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Original Scientific Paper

THE EFFECT OF ANESTHESIA ON POSTOPERATIVE COGNITIVE DYSFUNCTION

Miro Bilić[1], Martina Lukšić[2], Martina Miklić Bublić[3], Zrinka Orešković[3], Davor Mijatović[3,4] and Vilena Vrbanović Mijatović[3,4]

[1]Department of Surgery, Zagreb University Hospital Center, Zagreb, Croatia;
[2]Community Health Center of Split-Dalmatia County, Split, Croatia;
[3]Department of Anesthesiology, Resuscitation and Intensive Care Medicine and Pain Therapy, Zagreb University Hospital Center Zagreb, Zagreb, Croatia;
[4]School of Medicine, University of Zagreb, Zagreb, Croatia

SUMMARY – Postoperative cognitive dysfunction (POCD) is a newly developed cognitive function deficit after surgery. The aim of the study was to determine the incidence of POCD after anesthesia and possible risk factors. A prospective study was conducted on 90 patients scheduled for elective surgery under general (60 patients) or regional (30 patients) anesthesia. Each patient completed the Montreal cognitive assessment (MoCa) test the day before and the day after surgery. Data on comorbidities, previous COVID-19 infection, demographic and anesthesia related data were also collected. The day after surgery, POCD defined according to the 2 scores rule was present in 38 (42.2%) patients. A lower level of education (p=0.023), previous COVID-19 infection (p=0.032), higher Charlson comorbidity index (CCI) (p=0.014), and general anesthesia (p=0.035) were identified as risk factors, whereas a statistically significant negative correlation with preoperative (p=0.001) and postoperative result (p=0.001) was proven for age. The results indicated that a significant proportion of patients after general or regional anesthesia developed POCD depending on patient education, CCI, COVID-19 infection, and type of anesthesia. It was also shown that older age correlated with poorer MoCa test result independently of anesthesia. These factors can be identified before the procedure under anesthesia, thus offering the possibility of adjusting anesthesia and postoperative care in patients at risk of developing POCD.

Keywords: *Postoperative cognitive dysfunction; Anesthesia, general, regional; MoCA test*

Introduction

Postoperative cognitive dysfunction (POCD) refers to disorders that affect orientation, attention, perception, awareness, and judgement that develop after surgery[1]. Despite the many studies carried out so far, there is no unequivocal definition of POCD. Also, diagnostic criteria are not clearly established, neither are guidelines for treatment and prevention of POCD. The diagnosis of POCD is determined by psychometric testing of the patient before and after surgery, and cognitive impairment is indicated by a worse result on postoperative testing. The manifestations of POCD

Correspondence to: *Vilena Vrbanović Mijatović, MD, PhD*, Department of Anesthesiology, Resuscitation and Intensive Care Medicine and Pain Therapy, Zagreb University Hospital Center, Kišpatićeva 12, HR-10000 Zagreb, Croatia
E-mail: vilena.v@gmail.com

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are subtle, often unrecognized and transient but can also lead to permanent damage. POCD affects all age groups but the frequency is higher in older patients[2]. Risk factors include a lower level of education, duration and extent of surgery, previous operations, and postoperative complications[1,3]. Development of POCD in patients carries a higher rate of morbidity and mortality, as well as reduced work ability and quality of life[4].

The etiology of POCD remains undetermined. A number of conducted studies indicate the possible causes of POCD but the pathophysiological mechanisms of the disorder itself still remain unknown[5-8]. Many studies state that a systemic inflammatory response is the cause. Peripheral trauma stimulates the production of cytokines that can damage brain function in a number of ways. One way is the entry of cytokines into the central nervous system (CNS) through the blood-brain barrier, where they stimulate microglial cells to further produce cytokines, especially in the hippocampus. In response to inflammatory mediators produced in the periphery, microglia cells amplify inflammation in the CNS and lead to cognitive dysfunction[9]. More recent research is paying attention to the role of intestinal microflora in the development of POCD. The role of anesthesia in the development of POCD has not yet been fully elucidated. Anesthetics can lead to changes in the cholinergic system in the brain by the mechanism of inhibition of neurotransmission depending on the type and concentration of anesthetic[10,11]. Volatile anesthetics that are administered by inhalation can potentiate the accumulation and oligomerization of β-amyloid associated with the impairment of learning and memory processes, especially in the elderly. They can also stimulate various cellular processes such as apoptosis[10]. Volatile anesthetics can also increase the expression of proinflammatory cytokines, which has a significant role in the etiology of POCD. This can explain the effect of volatile anesthetics on prolonged cognitive recovery after surgery[12,13]. Such effects have not been observed with intravenous anesthetics such as propofol[12,14]. However, the question of the effect of the type of anesthetic on the development of POCD still remains controversial and requires further investigation. The role of other drugs, especially opioids and those with anticholinergic activity, should not be neglected either. When comparing general and regional anesthesia, as well as their combination, differences in the incidence of POCD are nonsignificant but differences are still observed in certain cognitive domains. Short-term memory, visuospatial and verbal skills are better preserved postoperatively in patients who were under regional anesthesia. This has been attributed to the effect of regional anesthesia on better pain modulation by omitting perioperative opioids and modulating stress and inflammatory responses[15].

