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Original Article

Effects of Different Anesthetic Agents on Postoperative Cognitive Functions in Laparoscopic cholecystectomy

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ABSTRACT

Objective: In this study, it was aimed to compare the effects of inhalation anesthesia applied with sevoflurane or desflurane and intravenous anesthesia with propofol on early postoperative cognitive functions.

Methods: This study included patients with the ASA I-III classes, aged between 30-70 years and who underwent elective laparoscopic gallbladder surgery. The cognitive function levels of the patients were determined by performing the Mini-Cog test the day before the surgery. The patients were randomly divided into three groups as Group I (Desflurane), Group II (Sevoflurane), and Group III (Propofol). After induction of anesthesia with propofol and remifentanil rocuronium, endotracheal intubation was performed in all patients. In addition to the remifentanil infusion administered to all patients during the maintenance of anesthesia, anesthesia depth was provided with desflurane, sevoflurane inhalation or propofol infusion, with a bispectral index (BIS) of 40-60. The Modified Aldrete Recovery Scores (MARS) were measured and recorded at the postoperative 5th, 10th, 20th, and 30th minutes in all patients. Pain levels were evaluated with a visual analog scale (VAS) at the 10th, 20th, and 30th minutes postoperatively. The Mini-Cog test was repeated by the same physician at the postoperative 24th hour and compared with the preoperative values.

Results: There was no difference in demographic characteristics, duration of surgery and anesthesia, postoperative MARS and VAS values between the three groups (for all, $p>0.05$). While there was no significant difference between the preoperative and postoperative Mini-Cog test scores in the Desflurane and Propofol groups ($p>0.05$), it was observed that the Mini-Cog test in the sevoflurane group was significantly lower than in the Propofol group and Desflurane group ($p=0.002$ and $p=0.012$, respectively).

Conclusion: It was concluded that desflurane and propofol did not have negative effects on cognitive functions, while sevoflurane had a negative effect on postoperative cognitive functions.

INTRODUCTION

Postoperative cognitive dysfunction can lead to varying degrees of morbidity, from mild concentration disorders to memory loss. This results in a low quality of life after surgery. Furthermore, postoperative cognitive dysfunction was associated with mortality at 3 months and 1 year.[1-3]

Although the pathogenesis of postoperative cognitive dysfunction is not fully known, old age, pre-existing neurological diseases, cardiovascular disease, and alcohol use were considered as risk factors.[4] On the other hand, the effects of anesthetic drugs on postoperative cognitive functions and recovery have been the subject of research for many years.[5]

Sevoflurane and desflurane among inhalation anesthetics, and propofol among intravenous anesthetics, provide rapid recovery. The effects of these three popular anesthetic agents on postoperative cognitive functions may differ with their effects on recovery.[6]

Neuropsychological tests have been developed for rapid and practical evaluation of cognitive functions. In order to both standardize the examination and reduce time loss, pre- and postoperative cognitive functions can be evaluated with these tests, and how the postoperative cognitive functions are affected can be measured.

The aim of this study was to investigate the effects of different general anesthesia agents and techniques on postoperative cognitive functions in elective laparoscopic cholecystectomy operations.

MATERIALS AND METHODS

Before the beginning of the study, ethics approval was obtained from the local ethics committee (Dr. Lutfi Kirdar City Hospital ethics committee, approval date: 25.09.2019, number: 2019/514/162/8). This study was conducted in accordance with the principles of the Declaration of Helsinki. A total of 101 patients in ASA I-III physical condition, aged 30-70 years, literate, and without any neurological or psychological disease, and who were scheduled for elective laparoscopic cholecystectomy were included in the study. The patients were enrolled in the study after they were informed about the objectives of the study and their written consent was obtained.

Patients with neurological or psychiatric diseases affecting the central nervous system and cognitive functions, and patients using any medication affecting the central nervous system were excluded from the study.

