ORIGINAL ARTICLE

Cognitive function and recovery after sevoflurane anesthesia: A comparison of low-flow and medium-flow anesthesia

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ABSTRACT

Aim: The aim of this study was to compare the effects of low-flow and medium-flow sevoflurane anesthesia on cognitive function of the patients as well as on recovery time.

Methodology: Thirty-six patients were allocated randomly to the low-flow group (n=18) or medium-flow group (n=18). General anesthesia was maintained with sevoflurane in both groups. The fresh gas flow rate was set to 1 L/min in the low-flow group and 4 L/min in the medium-flow group. The MMSE was applied preoperatively and at 1, 3, 6, and 24 h postoperatively to assess cognitive functions.

Results: There were no significant differences in recovery times or MMSE scores between the groups. One hour after tracheal extubation, three patients in the low-flow group (17%) and two patients in the medium-flow group (11%) experienced cognitive impairment (p=0.629). All patients in both groups demonstrated completely normal cognitive function 3 h postoperatively. There was no correlation between the consumption of sevoflurane and MMSE scores or emergence recovery times in either group.

Conclusions: We conclude that fresh gas flow rate does not affect cognitive function or recovery times, and cognitive dysfunction is not associated with the consumption of sevoflurane.

Keywords: General anesthesia; Mini Mental State Examination; Sevoflurane; Low flow anesthesia; Recovery; Cognitive dysfunction

Citation: Muslu B, Demircioglu RI, Yılmaz F, Sert H, Usta B, Gözdemir M. Cognitive function and recovery after sevoflurane anesthesia: A comparison of low-flow and medium-flow anesthesia. Anaesth Pain & Intensive Care 2012; 16(2): 142-46

INTRODUCTION

The cognitive dysfunction in patients undergoing general anesthesia can result in delayed functional recovery and a prolonged hospital stay. Especially in laparoscopic surgery this is of great importance with regard to discharge time after anesthesia. When providing general anesthesia for surgery, the goal is to achieve optimal surgical conditions while ensuring an early recovery without side effects.

Use of volatile anesthetics that are rapidly eliminated with minimal metabolic breakdown may reduce cognitive dysfunction in surgical patients and facilitating a faster recovery after general anesthesia. Sevoflurane is a volatile anesthetic that has low blood-gas partition coefficients, and this has been shown to result in a rapid induction and a rapid recovery from anesthesia.[1,2] Frink et al. studied sevoflurane anesthesia in a low-flow system and examined the levels of the degradation products and their organ toxicity.[3] The effect of low-flow sevoflurane anestheia on postoperative cognitive dysfunction (POCD) and recovery is not clear and to our knowledge, no study to date have investigated whether or not the level of fresh gas flow (FGF) influences cognitive functions and recovery after low-flow anesthesia with sevoflurane. Our study is the first to compare the effects of low-flow and medium-flow sevoflurane anesthesia on cognitive function though low-flow anesthesia is widely

used in clinical practice. We designed this randomized, prospective study to compare the effect of low-flow sevoflurane anesthesia with that of medium-flow sevoflurane anesthesia on cognitive function in patients undergoing laparoscopic cholecystectomy under general anesthesia.

METHODOLOGY

The study was approved by our institution's committee on human research, and informed consent was obtained from all patients. The study group included 36 patients categorized as American Society of Anesthesiologists physical status 1 or 2 who were scheduled for laparoscopic cholecystectomy. Patients whose medical history, laboratory data, or physical examination showed evidence of abnormal hepatic or renal function or severe cardiovascular, pulmonary, neurological, psychiatric, or metabolic disease were excluded from the study. All patients were asked to provide detailed medical histories, including alcohol and drug consumption. Patients were randomly selected to receive either low-flow sevoflurane anesthesia (low-flow group; n=18) or medium-flow sevoflurane anesthesia (medium-flow group; n = 18).

Baseline scores of Mini Mental State Examination (MMSE) were obtained one day before operation. The criterion used to define a decline in cognitive function was a decrease of 2 or more points on the MMSE.[4] The visual analogue scale (VAS) for pain (0=none; 10=maximum) and Ramsey scale for level of sedation were recorded one day before the operation in a quiet room.[5] These tests were repeated postoperatively as follows: the MMSE, VAS for pain, and sedation scoring were performed 1, 3, 6, and 24 hours after tracheal extubation. The MMSE and the evaluation of recovery were performed by a blinded, independent anesthesiologist.

