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RESEARCH

THE EFFECTS OF LOW FLOW AND NORMAL FLOW DESFLURANE ANESTHESIA ON LIVER AND RENAL FUNCTIONS AND SERUM CYSTATIN C LEVELS IN GERIATRIC PATIENTS: A PROSPECTIVE RANDOMIZED CONTROLLED STUDY

Abstract

Introduction: Aging is a physiological process and the elderly population is increasing. In parallel to the increasing of the elderly population, the number of geriatric patients who required an invasive procedure or surgical intervention under anesthesia are also increasing. The geriatric patients who are frailty and have a loss of functional reserve in all organ systems are more sensitive to anesthetic agents. The purpose of this research was to investigate whether low flow desflurane anesthesia also affects hepatic and kidney functions, in elderly patients.

Methods: After approval from the local ethics committee, the patients were divided into two groups; as the low flow desflurane anesthesia group and the normal flow desflurane anesthesia group using the closed-envelope method. Calibration and leakage tests of the anesthesia device (Primus, Drager) were performed before anesthesia. Heamodynamics parametres, peripheral oxygen saturation, and bispectral index monitoring were performed to all patients in operating room. The blood samples were collected before anesthesia induction, after surgery, and at the postoperative 24th hour. The serum alanine aminotransferase and aspartate aminotransferase levels were measured to assess the liver damage. The serum creatinine, blood urea nitrogen, and cystatin C levels were measured to assess the kidney function.

Results: The serum alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, creatinine and cystatin C levels and hemodynamic parameters, peripheral oxygen saturation and bispectral index values were similar in both groups.

Conclusions: It was concluded that low-flow desflurane anesthesia does not adversely affect liver and kidney functions in geriatric patients and is as safe as normal-flow desflurane anesthesia.

Keywords: Anesthesia; Cystatin C; Desflurane; Aged; Kidney; Liver.

INTRODUCTION

Aging, which is a physiological process; it is characterized by loss of functional reserve in all organ systems, regression in anabolic processes, and increase in catabolic processes (1). In parallel to the increase in the life expectancy of geriatric patients, it is predicted that we will provide medical treatment under anesthesia to more and more elderly patients (2). Low-flow anesthesia an inhalation technique applied with a semi-closed rebreathing system, has a rebreathing rate of at least 50% (3, 4). With this anesthesia technique, cost is reduced, environmental pollution is lower, and the humidity and temperature of the inhaled gases can be protected (5, 6). Volatile anesthetic agents such as sevoflurane and desflurane are commonly used in anesthesia practice (7). They affect hepatic blood flow and cardiac output to varying degrees. For this reason; liver and kidney functions are also affected. In addition, teh metabolic rates and excretion in the liver and kidneys are also a determining factor in their effects on liver and kidney functions. Sevoflurane undergoes defluorination in the kidneys to form inorganic fluoride ions. The carbon dioxide absorber converts sevoflurane to compound A. Both inorganic fluoride and compound A were associated with nephrotoxicity. The renal excretion rates of inhalation agents and their stability to degradation by standard carbon dioxide absorbents are also effective on renal function (8,9). Desflurane, which is highly proof to defluorination, has not been associated with nephrotoxicity (10). The hepatotoxic effects of inhalation agents may vary according to their effects on hemodynamic parameters and hepatic blood flow, and their metabolism rates in the liver (11). Does low-flow desflurane anesthesia affect liver and kidney functions in elderly patients who are frail and have losses of functional reserve in their organ systems? The aim of this study is to investigate the effects of low-flow and normal flow desflurane anesthesia on hepatic and kidney functions in geriatric patients.

MATERIALS AND METHODS

This prospective, randomized-controlled study (ClinicalTrials ID: NCT05414721) was conducted following the approval of the Faculty of Medicine's ethics committee at Yuzuncu Yil University (April 16, 2021; Decision no: 05-27). Writen consent from the patients was obtained.

Sixty patients, aged 65 years of age or older and undergoing elective surgery (other than thoracic surgery and neurosurgery), duration of the surgery longer than 1 hour and physical status I-III according to the American Society of Anesthesiologists (ASA) were included. Patients were excluded if they exhibited cardiorespiratory disease, uncontrolled diabetes mellitus, coagulopathy, signs of infections, and/or abnormality in preoperative liver and kidney functions; if they used nephrotoxic or hepatotoxic drugs, if they displayed major bleeding in surgery (> 1000 cc); and/or if they suffered from chronic alcoholism, active drug use, and/or withdrawal symptoms.

