interesting but still obscure.

The aim of this study was to compare the effect of general anesthesia and subarachnoid (spinal) anesthesia on the development of POCD up to 30 days after surgery in elderly patients undergoing hip fracture surgery.

**Patients and Methods**

*Patient population and study design*

Between May 2015 and May 2017, 198 patients with femur fracture were admitted at General Hospital of Piraeus “Tzaneio”-Greece. Of those, patients over 65 years with hip fracture undergoing surgery under general or spinal anesthesia were recruited for this study (Figure 1). All subjects provided informed written consent before participation. Patients were randomly allocated to receive either general anesthesia (GA group) or subarachnoid anesthesia (S group) based on a closed envelope method. All patients were subjected to a battery of neuropsychological tests (Table 1) that were chosen to represent a wide range of cognitive domains by a member of the team, who was blinded to the study group. Cognitive function was assessed preoperatively (within 24 h before surgery) and on the 30th day after surgery. The tests were carried out in quiet rooms and only the patient and the examiner were present. We used the following neuropsychological instruments: Confusion Assessment Method (CAM) [10], Mini-Mental State Examination [11], Beck Depression Inventory [12], Trail Making test A and B [13], Stroop Neuropsychological Screening test
Controlled Oral Word-Association test [15], Three Word -Three Shapes test [16] and Clock Drawing test [17] and Instrumental Activities of Daily Living Scale test [18] which is suitable for assessing the patient's functional status. Each patient was also screened on 1st, 2nd, 3rd and 4th postoperative day with CAM test for detecting postoperative delirium. When the test was positive on one of the visits the patient was considered as delirious. The primary outcome was the development of POCD at 30 days postoperatively among the recruits and the detection of possible differences between the two anesthesia groups. The secondary outcome was to compare the incidence of delirium at 1st, 2nd, 3rd and 4th postoperative day between groups.

Participants were required to be native speakers of the Greek language, to have at least elementary level of education, to be able for unimpeded oral communication and to be disposable for re-testing by the end of the foreseen follow-up period. We excluded patients that had contraindication to receive general or spinal anesthesia, had previously undergone neuropsychological testing; had any severe visual or auditory disorder or a debilitating previous cerebral vascular event; diseases of the central nervous system, e.g. Parkinson’s disease or had mental diseases e.g. dementia, alcoholism, drug dependence or were taking tranquillizers or antidepressants; we also excluded those patients who underwent an emergency surgical procedure or had periprocudural desaturation (≥1 events of SpO2 <80 % for more than 2 minutes) or were hemodynamically unstable.

Anesthesia regimens

Anesthesia management was conducted according to routine clinical practice.
**General anesthesia**

General anesthesia was induced with fentanyl 3-5 $\mu$g.kg$^{-1}$ and propofol 1.5 mg.kg$^{-1}$. Intubation was facilitated using rocuronium 0.6 mg.kg$^{-1}$ and mechanical ventilation was initiated using a 50% oxygen-air mixture and was adjusted to tidal volumes of 6-8 ml/Kg, respiratory rate of 10-12/min, aiming at SpO$_2$ values $>97\%$ and end-tidal carbon dioxide values of about 35 mmHg. Anesthesia was maintained with Desflurane by adjusting end-tidal concentrations.

**Spinal**

In the group receiving subarachnoid anesthesia (S group), the L3-L4 or L4-C5 intervertebral spaces were selected for spinal puncture, a Quincke 25 G needle was used. Fentanyl 20 mcg and ropivacaine 0.75% were administered in volume according to the somatometric characteristics of the patient. In case of hypotension, (reduction of systolic arterial blood pressure $>30\%$ of the pre-procedure values or $<100$ mmHg), Etilefrine Hydrochloride was administered intravenously at doses of 1 mg. None of the patients received any sedation in the spinal group.

