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Postoperative Cognitive Dysfunction After Major Orthopedic Surgery: Regional vs General Anesthesia

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Abstract **Background:** Postoperative cognitive dysfunction (POCD) is associated with poor postoperative outcomes and these patients are at greater mortality risk compared to patients without neurocognitive decline. Numerous risk factors have been implicated in the development of POCD such as older age, lower level of education, preoperative cognitive impairment or delirium, type and invasiveness of surgery, depth of anesthesia, perioperative pain etc. Our objective was to compare the incidence of POCD after major orthopedic surgery receiving either general or regional anesthesia alone. **Methods:** A prospective, single centre, observational study included 112 patients undergoing major orthopedic surgery. Patients were allocated to either regional or general anesthesia groups. The perioperative neuropsychological testing included preoperative and two postoperative (7 days and 3 months after surgery) testing. **Results:** The incidence of POCD at 1 week after general and regional anesthesia was 9/62 (14.5%) vs 8/50 (16%), P=0.83. In 5 patients from each of the groups (8% vs 5%) delayed POCD after 3 months were diagnosed, P=0.52. Pain scores and postoperative complications did not differ significantly between groups. **Conclusion:** No significant difference was found in the incidence of cognitive dysfunction 3 months after either general or regional anesthesia.

Keywords Major orthopedic surgery, Neuropsychological testing, Perioperative neurocognitive disorders, Postoperative cognitive dysfunction

1. Introduction

Postoperative cognitive dysfunction (POCD), a condition that has been poorly recognized and defined for decades, is one of the most common postoperative complications, especially for the elderly [1].

POCD is associated with poor postoperative outcomes. Patients classified as having POCD at the time of hospital discharge after noncardiac surgery are at greater risk of dying within 3 months than those without it, and if they have POCD at both hospital discharge and 3 months postoperatively, are nearly 5 times more likely to die 1 year later [2,3]. According to different authors, the incidence of POCD varies from 10% to 45% [4].

Numerous risk factors have been implicated in the development of POCD such as older age, lower level of education, frailty, cerebrovascular disease, type and invasiveness of surgery, repeat procedures, depth of anesthesia, perioperative pain etc. Advanced age is the best-established risk factor [5-7]. Low educational achievement is associated with greater risk and higher educational achievement is protective and this is a component of “cognitive reserve” [8].

General anesthesia intuitively seems to produce long-lasting changes in cognition. Numerous preclinical data support this statement [9-12]. However, the clinical data are much less clear and a few studies which directly compared general anesthesia to regional anesthesia have found little or no difference in POCD [13,14].

Newly proposed consensus recommendations suggest the term perioperative neurocognitive disorders (PND) which is any new cognitive dysfunction identified in the postoperative period. This includes delayed neurocognitive recovery (dNCR) when the decline occurs acutely postoperatively (including delirium) but persists for up to 30 days after surgery and neurocognitive disorder (NCD) when it lasts up to 12 months [15,16]. Taking into account the novelty of this nomenclature, in this paper we used the term POCD for clarity. The objective of this study was to compare the incidence of POCD after a major orthopedic surgery receiving either general or regional anesthesia alone.

2. Methods

Clinical material

A prospective, single centre, observational study was conducted at the Republican Research Centre of Emergency Medicine (RRCEM), Tashkent, Uzbekistan. The study was

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approved by the Institutional Review Board. 123 patients aged 30 to 80 undergoing unilateral major orthopedic surgery were enrolled prospectively from November 2018 to June 2019. They were allocated either to regional anesthesia (spinal, epidural or peripheral nerve block) or general anesthesia group.

Exclusion criteria were those who could not read or write; color-blind people; patients with hearing problems, those whose native language was not Uzbek nor Russian; patients with combined traumatic brain injury and trauma of the dominant upper limb; those with a history of psychiatric or neurological disorders (history of stroke, transient ischemic attacks, seizures, generalized anxiety, alcoholism or drug addiction); American Society of Anesthesiologists (ASA) physical status score > III; moderate and severe anemia (hemoglobin less than 90 g/l); severe intraoperative bleeding; those who had already undergone neurosurgical or cardiac procedures; those who refused to participate in the study. To identify and exclude patients with asymptomatic preoperative cognitive impairment The Short Test of Mental Status (STMS) was used as a screening method [17]. The maximum score of the method is 38 and those who did not obtain a minimum standard score of 29 points were excluded.