The objectives of the research were to determine the incidence and characteristics of POCD after surgery under general and regional anesthesia and to investigate the effect of the possible risk factors.

Patients and Methods

Patients

The prospective study was conducted at the Department of Anesthesiology, Intensive Care and Resuscitation and Pain Therapy, Department of Surgery, Department of Ear, Nose and Throat Diseases and Head and Neck Surgery, and Department of Orthopedics, Zagreb University Hospital Center (UHC). Ninety patients aged 18-80, scheduled for elective surgical procedures, participated in the research. Their median age was 60 years. The youngest patient was 20 years old, and the oldest 79 years old. Nine (10%) patients had completed only elementary school, 50 (55.6%) had secondary school, and 31 (34.3%) patients had completed higher education.

Inclusion criteria were American Society of Anesthesiologists (ASA) perioperative risk category I to III, surgical procedure under general or regional anesthesia, signed informed consent for participation in the study after an interview in which the patients were informed about the goals and methodology of the study, signed informed consent for anesthesia and surgical treatment at Zagreb UHC, planned postoperative hospital stay for more than 24 hours.

Exclusion criteria were inability to refuse informed consent, CNS disease and psychiatric disease (e.g., schizophrenia, severe anxiety or severe depression), addiction to psychoactive drugs or alcohol (>5 units of alcohol *per* day for the last three months), illiteracy, lack of knowledge of the language, aphasia, severe visual or

hearing impairment that would affect performance of the test, refusal of treatment, treatment with sedatives (except for benzodiazepines at nighttime and preoperative sedation) and antidepressants, reduced probability of surviving the procedure, and severe reaction to the anesthetic applied. A patient could not be enrolled two or more times, even for unrelated operations.

To conduct the research, a permit was obtained from the Ethics Committee of Zagreb UHC (class 8.1-22/4-2; no. 02/21 AG).

Anesthetic procedure

Out of a total of 90 patients, 60 (66.7%) patients underwent surgery under general anesthesia, and 30 (33.3%) patients had surgery under regional anesthesia. General endotracheal anesthesia with the use of the muscle relaxant rocuronium was induced in 32 (53.3%) patients, whereas general anesthesia with the use of a laryngeal mask and without the use of a muscle relaxant was induced in 28 (46.7%) patients. Out of 30 patients under regional anesthesia, 27 (90%) patients underwent the procedure under spinal anesthesia, and 3 (10%) patients had the procedure under axillary block. For induction of general anesthesia, propofol was used in 56 (93.3%), etomidate in three (5%) patients, and thiopental in one (1.7%) patient, and sevoflurane was used to maintain general anesthesia. Sufentanil was used as an analgesic in all patients under general anesthesia, and remifentanil was used in 7 (11.7%) patients. Patients under regional anesthesia received the local anesthetic levobupivacaine. Twenty-two (36.7%) patients received midazolam before introduction to general anesthesia, while the remaining 38 (63.3%) patients under general anesthesia did not. All patients under regional anesthesia also received midazolam.