The patients did not receive any premedication. In the operating room, monitoring of the patients included ECG, pulse oximetry, non-invasive blood pressure, temperature and end-tidal carbon dioxide. Inspired oxygen and anesthetic gas concentrations (S/5, Datex-Ohmeda, Finland) were monitored. In both groups, the patients were preoxygenated for 3 minutes, anesthesia was induced with inj. fentanyl 1 μg/kg, propofol 2-2.5 mg/kg, and cisatracurium 0.1 mg/kg intravenously (IV). After tracheal intubation, anesthesia was maintained with sevoflurane 1.8-2% in combination with N_2O 50% and oxygen 50%, and the FGF was set to 4 L/min in both groups. In low-flow anesthesia, the FGF rate was reduced to 1 L/min after 10 min; the flow rates of both N_2O and oxygen were set to 500 ml/min. The flow rates of N_2O and oxygen were adjusted to maintain the inspiratory oxygen concentration at approximately 40% to 50%. Percutaneous arterial blood oxygen saturation was monitored throughout the anesthesia and maintained at >98%. Ventilation was controlled with a tidal volume of 8 to 10 ml/kg, and the ventilation rate was adjusted to maintain an end-tidal PCO_2 of 30 to 35 mmHg. End-tidal concentrations of sevoflurane were analyzed with an M Cov gas analyzer (Datex-Ohmeda, Finland) that was calibrated immediately before each study. The anesthesia machine was an S/5 (Datex-Ohmeda, Finland) which automatically calculated the consumption of sevoflurane.

Sevoflurane concentration was decreased only in response to hypotension that was not responsive to replacement of intraoperative fluid losses or bradycardia. A fall of mean arterial pressure (MAP) below 25% of preinduction baseline value was corrected with ephedrine 5 mg. Bradycardia was defined as heart rate < 50 bpm and was treated with atropine 0.5 mg IV. Sevoflurane concentration was increased to control the hemodynamic responses to surgical stimulation, assigned by MAP >25% of the preinduction baseline values and/or heart rate >90 bpm or clinical signs of light anesthesia. At the last skin suture, sevoflurane and N_2O were turned off simultaneously without previous tapering, and ventilation was controlled with 6 L/min of oxygen until the return of spontaneous ventilation. The trachea was extubated when adequate spontaneous ventilation (tidal volume >4 ml/kg) was achieved. The patients received meperidine 1 mg/kg intramuscularly at the end of surgery for postoperative analgesia and an equal dose was administered every 8 hours for the first postoperative day.

Emergence times from discontinuation of anesthesia to eye opening, squeezing fingers, spontaneous breathing, tracheal extubation, recalling name and date of birth, and a modified Aldrete's recovery score ≥9 were measured.[6] Intraoperative and postoperative adverse events or experiences were assessed and recorded.

Statistical analysis: A power analysis was performed based on differences in cognitive outcomes of sevoflurane,[5] which indicated that a sample size of 32 patients (16 per group) would have 80% power to detect a difference in means of 2 on the MMSE score (alpha=0.05). All statistical tests were performed using SPSS (v.13; SPSS, Chicago, IL, USA). All data had been checked for a normal distribution using the Shapiro-Wilk test. Quantitative variables were compared between the groups using Student's t-test or Mann-Whitney U-test, depending on whether normal or non-normally distributed variables were used, respectively. Qualitative variables were compared using Fisher's exact test or Pearson's χ^2 test. Repeated measures analysis of variance

was performed on the MMSE score. When multiple comparisons were made, a Bonferroni correction was applied. A correlation was sought among VAS for pain, sedation scores, MMSE scores, and consumption of sevoflurane, using Spearman's or Pearson's correlation coefficient. P values < 0.05 were considered statistically significant. The data were expressed as mean (SD), number (%), or median (range).

RESULTS

The two groups were similar with respect to physical characteristics of the patients. The duration of anesthesia and surgery, and consumption of propofol, fentanyl, and meperidine did not differ between the groups. Consumption of sevoflurane was significantly higher in the medium-flow group than in the low-flow group (Table 1).

Table 1: Patient demographic characteristics and drug requirements in two groups

	Low-flow group (n = 18)	Medium-flow group (n = 18)	P value
Age (yr)	55 (25-76)	45 (20-76)	0.194
Weight (kg)	81 (50-105)	78 (48-125)	0.476
Height (cm)	168 (155-181)	163 (142-178)	0.645
Sex (M/F)	5/13	6/12	0.717
ASA physical status (I/II)	7/11	6/12	0.729
Surgery time (min)	40 (20-99)	44 (24-85)	0.776
Anesthesia time (min)	47 (25-106)	50 (29-100)	0.547
Propofol (mg)	200 (130-250)	200 (100-260)	0.441
24 h meperidine (mg)	232 (140-300)	225 (150-320)	0.340
Fentanyl (μg)	100 (40-120)	85 (45-100)	0.214
Sevoflurane (ml)	9.9 (6.6-16.0)	24 (13-46)	0.001
Volatile anesthetic (MAC)	1.1 (1-1.3)	1.1 (1-1.3)	0.913

Values are expressed as median (range) or numbers. MAC = minimum alveolar concentration.