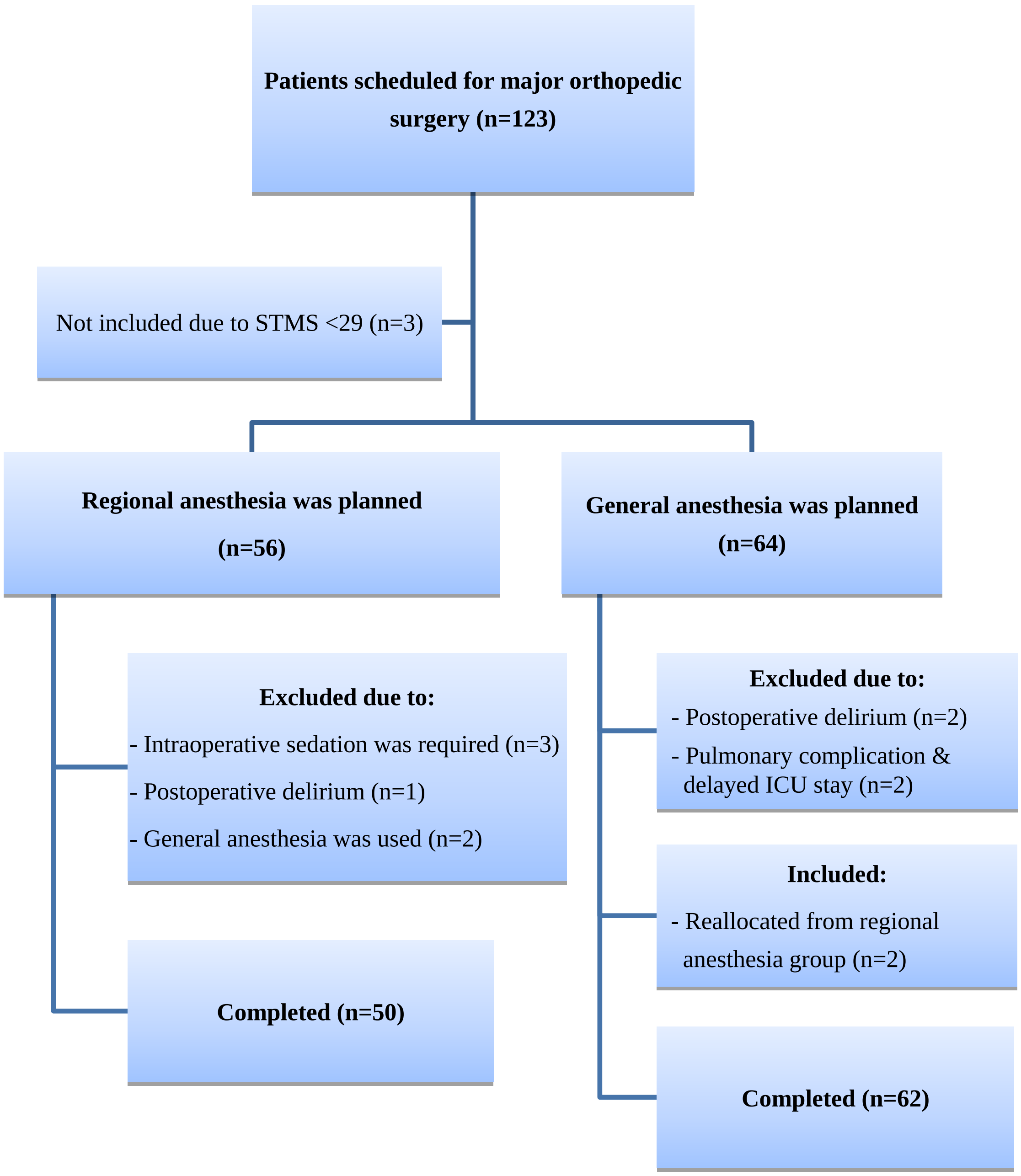

Figure 1. Flow chart of patient enrollment

Anesthetic management

Prior to surgery, all patients were clinically examined, and routine laboratory tests (blood counts, urea, creatinine, glucose, sodium, potassium, prothrombin index) were completed. After admission to the operating room, patients were monitored using pulse oximetry, three-lead electrocardiogram, and capnometry *(Triton Electronics, Russian Federation)*. Peripheral venous puncture was obtained in the upper limb with an 18 or 20G catheter. Ceftriaxone 1 g was given to all patients 15-30 min before the incision, and two other doses were given postoperatively.