Testing methods

The Montreal cognitive assessment scale (MoCA) was used in the research. MoCA is a rapid screening instrument for patients with mild cognitive impairment. MoCA examines several different cognitive domains, as follows: executive functions, naming, attention, language, abstract thinking, and orientation[16]. The test was chosen because of its specificity (87%) and sensitivity (90%) in detecting mild impairment of cognitive functions and time required to perform the test[17]. Before testing, the examiners underwent official training for conducting the MoCA test and received a certificate and permission to use the test. Before the test, the examiners informed each patient about the objectives and course of the research and each patient signed an informed consent form. The patients solved the test the day before the operation and the day after the operation. Both tests were carried out between 4:00 p.m. and 6:00 p.m. in a quiet and well-lit room, and only the examiner and the patient were present during the test, in order to minimize distraction of the examinees. In addition to test results, anesthesia related data (type of anesthesia, number of previous anesthesia procedures, ASA category, method of airway maintenance, administration of midazolam, duration of anesthesia), demographic data (patient age and education), data on comorbidities, and previous COVID-19 infection were collected. As a criterion for defining development of POCD, the 2 scores rule was applied, i.e., a drop in the test result after surgery by ≥2 points compared to the preoperative result. We chose this criterion because it shows the best combination of sensitivity (82.6%, 95% confidence interval (CI) 67.1%-98.1%) and specificity (82.2%, 95% CI 76.2%-88.3%) in determining POCD using the MoCA test[18]. Two versions of MoCA test were used. One version was used on preoperative testing and the other on postoperative testing in order to avoid the effect of exercise[19]. For each individual patient who developed POCD, information on all affected cognitive domains was collected.

Statistical analysis

The data collected were entered and prepared for analysis in the database for which the Microsoft Excel program was used. The SPSS program version 26.0© 2019 IBM SPSS Statistics for Windows (IBM Corp., Armonk, NY, USA) was used on statistical analysis. The normality of distribution was determined using a histogram, and the Kolmogorov-Smirnov and Shapiro-Wilk tests. Statistical data processing consisted of descriptive and inferential statistics. In case of regular distribution of numerical data (difference of results), arithmetic mean was used as a measure of central tendency and standard deviation (SD) as a measure of dispersion. In case of irregular distribution of numerical data (preoperative result, postoperative result, patient age, Charlson comorbidity index (CCI),

duration of anesthesia, number of previous anesthesia procedures), median was used as a measure of central tendency, and lowest and highest values as a measure of dispersion. Frequency and percentages were used to display categorical and ordinal data (development of POCD, patient education, recovery from COVID-19 infection, ASA, type of anesthesia, method of airway maintenance, administration of midazolam). When determining the correlation between numerical variables the distribution of which deviated from normal, Spearman's correlation was used. Pearson's correlation was used to determine the correlation between numerical variables with normal distribution. The χ^2-test was used to assess statistical significance of differences between groups according to categorical variables. In case of numerical variables the distribution of which deviated from normal, the Mann-Whitney test as a nonparametric test was used to compare two independent groups. The level of statistical significance was set at $p<0.05$.

Results

Descriptive statistical analysis of data

The median score of the preoperative MoCA test was 26 points. The lowest achieved test result was 15 points, and the highest was 30 points. The median score of the MoCA test after the procedure was 25 points, with a range of 12 to 30 points. The mean value of the score difference was -1.16 (SD=2.41). The preoperative MoCA score statistically significantly correlated with the postoperative MoCA score ($r=0.75$, $p<0.001$).

According to the 2 scores rule, on the day after surgery, POCD was present in 38 (42.2%) of 90 patients.

Demographic and anesthesia related data, as well as data on previous COVID-19 infection and comorbidities in all patients, patients who did not develop POCD, and patients who did develop POCD were described by descriptive statistics and are shown in Table 1.

Analysis of affected cognitive domains

Data on the involvement of cognitive domains were collected in patients who developed POCD (Fig. 1). Statistical analysis of differences in the involvement of each individual cognitive domain between the group of patients who were under general or regional anesthesia using the χ^2-test did not reveal a statistically significant difference (Executive functions ($p=0.451$), Naming ($p=0.888$), Attention ($p=0.989$), Language ($p=0.904$), Abstract thinking ($p=0.989$), Delayed recall ($p=0.606$), and Orientation ($p=0.947$)). Delayed recall was the most frequently affected cognitive domain in both general (n=21, 24.42%) and regional anesthesia (n=6, 30%) patients. On the other hand, the least affected cognitive domain was orientation; in was recorded in 4 (4.65%) patients under general anesthesia and one (5%) patient under regional anesthesia.