Emergence recovery times did not differ significantly between the groups (Table 2). Neither VAS score for pain nor sedation score was different after low-flow sevoflurane compared with medium-flow sevoflurane anesthesia, at baseline or 1, 3, 6, or 24 h (Table 3).

Cognitive function was measured by MMSE. Three patients in the low-flow group (17%) and 2 patients in the medium-flow group (11%) experienced significant decreases in MMSE scores 1 h postoperatively ($p = 0.629$). All patients in both groups demonstrated completely normal cognitive function at 3 h postoperatively. The MMSE score in the low-flow group was greater at 3 and 6 h compared with the baseline (respectively $p = 0.013$ and $p = 0.004$). The MMSE score in the medium-flow group was greater at 3, 6, and 24 h compared with the baseline (respectively $p = 0.001$, $p = 0.004$, and $p = 0.001$). However, there was no significant difference between the groups at baseline or 1, 3, 6, or 24 h, as shown in Figure 1.

Table 2: Comparative recovery criteria in two groups

Recovery criteria	Low-flow group (n = 18)	Medium-flow group (n = 18)	P value
Eye opening	10.5 (2-26)	12 (8-26)	0.640
Squeeze fingers	12(3-28)	14.5(9-26)	0.086
Spontaneous breathing	5 (1-15)	4.5 (1-12)	0.471
Extubation	9 (1-26)	8 (3-21)	0.347
State name	14 (8-27)	17 (11-27)	0.092
State birth day	14.5 (8-29)	17 (11-27)	0.098
Recovery score ≥ 9	15 (8-29)	17.5 (11-30)	0.072

Values are median (range) in minutes. Recovery variables are the time after discontinuation of anesthetics.

Table 3: Comparison of pain and sedation scores in two groups

Parameter	Low-flow group (n = 18)	Medium-flow group (n = 18)	P value
VAS			
baseline	0 (0-0)	0 (0-0)	1
1 h	5 (0-7)	4 (0-6)	0.459
3 h	4 (0-8)	3 (0-6)	0.640
6 h	3 (0-6)	3 (0-5)	0.606
24 h	2.5 (0-5)	1 (0-6)	0.091
Sedation score (1/2/3)			
baseline	18 / 0 / 0	18 / 0 / 0	1
1 h	3 / 11 / 4	6 / 8 / 4	0.473
3 h	9 / 8 / 1	9 / 8 / 1	1
6 h	13 / 5 / 0	11 / 5 / 2	0.266
24 h	16 / 2 / 0	17 / 1 / 0	0.543

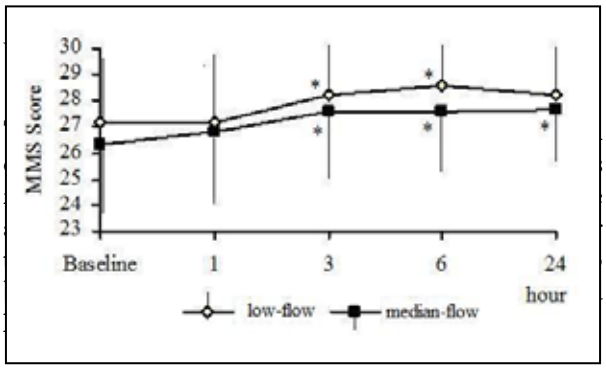

Figure 1: Mini-Mental State score in low-flow and medium-flow groups. Values are mean ± SD. *P < 0.01 vs. baseline values.