All patients included in the study were evaluated in the general surgery service the day before the surgery. Age, gender, marital status, education level, and smoking status of the patients were recorded. The Mini-Cog test [7] was applied and scored. The patients were randomly divided into three groups as Group I (Desflurane), Group II (Sevoflurane), and Group III (Propofol).

Electrocardiography (ECG), pulse oximetry, non-invasive arterial blood pressure, and bispectral index (BIS) monitoring were performed in the operating room. Anesthesia was induced with propofol 2 mg/kg and remifentanil 1 μg/kg, muscle relaxation was achieved with rocuronium 0.6 mg/kg, and the patients were intubated endotracheally. The patients were ventilated perioperatively with a 50% air-oxygen mixture with EtCO2: 35-45 mmHg. In the maintenance of anesthesia with remifentanil (0.05-1 μg/kg/min) infusion, desflurane at a concentration of 4%-6%, or sevoflurane inhalation at a concentration of 1%-2.5%, or propofol (6-10 mg/kg/hour) infusion was administered with a BIS of 40-60 for depth of anesthesia.

At the end of the operation (while the gallbladder was taken out and the port entrances were closed), all anesthetics were discontinued, and the standard postoperative analgesia protocol (1 mg/kg tramadol iv bolus and 1 g paracetamol infusion) was applied. The recovery of the patients who were taken to the recovery room was evaluated at the 5th, 10th, 20th, and 30th minutes postoperatively using the Modified Aldrete Recovery Scoring (MARS). Pain assessments were made with a visual analog scale (VAS) at the 10th, 20th, and 30th minutes postoperatively. The Mini-Cog test was repeated by the same physician at the postoperative 24th hour and compared with the preoperative values.

To understand the difference between the preoperative Mini-Cog value (pre-Mini-Cog) and the postoperative Mini-Cog value (post-Mini-Cog), a new variable we named the "adaptation cog" was created. This variable was found by subtracting the preoperative Mini-Cog value from the postoperative Mini-Cog value. The value found was marked -1 if negative, 0 if equal, and +1 if positive. Based on this variable, the change in patients was divided into 3 groups as positive (+1), negative (-1), and ineffective (0).

Statistical Analysis

The data obtained in the study were statistically analyzed using IBM® SPSS® (The Statistical Package for the Social Sciences) Statistics version 25.0.

The variables were characterized using mean values. Percentage values were used for qualitative variables. Normal distributions were reported as mean±SD. The ANOVA Welch test was used to measure the difference between groups. Tamhane's T2 test was used for comparison between groups. Pearson Chi-square test was used to analyze the qualitative variables and show that the data were homogeneously distributed. $p<0.05$ values were considered statistically significant.

RESULTS

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Table 1. Distribution of demographic characteristics of the groups

		Desflurane	Sevoflurane	Propofol	Total	p value
Gender						
Male	(n, %)	14, 13.90	10, 9.90	10, 9.90	34, 33.70	0.315
Female	(n, %)	22, 21.80	23, 22.80	22, 21.80	67, 66.30	
Education						
Literate	(n, %)	1, 1.00	5, 5.00	0, 0.00	6, 5.90	0.139
Primary school	(n, %)	25, 24.80	18, 17.80	21, 20.80	64, 63.40	
High School	(n, %)	8, 7.90	6, 5.90	9, 8.90	23, 22.80	
University	(n, %)	2, 2.00	4, 4.00	2, 2.00	8, 7.90	
Marital Status						
Single	(n, %)	2, 2.00	2, 2.00	3, 3.00	7, 6.90	0.802
Married	(n, %)	34, 33.70	31, 30.70	29, 28.70	94, 93.10	
Smoking						
No	(n, %)	26, 25.70	19, 18.80	18, 17.80	63, 62.40	0.065
Yes	(n, %)	10, 9.90	9, 8.90	13, 12.90	32, 31.70	
Ex-Smoker	(n, %)	0, 0.00	5, 5.00	1, 1.00	6, 5.90	
ASA Class						
I	(n, %)	11, 10.90	7, 6.90	8, 7.90	26, 25.70	0.429
II	(n, %)	20, 19.80	15, 14.90	17, 16.80	52, 51.50	
III	(n, %)	5, 5.00	11, 10.90	7, 6.90	23, 22.80	

Abbreviations: N: number; ASA: American Society of Anesthesiologists.