Inferential statistical analysis of data

Comparison of clinical groups under general and regional anesthesia according to the development of POCD using the χ^2-test yielded a p-value of 0.035, and it was concluded that there was a statistically significant difference in the development of POCD between the mentioned groups.

The group of patients who developed POCD and the group of patients who did not develop POCD were compared according to CCI, and a statistically significant difference in the distribution of CCI between the two groups was determined ($p=0.014$). Also, there was a statistically significant difference ($p=0.032$) in the incidence of POCD between the group of patients who had a COVID-19 infection (n=52, 57.8%) and those who had not (n=38, 42.2%).

The level of education was compared according to the development of POCD and yielded a statistically significant difference ($p=0.023$).

Statistical testing did not reveal a significant difference in the age distribution between the groups of patients who developed and did not develop POCD. However, the results showed a statistically significant negative correlation between patient age and preoperative result ($r=-0.438$, $p<0.001$), and between patient age and postoperative result ($r=-0.446$, $p<0.001$), whereas there was no statistically significant correlation between patient age and difference in results ($r=-0.077$, $p=0.472$).

Comparison of the group that developed POCD and the group that did not develop POCD according to other factors (number of previous anesthesia procedures ($p=0.336$), ASA ($p=0.415$), method of airway

Table 1. Comparison of data between groups of patients who developed and those who did not develop POCD

		All patients	Patients who did not develop POCD	Patients who developed POCD
		Median (maximum, minimum)		
Age (yrs)		60 (20-79)	59 (20-79)	60 (21-78)
Anesthesia duration (min)		90 (40-270)	90 (40-270)	90 (40-270)
CCI (points)		2.5 (0.9)	2.00 (0.9)	3 (0.9)
Mean number of previous anesthesia episodes (SD)		2 (0.11)	2 (0.11)	2 (0.10)
		Number (%)		
Education:	≤8 yrs	9 (10.0%)	4 (7.7%)	5 (13.2%)
	8-12 yrs	50 (55.56%)	24 (46.2%)	26 (68.4%)
	≥12 yrs	31 (34.4%)	24 (46.2%)	7 (18.4%)
COVID-19:	No	52 (57.8%)	35 (67.3%)	17 (44.7%)
	Yes	38 (42.2%)	17 (32.7%)	21 (55.3%)
Type of anesthesia:	General	60 (66.7%)	30 (57.7%)	30 (78.9%)
	Regional	30 (33.3%)	22 (42.3%)	8 (21.1%)
ASA:	1	6 (6.7%)	5 (9.6%)	1 (2.6%)
	2	65 (72.2%)	36 (69.2%)	29 (76.3%)
	3	19 (21.1%)	11 (21.1%)	8 (21.1%)
	Airway I-gel	28 (46.7%)	15 (50%)	13 (43.3%)
	ETA	32 (53.3%)	15 (50%)	17 (56.7%)
Midazolam:	Yes	52 (63.3%)	32 (61.5%)	20 (52.6%)
	No	38 (36.7%)	20 (38.5%)	18 (47.4%)

ASA = American Society of Anesthesiologists classification of the patient's physical status; POCD = postoperative cognitive dysfunction; CCI = Charlson comorbidity index; SD = standard deviation; ETA = endotracheal anesthesia