Regional anesthesia group included patients operated under spinal anesthesia, epidural anesthesia or peripheral nerve block alone (without sedation).

Spinal anesthesia was induced via subarachnoid injection of 12.5–15 mg 0.5% heavy bupivacaine (*Yuria-Pharm, Ukraine*). 25 G or 26 G Quincke spinal needle was used and inserted midline at either L2/L3 or L3/L4 interspace via lateral decubitus or sitting position.

For epidural anesthesia 18 G Tuohy needle w as inserted to epidural space via loss of resistance technique using air, in the lateral decubitus or sitting position and using midline approach and a 20 G epidural catheter was inserted up to about 4 cm cephalad. The catheter tip position inside the epidural space was confirmed with the test dose (0.5% bupivacaine, 3 mL). Postoperative epidural analgesia was obtained by infusing 0.25% bupivacaine at 5 ml/hour basal flow using an elastomer pump.

For humerus fixation in patients of regional anesthesia group interscalene or supraclavicular block was used depending on fracture level. 20-25 ml 0.5% bupivacaine was administered under ultrasound guidance. These methods of regional analgesia were also used postoperatively in patients receiving general anesthesia.

General anesthesia was provided using combined technique. After preoxygenation with 100% oxygen in spontaneous ventilation, an intravenous administration of 3 µg/kg fentanyl (*LLC Pharmaceutical company "Zdorov'e narodu", Kharkiv, Ukraine*) followed by 2-3 mg/kg propofol (*Claris Lifescience, India*). Laryngeal mask insertion (#4 or 5) or tracheal intubation was performed to maintain mechanical ventilation. In cases of tracheal intubation muscle relaxation was obtained with 1 - 1.5 mg/kg succinylcholine *(Ditilin, "Darnica", Ukraine)*, followed by tracheal intubation. Mechanical ventilation was performed in a circular valve system with carbon dioxide absorber as part of an anesthetic machine *(Chirana Venar, Slovakia)*. It was adjusted to a tidal volume of 6-8ml/kg, FiO_2 1.0, I:E ratio of 1:1, positive end expiratory pressure of 5 mbar, mean respiratory rate of 12 breaths/min, adjusted to maintain end-tidal carbon dioxide between 30 and 40 mmHg. Anesthesia was maintained with isoflurane ("*Isoflurane USP" Piramal Enterprises Limited, India*) adjusted between 0.5 and 1.5 minimum alveolar concentration (MAC) and intravenous fentanyl 3-6 µg/kg/h; neuromuscular block was maintained using intravenous pipecuronium bromide *(Arduan, "Gedeon Richter", Hungary*) 15-20 µg/kg/h.

Postoperative analgesia was obtained using basic multimodal analgesia including nonopioid analgesics. Patients who undergone general anesthesia or spinal anesthesia peripheral nerve blocks of ipsilateral extremity (femoral block, sciatic block, interscalene block, supraclavicular block) were additionally obtained for multimodal postoperative analgesia. An 8 cm 20 G needle was used for it and 20 ml of 0.5% bupivacaine was administered under ultrasound guidance.

In all patients, any decrease in intraoperative systolic blood pressure greater than 20% from the preoperative values was corrected by fluid administration and incremental intravenous injections of vasoconstrictors (phenylephrine, norepinephrine).

The effectiveness of postoperative analgesia was assessed by the Numerical Rating Scale (NRS), from 0 (no pain) to 10 (unbearable pain), every 4 hours during first 48 hours and rescue analgesia with intravenous trimeperidine (*Promedol, Russian Federation*) was administered when required.