**Monitoring**

Intraoperative monitoring consisted of 5-lead electrocardiography including ST-segment analysis, oxygen saturation via pulse oximetry (SpO$_2$), non-invasive blood pressure measurement (NIBP), respiratory gas analyzer (end-tidal CO$_2$ Desflurane and inspiratory O$_2$).
Analgesia

All patients were treated for postoperative pain to keep Visual Analogue Scale, (VAS) score below 44 mm without any analgesic restriction. In case of reported opioid use due to postoperative pain the previous 24 hours, the psychometric evaluation of the patient was postponed.

Statistical Analysis

A sample size of 70 patients was estimated by power analysis (confidence level 5%, confidence interval 95%). Categorical, numerical and ordinal data were recorded as appropriate. Chi Square test was used for comparisons among categorical variables. Kolmogorov Smirnov test was used to assess normality of numerical variables. For those variables meeting the normality requirement, t-test was used for the independent responses while paired t-test was used for repeated measures (before and after the surgery). For non-parametric variables, Mann Whitney U-test and Wilcoxon's test were used accordingly. The significance level was set to 5%. The statistical analysis was performed with the statistical package IBM SPSS v.20.

Results

A total of seventy patients, 33 men and 37 females, mean age of 76 years and ASA physical status I-III, were included in both anesthesia groups of this study. Thirty-three patients were randomized to receive general anesthesia (GA group) and 37 subarachnoid anesthesia (S group). One patient, from the GA group, died within the 30 days between the assessments, two patients refused re-evaluation (one from each group) and in one case the subarachnoid...
anesthesia was not considered sufficient for the surgical procedure, so the patient received general anesthesia as well. Demographic, clinical characteristics and perioperative data of the two groups of patients are presented in Table 2. Both groups were similar with respect to baseline characteristics, comorbidities and perioperative data (p>0.05) (Table 2).

The results of neuropsychological testing between the general and spinal anesthesia groups on individual tests at baseline and 30 days after surgery indicate that there were no significant differences between the groups in eight out of ten neurocognitive tests. Specifically, no differences were presented in Mini-Mental State Examination, Confusion Assessment Method (CAM), Trail Making test A and B, Color Task test, Controlled Oral Word-Association test, Three Word Three Shapes test and Clock Drawing test (Table 3). There was a statistically significant decline of the Instrumental Activities of Daily Living Scale score in S group compared with group GA on the 30th postoperative day (p=0.043). This significant decline was also present in Color-Word Task test in S group compared with group GA at baseline (p=0.014) and 30 days postoperatively (p=0.003) (Table 3).

There was no significant difference in depression as stated by Beck Depression Inventory test before and after surgery for patients who received general anesthesia. On the contrary, the group that received subarachnoid anesthesia had significant higher score in Beck Depression Inventory test 30 days after surgery compared with baseline (p<0.001). Comparing the two groups at baseline and 30 days postoperative tests, Beck Depression Inventory test was significant higher in S group compared with GA group only on the 30 days postoperative test (p=0.022).
Postoperative delirium was present in four patients (12%) for the GA group, and in 10 patients (27%) for the group receiving subarachnoid anesthesia. The difference in the incidence of postoperative delirium between groups did not reach statistical significance.

There were no significant differences between the two groups regarding the pain intensity using VAS score both preoperatively (p=0.934) and postoperatively (p=0.186).

**Discussion**

In this study, we compared general versus subarachnoid anesthesia in elderly patients undergoing hip fracture surgery, in order to investigate whether the type of anesthesia contributes to the development of POCD at 30 days after surgery.

Our results indicate that there were no significant differences between the groups in eight out of ten neurocognitive tests that represent a wide range of cognitive domains. However, significant differences were observed in the second part of Stroop Neuropsychological Screening test, Color-Word Task test, Instrumental Activities of Daily Living Scale and Beck Depression Inventory tests.