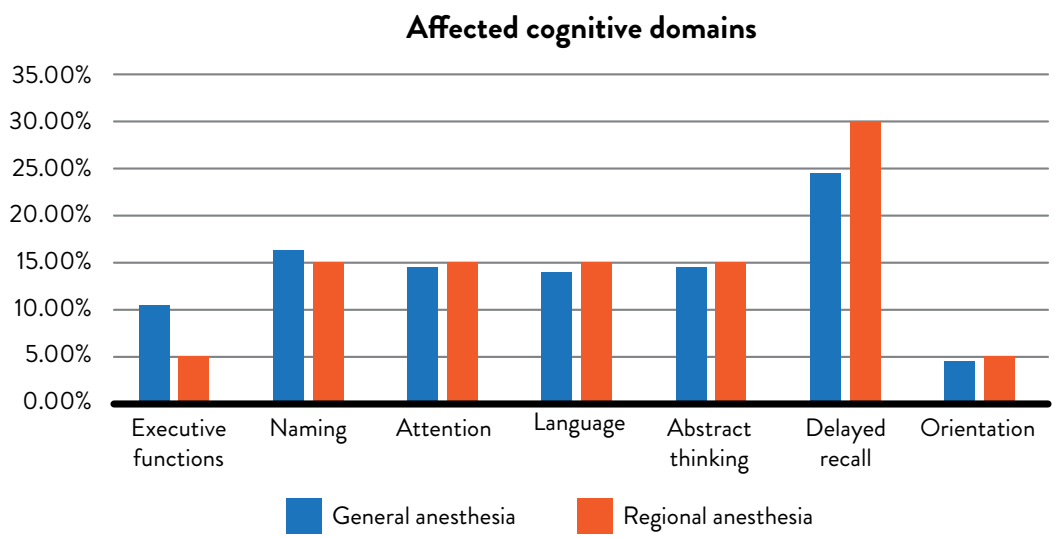

Fig. 1. Affected cognitive domains in patients with postoperative cognitive dysfunction after general and regional anesthesia.

maintenance (p=0.605), administration of midazolam (p=0.398), and duration of anesthesia (p=0.415)) yielded no statistically significant result.

Discussion

The research results indicated that a significant part of patients after surgery under general or regional anesthesia developed POCD. The incidence of POCD varies significantly among individual studies[2,20,21]. This difference can be attributed to different definitions of POCD, the population observed, and different time frames of the test. The first large prospective study by ISPOCD in 1998 described the occurrence of POCD in 25.8% at one week and 9.9% at three months after surgery in patients aged over 60[2]. Monk *et al*. describe the incidence of POCD in younger, middle-aged and older patients. At discharge, the incidence of POCD was 41.1%, while three months after surgery, it was 12.7% among those aged over 60[20]. In this study, the incidence of POCD defined according to the 2 scores rule was 42.2%. Out of 30 patients undergoing surgery under regional anesthesia, eight (26.67%) patients developed POCD *versus* 30 (50%) of 60 patients that underwent surgery under general anesthesia.

Our research showed a difference between the effect of general and regional anesthesia on the development of POCD. Also, we compared the group of patients under general anesthesia with the group of patients under regional anesthesia according to the involvement of cognitive domains. Since the subject who developed POCD usually has multiple cognitive domains affected, all affected domains were recorded in each such subject. Statistical analysis showed no difference between the affected domains of cognition in the two groups of patients. This result is in contrast to the results of other studies that report on a slight difference in the incidence of POCD between the types of anesthesia applied but report significant differences between involvement of particular cognitive domains[15]. Differences in the results can be attributed to other risk factors and mechanisms that should be further investigated. In our study, delayed recall was the most frequently affected domain of cognitive function. It was tested with a series of five words that the examiners read to the patient and which the patient then repeats in the initial part of the test. Toward the end of the test, the examinee is asked to recall a series of words, and points are awarded based on recall without the examiner's help. The least affected domain in the MoCA test was orientation. The patients had to show the correct spatial orientation according to the city and location where they were located, as well as the temporal one by specifying the date, month and year.

Of the possible risk factors in this research, the following were addressed: patient age, patient education, CCI, number of previous anesthesia procedures, duration and type of anesthesia, ASA, way of maintaining the airway, administration of midazolam, and recovery from the COVID-19 infection. The research showed that older age was not related to difference between the two results, or to the development of POCD but led to worse result on the MoCA test regardless of anesthesia. The connection between the level of education and development of POCD was confirmed, which was also shown in other studies[2,21]. Education as one of the aspects of life experience plays a considerable role in the formation and development of an individual's cognition. Therefore, the years of schooling and the level of education have a positive and protective effect on cognitive functions of an individual. This can be explained by the concept of cognitive reserve, a kind of resistance of the brain to changes, and a higher threshold for pathological changes, which results in the preservation of cognitive functions throughout life and a lower risk of developing dementia in old age[22,23]. The research also showed significant difference between patients operated under general endotracheal anesthesia and those under regional anesthesia. The reason is that the application of regional anesthesia reduces inflammation and the body's stress response that comes with surgery and reduces the need of sedatives and opioids that can interfere with cognitive functions of the individual[15].