Neurocognitive tests and criteria for diagnosis of POCD

The perioperative neurocognitive assessment protocol in 2 languages (Uzbek and Russian) was used to evaluate general cognitive function and identify patients with POCD. Patients were assessed before surgery and 7 days after surgery by applying a validated cognitive test battery: Auditory Verbal Learning Test (AVLT), Trail Making Test (TMT), Stroop Colour Word Test (SCWT), Digit Span Test (DST) and Digit-Letter Substitution Test (DLST). In summary, the tests are as follows:

1-AVLT. The test assesses immediate memory span, learning, susceptibility to interference and recognition memory. It consists of the same 15 nouns read aloud, with a 1 s interval between words, for three consecutive trials (AVLT-1, AVLT-2 and AVLT-3); each trial is followed by a free recall test. A delayed recall of these 15 words (AVLT-4) was performed 20 min after the third trial. Instructions were repeated before each trial to minimize forgetting. We evaluated the number of words recalled for each presentation, adding up the words recalled total result was registered [18].

2-TMT. It evaluates the executive processes i.e. the frontal lobe function. The test consists of three parts (TMT-A, TMT-B and TMT-C). In TMT-A and TMT-B, the study participant must draw lines connecting numbered circles in order and reverse-order. In TMT-C, the study participant must draw lines connecting circles alternately with letters and numbers in an ordered sequence. Time spent in TMT-C is assessed [19].

3-SCWT. The test assesses selective attention, inhibitory ability and mental flexibility. It consists of three main components (SCWT-1, SCWT-2 and SCWT-3) using four different colours. For SCWT-1 the patient is shown a colour name word (written in black) and must say the colour name word. For SCWT-2 the patient is shown a coloured rectangle and the colour name word is also printed in black within the rectangle. The patient must say the colour that fills the rectangle. For SCWT-3 the patient is shown a colour name word printed in a colour different from the colour name word and they must tell the tester the colour of the printing. The name words for the colours all followed the same order as for SCWT-1. In this test, we evaluate the time spent in SCWT-3 [20].

4-DST. The test assesses immediate memory. The subject is asked to listen of random numbers at a rate of one per second. In the digit span forwards (DSF), the subject repeats the numbers in a forward order, while in the digit span backwards (DSB) in reverse order. Starting with a two-number sequence, each correctly repeated series is followed by a sequence with one additional digit. For each sequence, the subject was given a second chance with another set of random numbers if he/she had failed in the first attempt. If the subject also failed in the second attempt, the test was interrupted and scored according to the longest series that was achieved. A maximum of nine digits are presented in the DSF, and eight digits in the DSB. DSF and DSB scores are summarized to get a total score and no time limitations were imposed [21].

5-DLST. The test measures short-term memory, visual-spatial skills and attention. The test is a task performed in 2 minutes and the study participant must write the letter referred to each number (from 1 to 9). A target of symbols and their numbers are displayed (80 symbols are provided). Time spent to fill all spaces is recorded [22].

For the diagnosis of POCD, a composite cognitive index was established and defined by the occurrence of cognitive impairment in at least two of five possible cognitive deficits: total AVLT score, SCWT-3, TMT-C, DST and DLST. The definition of POCD considered a reduction greater than or equal to 20% in two or more tests results compared with the preoperative assessment [22].

The primary outcomes of the study were the incidence of POCD in all patients and in the regional anesthesia and general anesthesia groups at 7 days and 3 months (the delayed cognitive dysfunction) after the surgery according to the set definition. The secondary outcomes were pain score profile and analgesic consumption.