The cases were using the closed envelope method divided into two groups: the low-flow desflurane anesthesia group (Group D; n=30) and the normal-flow desflurane anesthesia group (Group N; n=30) (Figure 1).

Calibration and leakage tests of the anesthesia device (Primus, Drager) were performed before anesthesia. The leak test was also repeated manually for each patient. Alarm settings of the anesthesia device, inspired oxygen concentration (FiO_2) lower limit 30%, inspired CO_2 upper limit 3%, end-tidal carbon dioxide ($etCO_2$) upper limit 45 mmHg, disconnection alarm 5 cmH2O lower than peak pressure, occlusion alarm 30 cm H_2O, and expiratory gas volume were adjusted to be 500 mL below the desired minute volume (MV). Soda lime (Sorbo-lime, Berkim, Turkey) was used as a carbon dioxide absorbent. The color and dryness of the carbon dioxide absorber was controled frequently and changed at appropriate times. A disposable

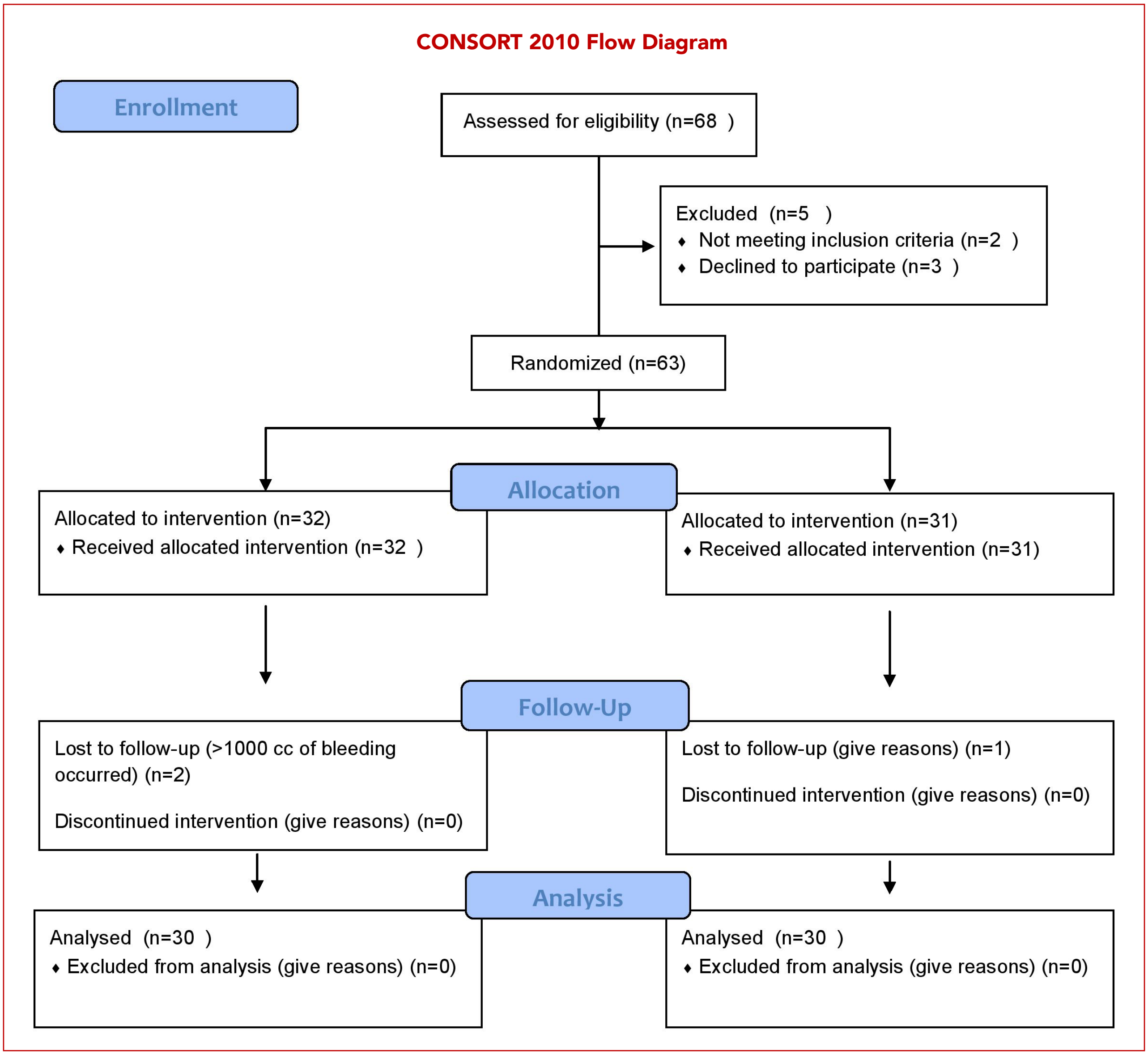

Figure 1. CONSORT 2010 Flow Diagram

bacterial filter and anesthesia circuit were used for every patient.