At the end of the operation (while the gallbladder was taken out and the port entrances were closed), all anesthetics were discontinued, and the standard postoperative analgesia protocol (1 mg/kg tramadol iv bolus and 1 g paracetamol infusion) was applied. The recovery of the patients who were taken to the recovery room was evaluated at the 5th, 10th, 20th, and 30th minutes postoperatively using the Modified Aldrete Recovery Scoring (MARS). Pain assessments were made with a visual analog scale (VAS) at the 10th, 20th, and 30th minutes postoperatively. The Mini-Cog test was repeated by the same physician at the postoperative 24th hour and compared with the preoperative values.

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DISCUSSION

In this study, no significant difference was found between the preoperative and postoperative Mini-Cog test scores in the desflurane and propofol groups. However, the Mini-Cog test scores decreased significantly in the sevoflurane group.

Postoperative cognitive impairment is a condition characterized by impaired memory and concentration. The goal of evaluating postoperative cognitive functions is to measure the expected and unexpected long-term effects of anesthesia and surgery on cognitive functions. In order for these adverse effects to be as minimal as possible, uneventful induction and maintenance of anesthesia should be ensured. The aim is to return to preoperative

Table 2. Comparison of age, anesthesia and surgery times, pain and recovery scores between the groups

	Desflurane	Sevoflurane	Propofol	Total	p value
Age (years)					
n	36	33	32	101	0.526
Mean±SD	51.86±8.96	53.9±10.4	53.4±10.3	53.03±9.82	
Surgery time (min)					
n	36	33	32	101	0.394
Mean±SD	82.14±14.36	91.2±17.4	86.09±10.4	86.6±14.9	
Anesthesia tıme (min)					
n	36	33	32	101	0.081
Mean±SD	95.6±14.12	101.5±19.5	98.59±10.2	97.5±16.9	
VAS10					
n	36	33	32	101	0.076
Mean±SD	3.89±2.08	4.06±1.78	3.94±1.95	3.97±1.82	
VAS20					
n	36	33	32	101	0.091
Mean±SD	4.39±2.38	4.82±1.26	4.28±2.16	4.57±2.02	
VAS30					
n	36	33	32	101	0.102
Mean±SD	4.58±2.29	4.81±1.4	4.38±1.99	4.47±2.03	
MARS5					
n	36	33	32	101	0.122
Mean±SD	5.52±1.09	5.18±1.15	5.25±1.01	5.34±1.10	
MARS10					
n	36	33	32	101	0.089
Mean±SD	7.64±1.07	7.33±1.41	7.26±1.29	7.36±1.27	
MARS20					
n	36	33	32	101	0.139
Mean±SD	9.05±1.22	8.97±1.38	8.96±1.21	8.99±1.29	
MARS30					
n	36	33	32	101	0.079
Mean±SD	9.75±0.55	9.77±0.33	9.53±0.51	9.72±0.49	
Total					
n	36	33	32	101	
%	35.60%	32.70%	31.70%	100.00%	

Abbreviations: N: number; SD: standart deviation; min: minutes; VAS: Visual Analog Scale; MARS: Modified Aldrete Recovery Score.

