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The effect of total intravenous anesthesia on the postoperative cognitive functions of young and elderly patients after lumbar disk surgery

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Background/aim: The negative effects of surgery and anesthesia on cognitive functions and their relationships with many factors are well known. In the present study we aimed to investigate the effect of the total intravenous anesthesia (TIVA) method on the postoperative cognitive functions between young and elderly patients scheduled to undergo lumbar disk surgery.

Materials and methods: The TIVA method was applied to 40 patients less than 65 years old (young, Group Y) and ≥65 years old (old, Group O), whose Mini Mental State Examination (MMSE) results and serum S-100 beta protein levels were compared preoperatively and postoperatively at the 24th hour.

Results: Postoperative cognitive dysfunction was not observed in any of the groups in the early stage. MMSE results and mean S-100 beta protein levels determined before and after the operation did not have statistically significant differences between the groups over time.

Conclusion: In the present study, the TIVA method did not affect postoperative early cognitive functions in either old or young patients who underwent lumbar disk surgery.

Key words: Postoperative cognitive dysfunction, Mini Mental State Examination, S-100 beta protein, total intravenous anesthesia

1. Introduction

Early postoperative cognitive dysfunction (POCD), confusion, and delirium are frequently observed in advanced-aged patients after major surgery and appear with impairment in memory, concentration, social adaptation, and language capacity. Its incidence may reach up to 60%, particularly after cardiac surgery. It has been suggested that there was no age-unrelated decline in cognitive functions in patients who had ambulatory surgery under general anesthesia (1,2).

There are numerous risk factors for POCD, including advanced age, poor education level, diabetes mellitus, electrolyte imbalance, use of alcohol, and serious atherosclerosis as preoperative factors. Meanwhile, hypotension, hypoxia, and applied medication are considered intraoperative risk factors, in addition to postoperative risk factors like infections and insufficient analgesia (3–5). Despite anesthesia not being a sole factor, some anesthetic agents might cause POCD (6,7).

In the total intravenous anesthesia (TIVA) method, the most commonly used drugs are propofol as a hypnotic and remifentanil as an analgesic. Despite its advantages (rapid recovery, which allows for postoperative neurological evaluation, and no nausea or vomiting,), propofol might cause POCD (6,8,9).

S-100 beta protein is a Ca^{2+}-binding protein that is found in the cytosol of glial cells and has a high specificity for central nervous system (CNS) lesions. In several studies it was pointed out that S-100 beta protein could be a good indicator for diagnosing dysfunction (10–14). On the other hand, the Mini Mental State Examination (MMSE) test, composed of 30 points in total and produced as a cognitive evaluation tool for elderly patients in delirium and/or with dementia, is another valuable test for identifying POCD. Because the other neuropsychiatric tests used to quantitatively evaluate cognitive performance include many questions and their application takes more than 30 min, MMSE is very advantageous when application time is limited (4).

When studies investigate the relationship between age and POCD, researchers mainly focus on major surgeries like orthopedic or cardiac surgery. Because lumbar disk surgery has been considered to be a relatively minor type of neurosurgery and has less potential for bleeding, we

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aimed to investigate the effect of the TIVA method on age by assessing cognitive functions via MMSE test and S-100 beta protein level which were assessed pre- and postoperatively.

2. Materials and methods

After obtaining approval from the ethics committee of the Gazi University Faculty of Medicine, 40 patients having American Society of Anesthesiologists (ASA) I–II physical status scheduled to undergo lumbar disk surgery were divided into 2 groups as 'young' (<65 years, Group Y) or 'old' (365 years, Group O). The following patients were excluded from the study: patients having severe hepatic, renal, cardiovascular, or CNS disease; patients with uncontrolled hypertension, a history of hypersensitivity to the drugs to be used, malignant hyperthermia, or a control MMSE score ≤23; women who were pregnant or breast-feeding; patients taking Ca^{2+} channel blockers, opioids, anticoagulants, antidepressants, or antipsychotics; those with a history of cardiac surgery; those having difficulty understanding and using Turkish; those with vision or hearing problems; patients with Parkinson's disease; alcohol or drug addicts; morbidly obese patients with a body mass index of >40; and patients who refused to be involved within the scope of the research.