All patients underwent non-invasive blood pressure, heart rate (HR), electrocardiography (ECG) and peripheral oxygen saturation (SpO2) monitoring in the operating room. We also measured the depth of anesthesia in all patients using a bispectral index (BIS) monitor (A-2000 Aspect medical systems, USA). BIS values were kept between 40 and 60 throughout all operations.

Preoxygenation was performed with 100% O_2 for 3 minutes to all cases. After administering 0.03 mg/kg midazolam, 1.5 mcg/kg fentanyl, 2 mg/kg propofol, and 0.6 mg/kg rocuronium bromide, endotracheal intubation was carried out. All patients were ventilated in volume-controlled, mechanical ventilation mode with 12 breaths/min, 6-8 mL/kg tidal volume, I:E ratio 1:2, and 5 cm H_2O positive end-expiratory pressure (PEEP). The $EtCO_2$ was maintained at 30-40 mmHg. Patients in both groups were given a mixture of 50% O_2 + 50% air + 6-7% desflurane at a 4 L/min fresh gas flow rate (FGF) until the minimum alveolar concentration (MAC) value achieved +1, at which time Group D's FGF was reduced to 0.5 L/min and FiO_2 was increased to 60% (60% O_2 + 40% air + 8% desflurane), and Group N's FGF was reduced to 2 L/min and the FiO_2 was reduced to 40% (40% O_2 + 60% air + 6% desflurane). In both groups, the MAC value was kept in the range of 0.9-1.1 by titrating the concentration of desflurane. During all surgeries, the patients' FiO_2, fractional inspirium carbon dioxide pressure ($FiCO_2$), $etCO_2$, fractional inspirium desflurane concentration, fractional expirium desflurane concentration, and MAC values were continuously monitored.

Because geriatric patients are more sensitive to hypoxia, it was not acceptable for the inspiratory O_2 concentration to fall below 35%. In this case, the amount of O_2 in the fresh gas increased by 10%. If the inspiratory O_2 ratio did not exceed 35% despite intervention, the low flow desflurane anesthesia was terminated and the operation continued with normal flow anesthesia in the patients who were excluded from the study. After intubation, a Foley catheters were used in all patients to monitor intraoperative urine flow.

The patients' blood pressure (non-invasive), SpO_2, and BIS values were monitored and recorded before and after induction, at the start of low flow desflurane anesthesia, and every 5 minutes thereafter during the operations.

The vaporizer was closed approximately 10–15 minutes before the end of the surgery. The FGF was increased to 6 L/min and ventilation was continued manually with 100% FiO_2. When the MAC value of desflurane reduced to 0.1-0.3 and the BIS value reached 80 in the anesthesia device, the neuromuscular blockade was reversed using atropine sulphate (0.015 mg kg−1) and neostigmine (0.03 mg kg−1). Patients who had spontaneous ventilation were extubated.

The patients were monitored for side effects such as medication allergies, nausea and vomiting, tremor and agitation, and complications such as hypoxia, hypercarbia, hypoventilation, and insufficient depth of anesthesia, both during the procedure and in the postoperative period.

The blood samples were collected before anesthesia induction, after surgery, and at the 24th hour, postoperatively by venepuncture. Samples were immediately centrifuged at 2000 rpm for 10 minutes, and the supernatant was used for biochemical analysis such as levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), blood urea nitrogen (BUN) and creatinine. The levels of ALT, AST, BUN and creatinine were analyzed within 30 minutes after sampling. The cystatin C levels were measured in the serum. For serum separation, blood was centrifuged at 4000 rpm for 10 minutes. The obtained serum was transferred to Eppendorf tubes and stored at -80°C until biochemical analysis. The serums stored at -80°C were thawed at room temperature for analysis. Serum cystatin C was measured on the Abbott Architect C16000 fully automatic analyzer using the multiagent cystatin C kit (Milan, Italy).