Considering the Color-Word Task test, pre-existing significant difference between the study groups in preoperative testing was observed. The subjects in GA group had significantly higher average performance compared with S group. This result deteriorated significantly at 30 days postoperatively only for the subarachnoid group. This could be explained by the fact that pre-existing
cognitive impairment can influence the performance and compensation for this predisposing factor does not exist. [19, 20]

At the Beck Depression Inventory test, patients were found to be more depressed after spinal anesthesia, but their scores remained in the normal range (0-9), so we can make no assumptions on these changes.

Instrumental Activities of Daily Living Scale is an appropriate tool to assess the patient’s functional status and independent living skills such as using a telephone, doing laundry, and handling finances [18]. There is evidence of poorer scores in mild cognitive impairment compared with normal ageing [21]. As expected, we observed significant differences in both groups between the preoperative and the 30 days postoperative essay in the Instrumental Activities of Daily Living Scale score. However, in our study, participants who received GA were proven more functional and independent compared with S group in the postoperative test. But the statistically significant result of this comparison might not translate to a clinical difference. Besides, although functional recovery depends on many individual variables, such as demographic factors (i.e., age, gender), co-morbidities, previous functional and mental status, success of surgical intervention, and even social factors, [22] all baseline demographic and clinical characteristics of the studied patients were comparable in both groups.

Some older studies did not show any differences in the effect of the type of anesthesia on postoperative neurocognitive dysfunction [23-26], while others [27-29] presented differences in elderly patients in favor of regional anesthesia (spinal or epidural).
In contrast to our results, Rasmussen et al [29] found that the incidence of POCD was significantly greater one week after surgery in patients receiving general anesthesia compared to regional analgesia. Anwer et al, [27] also reported that elderly patients who received general anesthesia had significant decline in cognitive function one day after surgery. Similarly, a study examined whether the type of anesthesia (general or regional) plays a role in the development of cognitive impairment in elderly patients during the immediate postoperative period concluded that elderly patients subjected to general anesthesia displayed more frequent cognitive impairment during the immediate postoperative period in comparison to those who received a regional technique [28].

According to a meta-analysis, concerns that general anesthesia contributes to POCD are not supported by the evidence from randomized control trials. The authors concluded that general anesthesia does not significantly contribute to long-term permanent POCD in adults after non-cardiac surgery [30]. This finding is in line with our study which showed that general anesthesia is not associated with the presence of POCD in comparison with regional anesthesia.

After hip fracture surgery approximately 30 to 65% of elderly patients develop postoperative delirium [2]. In our study, more patients (27%) in the subarachnoid anesthesia group experienced postoperative delirium compared with GA (12%). However, statistically, the type of anesthesia did not influence significantly the incidence of postoperative delirium. This is in line with the results of a recent meta-analysis that showed no significant differences in
delirium in patients with hip fracture undergoing surgery submitted to either regional or general anesthesia [31].

Our study showed no significant differences between the two types of anesthesia in most of the neurocognitive tests performed. Of note, a matched analysis of the American College of Surgeons National Surgical Quality Improvement (ACS-NSQIP) database regarding the effect of anesthesia type on postoperative mortality and morbidities revealed that after adjusting for clinical and patient characteristic confounders, regional anesthesia was associated with significantly lower odds of several postoperative complications, decreased hospital length of stay, but not mortality when compared with general anesthesia [32]. However, recently, O’Donnell and co-workers emphasized the need for agreement on outcome definitions and for a minimum core outcome set to be measured and reported in hip fracture studies [31]. Thus, further prospective, large-scale human trials with long-term follow-up are required to clarify the association between anesthesia and patients’ outcomes [33].