After all patients were informed about the tests and collection of blood, written consent was obtained from each of them. The MMSE was then applied and preoperative hemoglobin (Hb) values were recorded. Heart rate (HR), systolic blood pressure, diastolic blood pressure, mean arterial pressure (MAP), and peripheral oxygen saturation (SpO_2) were monitored in the operating room. Bispectral index (BIS) monitoring was done in order to evaluate the depth of hypnosis (A-2000 Bispectral Index, Aspect Medical Systems, the Netherlands). To determine S-100 beta protein levels (Elecsys, Roche Diagnostics GmbH, Germany), 3 mL of venous blood was collected from an intravenous cannula on the dorsum of the hand before the induction of anesthesia. After collection, 3 mL kg^{-1} h^{-1} intravenous Ringer's lactate or normal saline infusion was started.

Following 100% oxygen of 5 L/min for 3 min, 1% lidocaine at 0.5 mg/kg was given intravenously in order to prevent potential injection pain due to propofol and to suppress hemodynamic response to endotracheal intubation. In both of the groups, at the onset of induction, remifentanil infusion was started with a dosage of 0.2 µg kg^{-1} min^{-1}. After 1 mg/kg propofol was delivered by intravenous bolus, dosage additions of each 10 mg were applied until BIS value decreased to 60. Infusion was commenced at a rate of 8 mg kg^{-1} h^{-1}. Pancuronium at 0.1 mg/kg was administered to facilitate endotracheal intubation. Remifentanil and propofol infusions were applied using an infusion pump (Baxter Healthcare volumetric infusion pump, Eczacıbaşı, Turkey). Mechanical ventilation was provided with 6 mL/kg tidal volume and a frequency of 8–12/min with total of 4 L/min in 40% O_2 air mixture to keep $EtCO_2$ between 30 and 35 mmHg. After intubation, patients were turned to the prone position and onset of surgery was allowed. Anesthesia was maintained in both groups by remifentanil and propofol infusions. Infusion rates of remifentanil and propofol were adjusted according to the hemodynamic variables and BIS values.

Heart rate, mean arterial pressure, SpO_2, and BIS values were recorded before induction and recorded at 1 min after completing induction, at the first minute of intubation, and once every 5 min thereafter until minute 30, at which point they were recorded every 15 min until the operation ended. $EtCO_2$ values were recorded after intubation and also followed in the same intervals until the end of the operation.

Propofol infusion was discontinued when skin closure began. Remifentanil stopped together with the last suture, at which point the total drug delivery and remeasured Hb value was recorded. For postoperative pain control, 20 mg of tenoxicam (a nonsteroid antiinflammatory drug) and 0.05 mg/kg morphine were administered intravenously. After extubation, the patients were transferred to recovery rooms and observed for at least 30 min. Patients were visited at postoperative hours 12 and 24 for additional morphine (0.05 mg/kg) if the visual numeric scale (VNS) score was ≥4. Twenty-four hours after the operation, 3-mL blood samples were collected from the patients in order to measure S-100 beta protein levels again. The MMSE test was also repeated.

2.1. Assessment of S-100 beta protein

Serum specimens were prepared by centrifugation at 3000 rpm for 5 min and they were stored at –80 °C in a refrigerator in the Gazi University Hospital Central Biochemistry Laboratory until they were analyzed. S-100 beta protein levels were analyzed using ready-to-use kits by autoanalyzer based on electrochemiluminescence immunoassay. Normal values of S-100 beta protein were accepted to be 0–0.105 µg/L. Sensitivity of the test was <0.005 and CV% value was 1.8.

2.2. Statistical analysis

SPSS 12.0 was used for statistical assessment. Data were shown as [mean ± standard deviation (SD), minimum–maximum (min–max) values, n (%)]. Student's t-test was used in between-groups comparisons of age, body weight, height, anesthesia and surgery time, MMSE score, S-100 beta protein, and Hb; a matched t-test was used for within-group comparisons of MMSE score, S-100 beta protein, and Hb data; repeated-measurements variant analysis was applied in intragroup assessments; and the Mann–Whitney U test was used for intergroup comparisons of MAP, HR, BIS, $EtCO_2$, and SpO_2 values. Chi-square test (Fisher's exact chi-square test) was used in ASA and sex comparison. $P < 0.05$ was accepted as statistically significant.

3. Results

There were no statistically significant differences in the demographic features or operation and anesthesia times except for age and ASA score ($P < 0.0001$ and $P = 0.002$, respectively; Table 1).

When MMSE results before and after the operation were compared, no statistically significant differences were found between or within groups (Table 2). Mean S-100 beta protein levels before and after the operation did not show any statistically significant differences. They were found to be similar between the groups (Table 3).