Table 3. Preoperative and postoperative Mini-Cog values of the patients

	Desflurane	Sevoflurane	Propofol	Total	p
Pre-Mini-Cog					
n	36	33	32	101	0.394
Mean±SD	4.13±0.96	4.36±0.78	3.91±1.2	4.13±1.02	
Post-Mini-Cog					
n	36	33	32	101	0.338
Mean±SD	4.16±1.0	3.72±1.42	3.96±1.3	4.00±1.24	

Abbreviations: N: number; SD: standart deviation; Mini-Cog: Mini Cognitive Assessment.

performance as soon as possible and to avoid permanent cognitive impairment.[2]

The causes of postoperative neurologic dysfunction are still unclear. The general opinion is that there are changes in the activity of the central nervous system due to the

Table 4. Mini-Cog variation (adaptation Cog) by anesthetic agents and differences between anesthetic agents

	Maintenance agent	Mean difference	p	N	Mean	Standard deviation
Desflurane	Sevoflurane	0.449*	0.012	36	0.06	0.583
	Propofol	-0.069	0.934			
Sevoflurane	Desflurane	-0.449*	0.012	33	-3.9	0.659
	Propofol	-0.519*	0.002			
Propofol	Desflurane	0.069	0.934	32	0.13	0.492
	Sevoflurane	0.519*	0.002			

Abbreviations: N: number; p: p value; *: statistically significant difference.

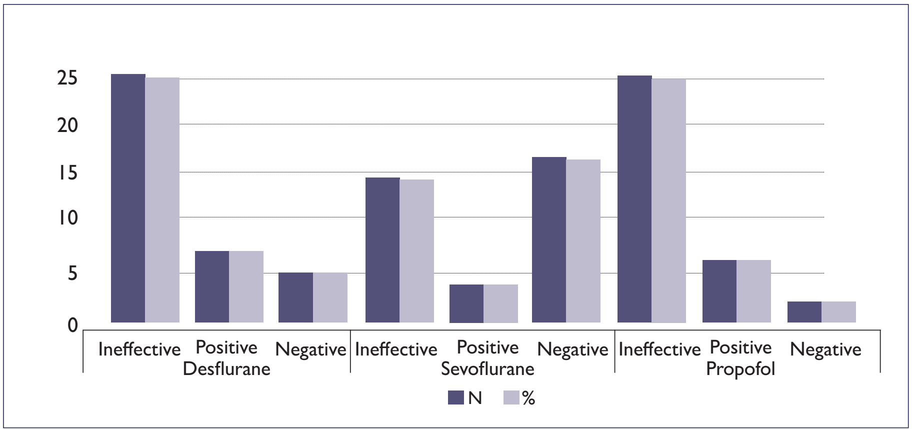

Figure 1. Anesthetic agent-based number and proportions of the adaptation Cog variable.

residual effects of the proven negative effects of anesthetic agents in postoperative cognitive dysfunction. In the study by Hussain et al.[8] investigating the effects of general anesthesia on dementia in elderly patients, general anesthesia was found to pose an increased risk of postoperative delirium and postoperative neurocognitive disorders compared to the population that did not receive general anesthesia.

It has been shown that anesthesia and surgery cause an increase in biomarkers in plasma suggestive of neuronal damage. Therefore, in addition to pre-existing neurological disease, hypoxia during the operation and advanced age, many other factors may be the cause of postoperative cognitive impairment.[9]

The choice of anesthetic drugs may also affect postoperative cognitive status, as residual levels of inhaled anesthetics may produce changes in central nervous system activity. Among inhaler anesthetics, desflurane and sevoflurane are known to provide early recovery due to their low blood-gas partition coefficients. However, this situation does not fully reflect their effects on cognitive functions.

Different results were obtained in studies investigating the effects of these two inhalation anesthetics on postoperative cognitive functions in different surgical procedures. For example, in a study by Bilotta et al.,[10] it was shown that desflurane provided earlier cognitive improvement in overweight patients who underwent craniectomy. In another study, it was shown that although postoperative recovery was faster in those treated with desflurane than those treated with sevoflurane, the effects of the two inhalation agents on cognitive functions were similar in patients over 65 years of age who had knee or hip surgery.[11]

Green et al.[12] compared the effects of desflurane and sevoflurane on neurocognitive functions after urological interventions in patients over 65 years of age but found no significant difference. It was reported that postoperative neurocognitive disorders can be induced, especially in elderly patients and in the presence of systemic inflammatory diseases. While the similar feature of these two studies is that the study groups consisted of elderly patients over 65 years of age, the characteristic of the patient groups in Bilotta's study was that they were overweight. Therefore, due to the low fat/blood partition coefficient of desflurane, it can be removed from the body faster in obese patients and may affect cognitive functions less.