Several limitations about this study should be noted. Although we recruited patients to our groups based on a power analysis prediction of sample size, it seems that more variables might have proven statistically significant differences with a larger number of patients. The strict study inclusion criteria have resulted in the exclusion of many patients in both groups. Moreover, many confounding perioperative and postoperative factors and surgical complications that we failed to recognize, may have influenced the occurrence of postoperative cognitive dysfunction and delirium. A control group of healthy volunteers matched with the experimental groups would also add to the strength of our study.
In conclusion, according to our study, the choice of anesthesia modality does not appear to influence the emergence of postoperative cognitive dysfunction in elderly patients undergoing hip fracture surgery. Regional anesthesia not only failed to show superiority over general anesthesia but in some aspects, general anesthesia seemed to offer benefits in terms of postoperative cognitive functions in aged patients. So far, no convincing evidence exists in the literature that indicates benefits from the type of anesthesia used. Additional well-designed, randomized, control research trials are needed to elucidate whether the type of anesthesia for hip fracture surgery in aged patients has a protective or adverse effect on postoperative cognitive function.

CONFLICT OF INTEREST STATEMENT

All authors state that they have not any conflict of interest or any potential relationship with industry to report.
References


Figure Captions

Figure 1. A flow diagram of study participants.
Table 1. Battery of tests used in the study population

<table>
<thead>
<tr>
<th>TEST</th>
<th>SCREENING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Instrumental Activities of Daily Living Scale</td>
<td>Functional status, the patient's ability to care for him- or herself.</td>
</tr>
<tr>
<td>Mini-Mental State Examination</td>
<td>Cognitive impairment. examines functions including registration (repeating named prompts), attention and calculation, recall, language, ability to follow simple commands and orientation.</td>
</tr>
<tr>
<td>Beck Depression Inventory</td>
<td>Severity of depression.</td>
</tr>
<tr>
<td>Confusion Assessment Method</td>
<td>Identification of delirium.</td>
</tr>
<tr>
<td>Trail Making Test A και B</td>
<td>Visual attention and task switching. The test can provide information about visual search speed, scanning, speed of processing, mental flexibility, as well as executive functioning.</td>
</tr>
<tr>
<td>Stroop Neuropsychological Screening Test (Color Task-Color-Word Task)</td>
<td>Selective attention, cognitive flexibility and processing speed, evaluation of executive functions.</td>
</tr>
<tr>
<td>Controlled Oral Word Association Test</td>
<td>Verbal fluency.</td>
</tr>
<tr>
<td>Three Words - Three Shapes Test</td>
<td>Learning, memory, recall and recognition.</td>
</tr>
<tr>
<td>Clock Test</td>
<td>Dementia</td>
</tr>
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</table>
Table 2.
Demographics, clinical characteristics and Peri-operative Data of two groups of Patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group-GA (n=33)</th>
<th>Group-S (n=37)</th>
<th>P</th>
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<tbody>
<tr>
<td>Age</td>
<td>75.09±6.08</td>
<td>77.11±6.5</td>
<td>0.211</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>72.94±8.90</td>
<td>78.38±9.25</td>
<td>0.283</td>
</tr>
<tr>
<td>Education (Years)</td>
<td>9.36±3.24</td>
<td>10.43±3.50</td>
<td>0.185</td>
</tr>
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<td>0.255</td>
</tr>
<tr>
<td>I</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>20</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>11</td>
<td>16</td>
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<tr>
<td>NYHA</td>
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<td></td>
<td>0.728</td>
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<tr>
<td>I</td>
<td>7</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>21</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>5</td>
<td>8</td>
<td></td>
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<tr>
<td>Hypertension</td>
<td>27 (81.8%)</td>
<td>25 (75.7%)</td>
<td>0.273</td>
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<tr>
<td>Diabetes</td>
<td>9 (27.2%)</td>
<td>11 (29.7%)</td>
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<tr>
<td>MI Hx</td>
<td>1 (3%)</td>
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<tr>
<td>Stroke Hx</td>
<td>2 (6%)</td>
<td>3 (8%)</td>
<td>1.000</td>
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<tr>
<td>COPD</td>
<td>6 (18.1%)</td>
<td>6 (16.2%)</td>
<td>1.000</td>
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<tr>
<td>Duration of Surgery (min)</td>
<td>56±19</td>
<td>57±25</td>
<td>0.823</td>
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<tr>
<td>Hospital Stay (days)</td>
<td>8.21±</td>
<td>8.25±</td>
<td>0.663</td>
</tr>
<tr>
<td>Preoperative Hb (mg/dl)</td>
<td>11.04</td>
<td>10.95</td>
<td>0.716</td>
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<tr>
<td>Postoperative Hb</td>
<td>10.12</td>
<td>10.07</td>
<td>0.962</td>
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<tr>
<td>RBC Transfusion (n of patients) (%)</td>
<td>32 (97 %)</td>
<td>35 (95%)</td>
<td>0.494</td>
</tr>
</tbody>
</table>