Statistical analysis

Descriptive statistics are presented as mean, median, minimum, maximum, standard deviation, frequency and percentage values. The normality of the variables were compared with Kolmogorov-Smirnov test. The Mann-Whitney U test and independent-samples t-test were used in the analyses of the quantitative data in independent groups. The chi-squared test was used in the analysis of the qualitative data in independent groups. When the conditions for the chi-squared test were not met, the Fisher's exact test was used. Statistical significance value was accepted as $p<0.05$ in all tests. Statistically significance level was considered as 5%. The Statistical Package for Social Science (SPSS) version 27.0 was used for data analysis.

RESULTS

Age, gender, ASA scores, smoking rates, and duration of anesthesia and surgery were found to be similar in both groups ($p > 0.05$) (Table 1-2).

Hemodynamic parameters, SpO_2 and BIS values

The HR, SpO_2 and BIS values measured at all times were similar in both groups ($p > 0.05$). In Group D, systolic blood pressure (SBP) values measured at the first minute after extubation ($p = 0.042$) were higher than Group N. In addition, mean blood pressure (MBP) values that measured at the 40th minute ($p = 0.038$) and at the first minute after extubation ($p = 0.035$) were significantly higher than group N. In Group N, diastolic blood pressure (DBP) values measured at the 5th minute after anesthesia

Table 1. Demographic characteristics in groups (mean ± SD).

		Group N		Group D		p
		Mean±SD/ n-%	Median	Mean ±SD/ n-%	Median	
Age (year)		69.6 ± 5.2	68.5	70.5 ± 5.9	68.0	0.731ŧ
Gender	Female	11	36.7 %	9	30.0%	0.584‡
	Male	19	63.3 %	21	70.0%	
Height (cm)		169.5± 9.5	168.5	171.8±9.9	174.5	0.428†
Weight (kg)		73.0 ± 9.8	72.0	74.1±11.4	74.5	0.690†
BMI (kg/m^2)		25.4 ± 2.3	25.0	25.0±2.7	24.7	0.626†

Values are mean ± standard deviation and medians [interquartile range]. †Mann–Whitney U-test. ‡Chi-square test. ŧIndependent sample t-test. SD: Standard deviation, BMI: Body Mass Index

Table 2. ASA scores, smoking rates, and the duration of anesthesia and surgery of patients.

		Group N				Group D				p
		Mean±SD/n-%			Medyan	Mean±SD /n-%			Medyan	
ASA Scores		2.2	±	0.6	2.0	2.1	±	0.5	2.0	0.349†
Smoking	(-)	21		70.0 %		22		73.3%		0.774‡
	(+)	9		30.0 %		8		26.7%		
Duration of Anesthesia (min)		113.8	±	13.0	110.0	116.0	±	16.6	115.0	0.868†
Duration of Surgey (min)		103.7	±	12.7	100.0	105.5	±	16.1	105.0	0.885†

Values are mean ± standard deviation and medians [interquartile range]. †Mann–Whitney U-test. ‡Chi-square test. SD: Standard deviation, min: Minute induction (p = 0.035) were significantly higher than in Group D. The SBP, DBP and MBP values that measured at all other times were similar in both groups (p > 0.05).

Hepatic and renal functions

The serum ALT, AST, BUN, creatinine and cystatin C levels measured pre anesthetic period, at the end of surgery and at the postoperative 24th hour were like in both groups (p > 0.05). Intragroup comparisons, serum ALT, BUN, creatinine and cystatin C levels measured at different times were also similar (p > 0.05). There was a significant increase in serum AST values that measured at the postoperative 24th hour in both groups compared to before anesthesia induction period values (Group N, p = 0.049; Group D, p = 0.028) (Table 3) (Graph 1).

Table 3. Comparison of serum ALT, AST, BUN, creatinine and cystatin C values measured at the different times in groups.

	Group N		Group D		p
	Mean±SD	Median	Mean±SD	Median	
ALT (U/L)					
Pre-Induction	20.2±9.9	17.0	19.9±9.7	17.0	0.982†
Post Extubation	20.5±11.1	18.5	19.3±10.2	17.5	0.662†
Change seen compared to Pre-Induction period (p)	0.713 w		0.927 w		
Postoperative 24th hour	22.3±12.1	19.0	20.5±11.4	17.5	0.520†
Change seen compared to Pre-Induction period (p)	0.914 w		0.714 w		
AST (U/L)					
Pre-Induction	20.6±6.2	18.5	20.2±8.0	18.0	0.473†
Post Extubation	22.6±8.1	20.1	21.5±11.1	16.7	0.162†
Change seen compared to Pre-Induction period (p)	0.608 w		0.085 w		
Postoperative 24th hour	24.0±8.6	21.5	23.4±10.4	21.0	0.505†
Change seen compared to Pre-Induction period (p)	***0.049*** w		***0.028*** w		
BUN (mg/L)					
Pre-Induction	18.1±5.9	17.2	19.3±4.2	20.5	0.201†
Post Extubation	17.2±4.6	17.3	17.9±4.5	18.0	0.662†
Change seen compared to Pre-Induction period (p)	0.105 w		0.345 w		
Postoperative 24th hour	18.4±7.3	17.7	18.7±4.7	18.2	0.482†
Change seen compared to Pre-Induction period (p)	0.472 w		0.665 w		