We also recorded significant difference in the development of POCD between patients who recovered from the COVID-19 infection and those who did not. By reviewing the literature, we did not find a scientific paper that investigated and proved the effect of the COVID-19 infection as a risk factor for the development of POCD. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can be considered a potential risk factor for the development of

neurological complications, including POCD, due to its neuroinvasiveness and synergistic effect with the body's inflammatory response to injury[24]. However, it should be taken into account that in a certain number of patients, the clinical course of the infection may be asymptomatic, which does not necessarily mean that they have not recovered from the COVID-19 infection.

Comorbidities as a risk factor for the development of POCD were evaluated using the CCI. This includes age and 16 comorbidities with their severity, which, when summed, predict the patient's 10-year survival. In our study, the group of patients who developed POCD had a higher CCI, i.e., more comorbidities.

Other risk factors studied in this research did not show an effect on the development of POCD.

The strength of this research was the use of the MoCA test which assesses a larger number of cognitive functions and achieves comprehensiveness of cognitive domains. Also, since postoperative testing was performed 24 to 30 hours after surgery, the research provided an insight into the immediate effect of surgery and anesthesia on cognitive functions. On the other hand, this research had several limitations. Not all types of surgical operations were covered. In addition, the patients were not monitored for a longer period, which would allow determination of the proportion of patients who still have a decline in cognitive functions at a certain point after the operation. In the continuation of this research, it is planned to include patients scheduled for other surgical procedures and to analyze in more detail the possible effect of anesthetic drugs.

Conclusion

In the study, POCD was present in part of the patients and risk factors associated with POCD were identified. On the day after surgery, POCD was present in 38 (42.2%) patients, whereby the 2 scores rule was used as the criterion for determining the presence of POCD. The analysis of the affected cognitive domains did not reveal any statistically significant differences for individual cognitive domains between patients operated on in general and those operated on in regional anesthesia. In both groups of patients, the most frequently affected domain was delayed recall while the least affected cognitive domain was orientation. A lower level of education, greater number of comorbidities, surgery under general anesthesia, and recovery from the COVID-19 infection that had not been previously investigated as a possible risk factor, were identified as risk factors. The aforementioned factors can be recognized before the procedure under anesthesia, thus offering the possibility of adjusting anesthesia and postoperative care in such patients.

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Sažetak

UČINAK ANESTEZIJE NA POSLIJEOPERACIJSKU KOGNITIVNU DISFUNKCIJU

M. Bilić, M. Lukšić, M. Miklić Bublić, Z. Orešković, D. Mijatović i *V. Vrbanović Mijatović*

Poslijeoperacijska kognitivna disfunkcija (POCD) novonastalo je oštećenje kognitivnih funkcija nakon kirurškog zahvata. Cilj istraživanja bio je utvrditi incidenciju POCD nakon anestezije i moguće čimbenike rizika. Prospektivno istraživanje provedeno je na 90 bolesnika naručenih na elektivne operacijske zahvate u općoj (60 bolesnika) ili regionalnoj anesteziji (30 bolesnika). Svaki je bolesnik dan prije i dan nakon operacije ispunio test *Montreal cognitive assessment* (MoCA). Prikupljeni su i podaci o supostojećim bolestima, prethodnoj infekciji COVID-19, demografski i anesteziološki podaci. Dan nakon operacije POCD definiran prema *2 scores rule* bio je prisutan u 38 (42,2%) bolesnika. Kao rizični čimbenici identificirani su niža razina obrazovanja (p=0,023), prethodna infekcija COVID-19 (p=0,032), viši *Charlson comorbidity index* (CCI) (p=0,014) i opća anestezija (p=0,035), a za dob je dokazana statistički značajna negativna korelacija s prijeoperacijskim (p=0,001) i poslijeoperacijskim rezultatom (p=0,001). Rezultati pokazuju da značajan dio bolesnika nakon opće ili regionalne anestezije razvije POCD u ovisnosti o razini obrazovanja bolesnika, CCI, preboljenju infekcije COVID-19 i vrsti anestezije. Također se pokazalo da starija dob korelira s lošijim rezultatom testa MoCa neovisno o anesteziji. Navedeni se čimbenici mogu identificirati prije zahvata u anesteziji, što nudi mogućnost prilagodbe anestezije i poslijeoperacijske njege kod bolesnika s rizikom od razvoja POCD.

Ključne riječi: *Poslijeoperacijska kognitivna disfunkcija; Anestezija, opća, regionalna; Test MoCA*