ASA: American Society of Anesthesiologists

NYHA: New York Heart Association

MI: Myocardial Infarction
**COPD: Chronic Obstructive Pulmonary Disease**

<table>
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<tr>
<th>Neuropsychological tests</th>
<th>Group-GA</th>
<th>Group-S</th>
<th>P</th>
<th>Group GA</th>
<th>Group-S</th>
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<td>Mini Mental State</td>
<td>25.70±2.85</td>
<td>25.32±0.90</td>
<td>0.325</td>
<td>25.70±2.86</td>
<td>24.30±4.32</td>
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<td>Examination</td>
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<tr>
<td>Instrumental Activities</td>
<td>7.57±0.90</td>
<td>7.35±0.85</td>
<td>0.139</td>
<td>3.03±1.55</td>
<td>2.35±1.06</td>
<td><strong>0.043</strong></td>
</tr>
<tr>
<td>of Daily Living Scale</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Beck Depression</td>
<td>6.70±3.53</td>
<td>6.97±3.21</td>
<td>0.733</td>
<td>7.03±3.16</td>
<td>8.78±1.06</td>
<td><strong>0.022</strong></td>
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<td>Inventory</td>
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<tr>
<td>Controlled Oral Word</td>
<td>29.06± 8.75</td>
<td>28.00±9.96</td>
<td>0.640</td>
<td>26.78±8.50</td>
<td>25.35±9.88</td>
<td>0.525</td>
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<td>Association Test</td>
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<td>Trail Making Test A</td>
<td>84.45±49.14</td>
<td>97.89±55.42</td>
<td>0.289</td>
<td>80.64±47.97</td>
<td>104.76±58.0</td>
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<td>Trail Making Test B</td>
<td>113.59± 99.87</td>
<td>143.05±112.36</td>
<td>0.254</td>
<td>113.16±91.49</td>
<td>158.08±125.19</td>
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<td>Three Words-Three</td>
<td>5.58±0.56</td>
<td>5.57±1.06</td>
<td>0.337</td>
<td>5.66±1.95</td>
<td>5.24±1.83</td>
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<td>Shapes-Copy</td>
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<tr>
<td>Three Words-Three</td>
<td>3.52±1.95</td>
<td>3.03±1.83</td>
<td>0.319</td>
<td>2.90±2.02</td>
<td>2.34±1.53</td>
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<td>Shapes-Incidental recall</td>
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<td>Stroop Neuropsychologi-</td>
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<tr>
<td>cal Screening Test</td>
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<tr>
<td>Color Task Test</td>
<td>69.12±35.82</td>
<td>63.14±35.82</td>
<td>0.490</td>
<td>70.44±37.06</td>
<td>64.30±34.84</td>
<td>0.481</td>
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<tr>
<td>Color-Word Task Test</td>
<td>24.67±12.81</td>
<td>18.10±8.80</td>
<td><strong>0.014</strong></td>
<td>25.84±14.12</td>
<td>16.97±9.00</td>
<td><strong>0.003</strong></td>
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<tr>
<td>The Clock-Drawing Test</td>
<td>3.35±0.79</td>
<td>3.06±0.96</td>
<td>0.222</td>
<td>3.27±0.98</td>
<td>3.00±1.00</td>
<td>0.250</td>
</tr>
</tbody>
</table>

**Table 3.** Neuropsychological test results for the patients at baseline and 30 days after surgery
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