All inhalation and intravenous anesthetic agents have different effects that are not yet known, in addition to their known effects on the central nervous system. Therefore, when investigating the negative effects of these agents on postoperative cognitive functions, not only their pharmacodynamic properties but also their pharmacokinetic properties should be considered.

Zhang et al.[13] investigated the improvement of neurocognitive functions after major cancer surgery in elderly patients and showed that the incidence of delayed neurocognitive recovery was lower in those treated with propofol compared to sevoflurane. As in the study by Zhang et al., BIS was used in our study to standardize the depth of anesthesia and the degree of sedation in all three groups, ensuring the concentration adequacy of the anesthetic agents and eliminating individual differences as much as possible. Consistent with Zhang et al.'s study, it was concluded in our study that cognitive functions were affected more in the sevoflurane group than in the other two groups.

However, a systematic review showed that propofol has a greater adverse effect on postoperative cognitive functions than sevoflurane in elderly patients with lung cancer.[14]

Xing et al.[15] investigated the early and late postoperative effects of sevoflurane and propofol anesthesia combined with remifentanil in intracranial tumors (subtentorial gliomas). Both types of anesthesia methods were found to be equally effective on postoperative neurocognitive functions.

Guo et al.[16] evaluated sevoflurane and propofol anesthesia in terms of cerebral oxygenation and neurocognitive dysfunction. According to the results of the study, which included patients aged 40-75 years who underwent abdominal surgery for more than two hours, it was determined that while sevoflurane and propofol did not cause a significant difference in terms of postoperative neurocognitive function, cerebral oxygenation was better preserved in the sevoflurane group.

In a study by Royse et al.[17] in which they evaluated early cognitive dysfunction in cardiac operations, it was found that propofol caused significant postoperative cognitive dysfunction compared to desflurane and had a significant effect on prolongation of hospital stay.

It was observed that the effects of sevoflurane, desflurane, and propofol on postoperative cognitive functions have not been clearly demonstrated. The results of many clinical studies differ from each other.

The effects of sevoflurane, desflurane, and propofol on postoperative cognitive functions were generally studied in pairwise comparative studies. Comparisons between anesthetic agents in each study yielded different results, albeit minimally. This may be due to the variety of tests used. In our study, the Mini-Cog test, which has been introduced more recently in clinical use, was used rather than the Mini Mental State test used in most of the other studies mentioned. Although the Mini Mental State test includes longer analyses than the Mini-Cog test, language differences may adversely affect the reliability of the test. It has been observed that the Mini-Cog test is more practical, is not affected by language differences, and shows no difference from the Mini Mental State test in measuring cognitive functions in clinical use.[18] It can be thought that the tests used may also be effective in the differing effects of sevoflurane, desflurane, and propofol on cognitive functions between studies.

The results of this study indicate that postoperative cognitive functions are affected more in the sevoflurane group than in the propofol and desflurane groups. High concentrations of sevoflurane (>1.5 MAC) may impair the autoregulation of cerebral blood flow (CBP), leading to a decrease in CBP. In order to provide 40%-60% BIS indicators in the preoperative period, sevoflurane levels >1.5 MAC may have been used in some cases, which could make it difficult to control cerebral blood flow regulation and explain the decline in postoperative neurocognitive functions. Sevoflurane tends to reach inspired concentration more slowly than desflurane. This indicates that induction and recovery may be slower. Additionally, sevoflurane potentiates muscle relaxants, both in terms of pharmacological effect and duration of action. Since the clock drawing part of the Mini-Cog test that we used in the evaluation may also be affected by muscle strength, the low results may have been related to the effect of sevoflurane. More studies are needed on this situation.