Table 3. Comparison of serum ALT, AST, BUN, creatinine and cystatin C values measured at the different times in groups.

Creatinine (mg/dL)						
Pre-Induction	0.84±0.18	0.80		0.89±0.16	0.86	0.201†
Post Extubation	0.82±0.23	0.76		0.84±0.21	0.81	0.539†
Change seen compared to Pre-Induction period (p)	0.055 w			0.666 w		
Postoperative 24th hour	0.86±0.24	0.80		0.90±0.27	0.81	0.450†
Change seen compared to Pre-Induction period (p)	0.113 w			0.604 w		
Serum Cystatin C (mg/L)						
Pre-Induction	1.12±0.24	1.11		1.18±0.17	1.17	0.160†
Post Extubation	1.12±0.33	1.15		1.16±0.28	1.16	0.673†
Change seen compared to Pre-Induction period (p)	0.171 w			0.593 w		
Postoperative 24th hour	1.18±0.35	1.10		1.22±0.28	1.14	0.359†
Change seen compared to Pre-Induction period (p)	0.914 w			0.234 w		

Values are mean ± standard deviation and medians [interquartile range]. †Mann–Whitney U-test. ‡Chi-square test. SD: Standard deviation. wWilcoxon test. AST: Aspartate aminotransferase. ALT: Alanine aminotransferase. BUN: Blood urea nitrogen. (p): P Value

Side effects and complications

Nausea, vomiting, tremor, agitation and complication rates were alike in both groups (p> 0.05).

DISCUSSION

The study's major finding is that low flow and normal flow desflurane anesthesia did not cause a significant change in serum AST, ALT, BUN, creatinine, and cystatin C levels in geriatric patients. However, in the intragroup comparison, we found a statistically significant increase in AST values measured at the postoperative 24th hour compared to the AST values measured before anesthesia induction in both groups.

The low - flow anesthesia decrease loss of humidity and heat from the patients' airway during anesthesia. Maintains intraoperative body temperature in geriatric patients. It has been reported that it allows to minimize the incidence of complications due to hypothermia. In contrast to high-flow anesthesia in elderly patients with severe comorbidities, the low-flow anesthesia technique has been reported to make better early mobilization conditions. It has been stated that low-flow desflurane anesthesia is effective and safe in routine geriatric surgeries and minimally affects the liver functions (12,13).

The modern anesthesia devices used today have high patient safety standards and monitors that can analyze the anesthetic gas components continuously and in detail. In addition, the increase in knowledge about the pharmacodynamics and pharmacokinetics of inhalation anesthetics has facilitated the safer application of low-flow anesthesia (14). While applying low-flow anesthesia, the airway pressure, volume, and concentrations of inspired and expired gases, FiO_2, and MAC value of the volatile agent should be monitored continuously. The alarm limits should be followed carefully (15, 16). We used the Drager Primus anesthesia device (Drager® Medizin technik, Lubeck, Germany), which allows for safely making these measurements.

Many studies have investigated how anesthesia methods applied with varied FGF affect hemodynamics. Elmacioglu et al. (17), in their study in which they applied desflurane anesthesia with 0.5, 1, and 2 L/min FGF, compared hemodynamic parameters and stated that there was not meaningful difference among the groups. Ceylan et al. (18) stated that perioperative MBP changes in both groups remained within normal limits in their study in which they applied low-flow desflurane and sevoflurane anesthesia. They reported that the perioperative MBP values remained within normal limits and were similar in patients who received low-flow desflurane and sevoflurane anesthesia. Xie et al. (19) reported that desflurane was associated with more stable hemodynamic results in their study in which they applied low-flow desflurane, sevoflurane, and enflurane anesthesia.