When the hemoglobin values before and after the operations were compared, no statistically significant differences were found between the groups. However, the postoperative hemoglobin values of both Group Y and Group O were significantly lower than the preoperative hemoglobin values ($P < 0.0001$ and $P < 0.0001$, respectively; Table 4).

When the mean arterial pressure, SpO_2, and $EtCO_2$ values were compared, no statistically significant differences were found between groups.

4. Discussion

A number of risk factors for cognitive dysfunction during the postoperative period have been identified. Among these factors, there are many studies about the operation type, stating that it has a direct influence on POCD development. POCD is mostly seen after major cardiac surgery at rates of 40%–60% (3–7,15). In another study, POCD and delirium had a rate of 1%–3% after cataract surgery, 10% after general surgery, 28%–61% after major orthopedic surgery, and 47% after cardiac surgery (16). Based on these studies, we investigated the impact of general anesthesia on POCD development in patients of advanced age versus young age after lumbar disk surgery. In addition, the facts that the age range of lumbar disk surgery patients is wide (making it possible to apply lumbar disk surgery in both young and old patients) and that intraoperative hemorrhage amounts were unremarkable were other factors that might have affected our selection. Furthermore, we have not found any relevant study for POCD development.

Table 1. Demographic properties and operation and anesthesia duration [mean ± SD].

	Group Y (n = 20)	Group O (n = 20)	P
Age (years)	40.8 ± 7.3	69.4 ± 4.4*	<0.0001
Weight (kg)	73.3 ± 13.1	78.2 ± 9.9	0.190
Height (cm)	167.3 ± 7.7	167.5 ± 8.5	0.938
Sex (F/M)	12/8	9/11	0.527
ASA (I/II)	18/2	8/12*	0.002
Time of surgery (min)	85.5 ± 32.6	93.3 ± 32.5	0.454
Time of anesthesia (min)	96.4 ± 34.2	106.6 ± 32.9	0.340

*: $P < 0.05$ between the groups.

Table 2. MMSE results before and after the operation [mean ± SD (min–max values)].

MMSE	Group Y (n = 20)	Group O (n = 20)	P
Before the operation	28.1 ± 2.5 (24–30)	27.5 ± 2.4 (24–30)	0.409
After the operation	28.8 ± 2.2 (23–30)	28.0 ± 2.6 (24–30)	0.305

One of the foremost factors that may cause cognitive dysfunctions, and the main element in our study, was advanced age. However, advanced age alone could not be held responsible for POCD development in many studies. In addition to advanced age, the type of surgery, like major or minor, might play an important role to a certain degree. When elderly patients undergo major surgery, POCD is more likely to be seen. Canet et al. (17) suggested that advanced age was a risk factor for POCD and the POCD rate of elderly patients who had minor surgery was lower than the rate seen in those who had major surgery.

Moller et al. (2) emphasized that the combination of major surgery and advanced age was one reason for cognitive dysfunction in the ISPOCD1 study. Monk et al. (18) observed that cognitive dysfunction was more frequent in elderly patients. Moreover, Chung et al. (19) investigated the role of minor surgery combined with advanced age on POCD development using 4 tests, including the MMSE, in 40 patients who underwent cholecystectomy. The patients were grouped as above or under the age of 60 where thiopental, fentanyl, and volatile anesthetics were administered for general anesthesia. Similar to our study, the POCD rates in the young and old patients who had minor surgery were found to be similar; thus, the factor of age alone was not responsible for POCD development. According to our results, lumbar disk surgery, which was a noncardiac and partially minor surgery, did not result in POCD in younger patients.

Cognitive dysfunction in the postoperative early or late periods, especially after general anesthesia, has been considered to be responsible for POCD development. Wu et al. (20) reviewed 24 studies that compared the effects of regional versus general anesthesia on POCD development in patients who underwent noncardiac surgery. It has been

Table 3. S-100 beta protein levels [mean ± SD].

S-100 beta protein	Group Y (n = 20)	Group O (n = 20)	P
Before the operation	0.12 ± 0.05	0.13 ± 0.1	0.619
After the operation	0.15 ± 0.12	0.10 ± 0.05	0.128

Table 4. Preoperative versus postoperative Hb values [mean ± SD (min–max values)].