Table 1. Patients' demographic and clinical characteristics

		Anesthesia type		
	All patients (n=112)	**Regional (n=50)**	**General (n=62)**	**P**
Gender, n (%)				
Male	60 (53)	27 (54)	33 (53)	>0.99*
Female	52 (47)	23 (46)	29 (47)	
ASA, n (%)				
II	78 (70)	31 (62)	47 (75)	0.14*
III	34 (30)	19 (38)	15 (25)	
Education, n (%)				
Less than 10 years	11 (10)	6 (12)	5 (8)	0.35*
Full School	73 (65)	29 (58)	44 (71)	
Higher education	28 (25)	15 (30)	13 (21)	
Age (years), median (IQR)	55 (39-63)	57 (46-64)	51 (39-58)	0.073**
Weight (kg), median (IQR)	77 (70-89)	74 (64-85)	76 (71-90)	0.152**
Height (cm), median (IQR)	170 (168-172)	170 (167-174)	170 (167-172)	0.704**
BMI (kg/m2), median (IQR)	26.3 (24.7-29.9)	26.7 (25.0-28.9)	26.0 (24.5-29.4)	0.66**
STMS results, median (IQR)	34 (31-36)	34 (31-35)	34 (31-36)	0.7**
Smoking, n (%)				
Yes	38 (34)	20 (40)	18 (29)	0.236*
No	74 (66)	30 (60)	44 (71)	
Surgery type, n (%)				
Femur Fracture Fixation	34 (30)	14 (28)	20 (32)	0.95*
Tibia Fracture Fixation	38 (34)	14 (28)	24 (39)	
Total Hip Replacement	13 (12)	5 (10)	8 (13)	
Shoulder Fracture Fixation	27 (24)	16 (32)	21 (34)	
Duration of surgery (min), median (IQR)	75 (62-108)	75 (60-120)	80 (62-105)	0.904**
Blood loss (ml), median (IQR)	250 (200-300)	250 (200-300)	250 (200-300)	0.596**