Conclusion

In conclusion, it was thought that desflurane or propofol may be more advantageous than sevoflurane in terms of postoperative cognitive dysfunction and that they may be preferred in the selection of anesthetic agents, especially in patients with preoperative neurological problems. However, it was concluded that further clinical studies are needed to reach clearer results.

Ethics Committee Approval

The study was approved by the Kartal Dr. Lütfi Kırdar City Hospital Ethics Committee (Date: 25.09.2019, Decision No: 2019/514/162/8).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: N.N.A., E.B.; Design: N.N.A., E.B., B.Ç.; Supervision: B.Ç., E.B.; Fundings: B.Ç.; Materials: N.N.A., E.B.; Data collection &/or processing: N.N.A.; Analysis and/or interpretation: N.N.A., E.B.; Literature search: N.N.A., E.B.; Writing: N.N.A., E.B.; Critical review: E.B., B.Ç., N.N.A.

Conflict of Interest

None declared.

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Laparoskopik Kolesistektomide Farklı Anestetik Ajanların Postoperatif Kognitif Fonksiyonlar Üzerine Etkileri

Amaç: Bu çalışmada, sevofluran veya desfluran ile uygulanan inhalasyon anestezisi ile propofol ile uygulanan intravenöz anestezinin postoperatif erken dönem kognitif fonksiyonlar üzerine etkilerinin karşılaştırılması amaçlandı.

Gereç ve Yöntem: Bu çalışmaya ASA I-III sınıfı, 30-70 yaş arası, elektif laparoskopik safra kesesi ameliyatı geçiren hastalar dahil edildi. Ameliyattan bir gün önce Mini-Cog testi yapılarak hastaların kognitif fonksiyon düzeyleri belirlendi. Hastalar rastgele Grup I (Desfluran), Grup II (Sevofluran) ve Grup III (Propofol) olmak üzere üç gruba ayrıldı. Propofol ve remifentanil roküronyum ile anestezi indüksiyonu yapıldıktan sonra tüm hastalara endotrakeal entübasyon uygulandı. Anestezi idamesi sırasında tüm hastalara uygulanan remifentanil infüzyonunun yanı sıra bispektral indeksi (BIS) 40-60 olan desfluran, sevofluran inhalasyonu veya propofol infüzyonu ile anestezi derinliği sağlandı. Tüm hastaların postoperatif 5., 10., 20. ve 30. dakikalarda Modifiye Aldrete Recovery Skorları (MARS) ölçüldü ve kaydedildi. Ağrı düzeyleri postoperatif 10., 20. ve 30. dakikalarda görsel analog skala (VAS) ile değerlendirildi. Mini-Cog testi ameliyat sonrası 24. saatte aynı hekim tarafından tekrarlanarak ameliyat öncesi değerlerle karşılaştırıldı.

Bulgular: Üç grup arasında demografik özellikler, ameliyat ve anestezi süresi, ameliyat sonrası MARS ve VAS değerleri açısından fark yoktu (hepsi için $p>0.05$). Desfluran ve Propofol gruplarında ameliyat öncesi ve ameliyat sonrası Mini-Cog test skorları arasında anlamlı fark görülmezken ($p>0.05$), sevofluran grubunda Mini-Cog testinin Propofol grubuna göre ve Desfluran grubuna göre anlamlı derecede düşük olduğu görüldü (sırasıyla $p=0.002$ ve $p=0.012$).

Sonuç: Desfluran ve propofolün kognitif fonksiyonlara olumsuz etkisinin olmadığı, sevofluranın ise postoperatif kognitif fonksiyonlara olumsuz etkisinin olduğu sonucuna varıldı.

Anahtar Sözcükler: Desfluran; Mini-Cog testi; postoperatif bilişsel işlev bozukluğu; propofol; sevofluran.