Systolic, diastolic, and mean blood pressures of the patients were closely monitored. There was not observed meaningful difference among the groups except the 5th and 40th minutes after anesthesia induction and the 1st minute after extubation. We observed that these differences in hemodynamic parameters did not exceed 20% of the preoperative measured values and remained within the clinically normal limits. The groups' HR and SpO_2 values as measured in all times throughout the surgery were found to be similar.

The serum levels of ALT and AST are mostly measured to assess liver damage. The half-lives of ALT and AST are approximately 47 and 17 hours, respectively. The AST and ALT levels measured within 24–48 hours after the anesthesia procedure provide information about changes in perioperative hepatic functions (20). Ebert and Arain (21) compared low-flow sevoflurane, low-flow desflurane, and intravenous propofol anesthesia, stated that there were significant increases in plasma AST levels in groups given volatile anesthetics. However, they reported that the values remained within the normal reference range. Bosna et al. (20) stated that low and high flow desflurane anesthesia had similar effects on serum ALT and AST levels measured in the postoperative period. Park et al. (22) compared postoperative AST values with preoperative AST levels in a study in which they compared high- and low-flow desflurane anesthesia. Postoperative AST levels increased significantly in both groups; however, this increase was clinically insignificant as the measured values remained within the normal reference range.

In this study, serum ALT and AST levels measured before anesthesia induction, after extubation, and at the postoperative 24th hour were detected to be similar in both groups. However, we observed a significant increase in both groups when the AST levels measured at the 24th postoperative hour were compared with the AST levels measured before inducing anesthesia. Despite the increase in AST levels, AST values remained within the normal reference range.

Serum creatinine, urea, BUN, creatinine clearance, and urine glucose and protein can be used to assess renal functions. In recent studies, serum cystatin C values were also used to evaluate renal functions, and are stated to be more sensitive. One study stated that, when glomerular filtration rate (GFR) fell below 80 mL/m^2 in intensive care patients, there was a 48% increase in the serum creatinine level and an 88% increase in the serum cystatin C level (23). When serum creatinine levels and serum cystatin C levels were compared in patients with acute renal failure, it was reported that serum cystatin C values increased in more patients and were more correlated with GFR compared to creatinine (24-27). Eger et al. (28) compared 8-hour normal flow sevoflurane and desflurane anesthesia in their study. They measured BUN and creatinine levels at the 24th and 48th hours after anesthesia and compared them with the values before anesthesia. They reported that there was no significant increase in either group. Ebert and Arain (24) compared low-flow sevoflurane, low-flow desflurane anesthesia, and intravenous propofol anesthesia, and reported that postoperative creatinine levels did not change in any of the groups and BUN levels decreased significantly. Yildirim et al. (29) compared the urea and creatinine values measured before surgery, after extubation, and at the postoperative 24th and 48th hours in patients receiving low-flow sevoflurane, desflurane and isoflurane anesthesia. When they compared the urea and creatinine levels inter- and intra-group, they stated that they were similar in both groups. Duymaz et al. (30) compared the effects of low-flow sevoflurane and desflurane anesthesia on the kidneys in their study. They compared the serum urea, creatinine and cystatin C values measured at the end of the surgery and postoperative 24th hour with the preoperative values, they reported that there was no significant difference intra- and inter gruop. A Foley catheter was used in all patients to monitor intraoperative urine flow. Oliguria (< 0.5 ml/kg/hr) was not observed in any patient. Serum creatinine, BUN and cystatin C levels were found to be similar in both intra- and inter-group comparisons.

In low-flow anesthesia, BIS monitoring can be used to minimize the risk of anesthesia awareness. Akbas et al. (31) stated that they found BIS values to be similar in both groups in their study in which they compared low-flow and normal-flow desflurane anesthesia in morbidly obese cases. In this study, we also observed that the mean BIS values did not exceed 60 and BIS values were similar in both groups.

The superiorities of this study

The management of geriatric anesthesia is special in terms of anesthesia applications and difficult to manage. In a literature review, we could not find enough studies on low-flow anesthesia in geriatric patients. We believe that our study is one of the few studies investigating whether low-flow desflurane anesthesia affects liver and kidney functions in geriatric patients.

Limitations of the study

The heterogeneity of surgical operations and the small number of patients were considered as limitations of the study.

In conclusion, the present study showed that low-flow desflurane anesthesia did not adversely affect liver and kidney functions in geriatric patients. It has also shown that it provides sufficient depth of anesthesia in the intraoperative period, does not cause hemodynamic instability, and is as safe as normal-flow desflurane anesthesia.

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