* *Fisher's exact test*
** *Mann Whitney U test*

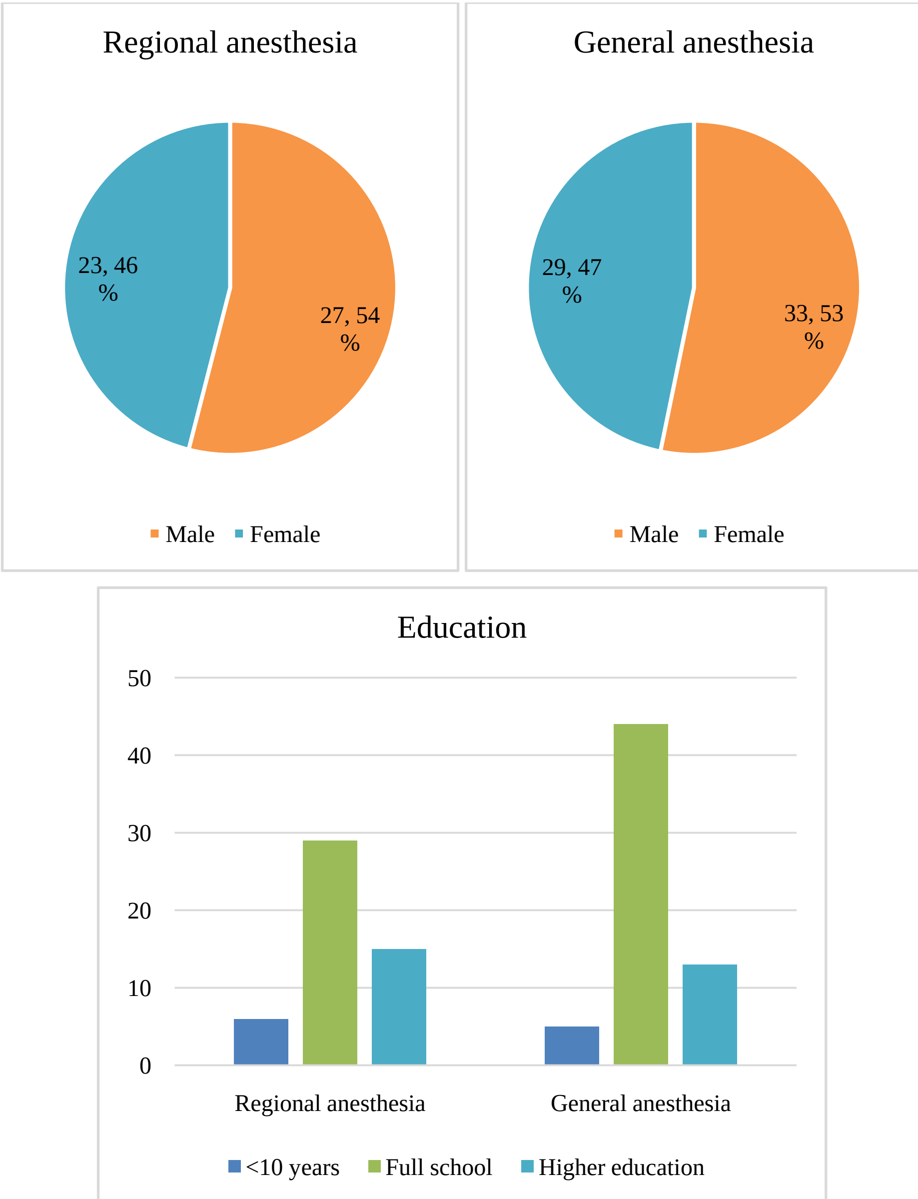

Figure 2

Statistical analysis

Category data are represented by absolute and relative frequencies. The numerical data are described by the median and limits of the interquartile range (IQR) or mean and standard deviation (SD). Variations of category variables were tested by Fisher's exact test. Normality of distribution of observed numeric variables was tested by the Shapiro-Wilk test. Differences between the normal distribution of numeric variables between the two independent groups were tested by the Mann-Whitney Test or t-test. To determine the difference between two dependent samples, Friedman test was used. $P<0.05$ was considered statistically significant. Statistical analysis was performed using Microsoft Excel 2010 (Microsoft, USA) and MedCalc Statistical Software V.14.12.0 (MedCalc, http://www.medcalc.org).

3. Results

Patient characteristics

After exclusion of 11 patients, the remaining 112 patients were eligible to participate in the study. Based on the type of anesthesia, patients were allocated into two groups: regional (n=50) and general (n=62) anesthesia groups. Regional anesthesia was unsuccessful in 2 patients allocated to regional anesthesia in whom general anesthesia was therefore necessary. Clinical, demographic and procedure data of patients are summarized in Table 1.

In the regional anesthesia group 25 patients (50%) received spinal anesthesia, 8 patients (16%) epidural anesthesia, 17 patients (34%) brachial plexus blocks.

Cognitive function assessment

The incidence of POCD at 1 week after general and regional anesthesia was 9/62 (14.5%) vs 8/50 (16%), P=0.83. 3 patients with early POCD (2 vs 1 patient in general and regional anesthesia groups) were 40 years old and younger. Reevaluation of patients who developed early POCD after 3 months revealed 5 patients (8% vs 5%) with remaining (delayed) POCD in each group, P=0.52.

Patients who developed POCD 7 days after surgery of regional anesthesia group tended to demonstrate decline in Trail Making Test (executive function) and Digit Span Test (immediate memory) whereas among POCD patients of general anesthesia group most vulnerable tests to decline was Auditory Verbal Learning Test (memory and learning) (Table 2).

Postoperative pain profiles and opioid consumption

NRS pain scores did not differ significantly between groups (p>0.05) during 2 postoperative days (Table 3). Opioid (trimeperidine) consumption was significantly higher in general anesthesia group Table 4.

Postoperative complications

Postoperative mortality for 3 months after surgery was 0 in both groups. The other postoperative complications were not significantly different between the groups (Table 5).

Table 2. Neuropsychological testing results of patients with POCD before and 7 days after surgery

Neuro-psychological test	Regional anesthesia (n=8)		p*	General anesthesia (n=9)		p*
	Preoperative baseline	7 days after surgery		Preoperative baseline	7 days after surgery	
AVLT total	32 (26-43)	33 (29-34)	0.48	28 (27-31)	23 (22-29)	0.02
TMT-C (sec.)	141 (94-144)	157 (111-188)	0.034	180 (173-188)	123 (170-227)	0.74
SCWT-C (sec.)	117 (84-132)	114 (97-148)	0.157	135 (117-144)	130 (123-152)	0.738
DST total	13 (11-14)	10 (8-11)	0.005	9 (8-11)	8 (8-9)	0.32
DLST (sec.)	184 (140-194)	173 (163-214)	0.157	191 (166-281)	228 (178-240)	0.317