Hemoglobin (g/dL)	Group Y (n = 20)	Group O (n = 20)
Before the operation	13.8 ± 1.4 (11.9–16.7)	13.6 ± 1.5 (9.7–16.6)
After the operation	12.9 ± 1.5* (11.0–15.8)	12.8 ± 1.5* (9.7–16.0)

*: P < 0.05 versus preoperative values.

concluded that the POCD incidence was not affected by the type of anesthesia.-

The TIVA method has been widely used in anesthesia practice due to its many advantages, like rapid recovery from anesthesia (resulting in earlier postoperative neurological evaluation), less intraoperative bleeding, and less nausea and vomiting (21). However, it has been reported that propofol, the most important component of TIVA and neuroleptic anesthesia in patients undergoing oral surgery lasting more than 10 h, could cause POCD in the early stages (6). Regardless of the use of propofol, longer surgery time and more intraoperative bleeding could have played roles in the development of POCD in some studies (22,23). Schütz et al. (24) also suggested that more POCD has been observed in anemic or hemorrhagic patients.

When the effects of propofol and sevoflurane anesthesia, which are used as a supplement to epidural anesthesia for cases of laparoscopic surgery of 3 h or longer, were examined, the incidence of delirium was greater in the propofol group compared to the sevoflurane group (7). The underlying mechanism might be related to the increase in the terminal elimination half-life of propofol as a result of long-term infusion; also, more propofol was consumed because of using targeted controlled infusion (TCI). Since the surgery time did not exceed 3 h and TCI was not utilized in our study, negative effects of propofol were not observed.

Kubitzs et al. (25) investigated patients aged 80 years or older, while Moffat and Cullen (26) evaluated patients 60 years and older. They concluded that propofol, in comparison with etomidate, did not have any effect on the extension of recovery time or increase in POCD incidence rates. When the effects of thiopental versus propofol on POCD in 60 patients aged 18–60 who had minor surgery were studied, no significant differences were found in the first-day results in terms of POCD when compared to a control group (27). It is noteworthy that the patients were under 60 years of age, which makes us think that the propofol did not cause POCD because of the young ages. However, in our study, the propofol did not cause POCD in the advanced-aged patients, either. Therefore, these results, as well as ours, are in agreement that propofol should not be held responsible for POCD.

In recent years, it has been pointed out that MMSE scores and the determination of S-100 beta protein as a marker might be indicators for cognitive dysfunction (10,14,28). The MMSE test has been used in patients of various age groups undergoing either cardiac or noncardiac elective surgery (29,30). The incidence of POCD was higher in patients who had lower preoperative MMSE scores after noncardiac surgery (29), whereas postoperative delirium was diagnosed in 14% of patients who received either high-dose fentanyl or thiopentone during induction of anesthesia after coronary artery bypass grafting surgery (30). However, in our study, the preoperative and postoperative MMSE results were similar in both groups. Since POCD was not observed concomitantly, MMSE results do not seem to be a good indicator, at least not in the present study.

It is of interest that S-100 beta protein and neuron-specific enolase (NSE) are considered serum indicators of cerebral impairment (31,32). Although Svenmarker et al. (33) investigated the impact of S-100 beta protein on postoperative memory functions after cardiopulmonary bypass in the early stage, S-100 beta protein has a better correlation in the early period with the magnitude of hypoxic damage in surviving patients compared to NSE (12). However, S-100 beta protein levels did not change in the patients who underwent urological surgery regardless of the occurrence of POCD (34).

Rasmussen et al. (35) searched for POCD after cardiac surgery using S-100 beta protein and NSE accompanied by neuropsychological tests during the postoperative period. In the ISPOCD study, while the S-100 beta protein levels of the patients in whom POCD was observed did not manifest statistically significant increases, NSE was considered to be more specific in the POCD diagnosis. We also did not find any significant differences in the S-100 beta protein levels and MMSE results at the postoperative 24th hour.

It was also shown that the analgesia methods and analgesics used in the postoperative period play active roles in POCD development. One frequently used opioid, meperidine, is among one of the most blamed agents. It has been argued that morphine hydrochloride causes less cognitive dysfunction and delirium than tramadol and meperidine (36,37). In our 24-h postoperative patient follow-up, we administered additional doses of morphine according to the VNS. In this way, we eliminated the possibility of additional analgesic delivery beyond the scope of our knowledge and the development of POCD due to postoperative pain.

In conclusion, the TIVA method did not constitute a risk factor for POCD development within the first postoperative 24 h in patients either less than 65 or ≥65 years of age who underwent lumbar disk surgery.

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