** Friedman test*

Table 3. Postoperative Numeric Rating Scale (NRS) score for pain intensity

	Regional anesthesia (n=50)	General anesthesia (n=62)	P*
Postoperative day 1	1.9 (1.49)	2.0 (1.5)	0.72
Postoperative day 2	2.0 (1.54)	2.2 (1.42)	0.48

*Data are shown as Mean, SD. * t-test*

Table 4. Average opioid consumption for two postoperative days, mg

	Regional anesthesia (n=50)	General anesthesia (n=62)	P*
Postoperative day 1	21 (15.1)	32 (17.3)	0.0005
Postoperative day 2	13 (9.3)	20 (13.2)	0.0016

*Data are shown as Mean (SD). *t-test.*

Table 5. Postoperative complications

Complication	Regional anesthesia (n=50)	General anesthesia (n=62)
Respiratory	0	1
Cardiac	1	2
Delirium	1	2
LAST	0	0
Severe intraoperative bleeding	0	0
Second operation	0	0
Wound Infection	1	1
ICU stay for >24	0	1
Death	0	0

P>0.05 between groups, LAST-local anesthetic systemic toxicity, ICU-Intensive Care Unit

4. Discussion

In our study postoperative cognitive dysfunction was detected in about 15% of patients, at 1 week with a cognitive recovery in some patients after 3 months with no significant difference between general and regional anesthesia. Major limitations of the study are the relatively small number of patients and that it is a single-centre study. Taking into account the estimated incidence of POCD, the statistical power of the study would be not as high as we wished to be. However, the study included young and middle-aged patients while most research on this issue is performed in elderly. Although most patients who developed POCD in this study are older people our results showed that young age is not an exception to be involved by postoperative cognitive decline.

The etiology of POCD is likely to be multifactorial. The effect of general anesthesia to cognitive function has been studied by many neuroscientists and clinicians in laboratory experiments as well as in clinical material. Xie et al. reported that exposure to isoflurane at 1.4% for 2 h increases caspase 3 and promotes the accumulation of amyloid beta which prevents new protein synthesis and one of the most evident mechanisms underlying Alzheimer disease activity in mice [23]. Saab et al. reported that an exposure to isoflurane of only 1 h impairs short-term memory [24]. Stratmann et al. reported decreased proliferation of progenitor cells in the hippocampal dentate gyrus in the P7 rat brain exposed to isoflurane, which lasted for at least 5 days, suggesting that this might be an important mechanism [25]. The neurotoxicity of anesthetic drugs has been studied by the same author in order to determine whether anesthesia in childhood might lead to cognitive impairment in later years. Studies have failed to yield any definitive evidence that anesthetic drugs are neurotoxic and findings are currently debated [26]. Earlier studies suggested an association between general anesthesia and a higher incidence of cognitive dysfunction relative to epidural anesthesia [27]. However, recent studies concluded that there was no relationship between anesthetic techniques and the magnitude or pattern of postoperative cognitive dysfunction [13,28]. Concerns that general anaesthesia would be susceptible to significantly contribute to POCD are not supported by the evidence from randomized controlled trials [29,30,31].

Our observation did not show the direct influence of anesthesia type on cognitive function and early cognitive impairment in the general and regional anesthesia groups could be the result of negative effects of the general anesthetic agents or surgical stress induced neuroinflammation.

In conclusion, we found no significant difference in the incidence of cognitive dysfunction 3 months after either general or regional anesthesia. Accordingly, there is no evidence to suggest any causative relationship between general anesthesia and long-term POCD and large, multicenter studies would help to clarify the role of etiologic factors in the development of perioperative neurocognitive disorders. When several options exist, we suggest that the choice of anesthesia type should be based on a discussion of patients' preference, possible postoperative complications, and the experience of the anesthesiologists and anesthesia team.

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Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board of Republican Research Centre of Emergency Medicine.

Competing interests: None.

Authors' Contributions

VSH conceived of study design and critically reviewed the manuscript. AVA made substantial contributions to data collection, analyzed and interpreted participant data. AAH performed neuropsychological testing and was the primary author of the manuscript. All authors read and approved the final manuscript.

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