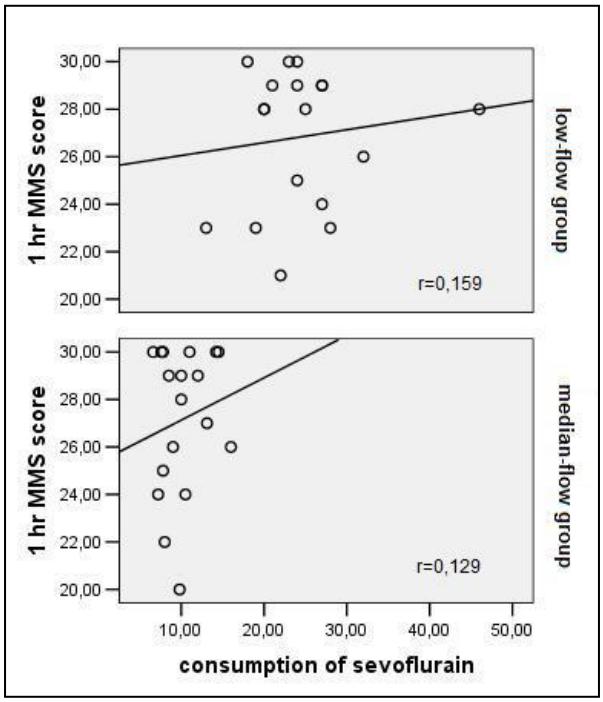

Figure 2: Correlation between consumption of sevoflurane and Mini-Mental State score. Relationship between intraoperative consumption of sevoflurane and Mini-Mental State score at 1 h in patients anesthetized with low flow (r=0.159, p=0.530) or medium flow (r=0.129, p=0.610).

All patients had an uncomplicated course and recovery was uneventful. For instance, no hypoxic inspired gas mixture was seen in any patient and no desaturation was observed. There were no differences between the two groups in respect to postoperative side-effects. The frequency of side-effects such as nausea and vomiting did not significantly differ between the groups. Two patients in the low-flow group and three patients in the medium-flow group had nausea and vomiting in the first 24 h after anesthesia. All patients in our study were discharged from hospital within two days.

DISCUSSION

We found that sevoflurane anesthesia, either low-flow or medium-flow, seemed to have no significant effects on cognitive function or early recovery in patients.

POCD is a condition characterized by impairment of memory and concentration, and its incidence has been reported to be extremely frequent in patients undergoing surgery. Incidence of POCD may change depending on the definition, composition of the test battery, and time of postoperative assessment. The objective has been to detect differences between the situations just prior to and a few days after anesthesia and surgery, or to compare the incidence of POCD after different anesthetic techniques.[7,8] Accordingly, the incidence is reported to be 3.5-45% at 24 h after outpatient surgery.[9,10] The choice of anesthetic drugs can affect postoperative cognition because of residual levels of volatile anesthetics. The mechanism of residual impairment has been proposed as the residual effect of anesthetic drugs on higher brain centres.[11,12] Therefore, the use of anesthetics with a rapid clearance and negligible metabolism may offer advantages.

It has been much more difficult to verify whether POCD exists after surgery, and many patients have probably not been taken seriously when they described a cognitive decline after such surgery, especially if this was a minor procedure. The MMSE can be used in the clinical setting to assess change in cognitive function in the immediate anesthetic period.[4] We used the MMSE because of its high reliability and ease of application and completion. The mini–mental state examination (MMSE) or Folstein test is a brief 30-point questionnaire test that is used to screen for cognitive impairment. It is commonly used in medicine to screen for dementia. It is also used to estimate the severity of cognitive impairment at a specific time and to follow the course of cognitive changes in an individual over time, thus making it an effective way to document an individual's response to treatment. The maximum MMSE score is 30 points, with scores of 23 or less being indicative of cognitive impairment. The test was easy to perform with the patients lying in bed, and took no longer than 10 minutes to complete. The MMSE can be used in the clinical setting to assess changes in cognitive function in the early anesthetic period.[13-14]

Previous studies have looked at different outcome measures of early recovery and cognitive function after general anesthesia with sevoflurane. Few previous studies showed no differences in cognitive function and recovery time between sevoflurane and desflurane[15]; however, most studies have shown desflurane to be better than sevoflurane in this respect in ambulatory patients.[4,16,17] In our study, patients in the two groups did not demonstrate a significant delay in recovery of cognitive function during the first hour after anesthesia administration compared with pre-anesthesia values, with no difference between groups in the MMSE scores. POCD developed in 17% of patients in the low-flow group and in 11% of patients in the medium-flow group 1 h after surgery. MMSE scores increased in both groups at 3 h due to the patients' learning the test. Chen and colleagues[4] used the MMSE and found, only at 1 h after anesthesia, impairment in the test compared with the baseline in patients that received sevoflurane. This disparity between the two studies may be because of the difference in anesthesia duration. In their study the anesthesia time was over 150 minutes while it was less than 90 minutes in ours. Bailey[18] showed that after anesthesia administration of intermediate duration (90 minutes) the 80% decrement time (time needed for an

80% decrease in anesthetic concentration) of sevoflurane is approximately 5 minutes, regardless of the duration of anesthesia. There is very little difference in the 90% decrement times of sevoflurane for the first 90 min of anesthesia, but after that duration the 90% decrement time for sevoflurane begins to increase significantly.

Previous studies show that the consumption of anesthetic is reduced with low-flow anesthesia.[19] Most authors consider low-flow anesthesia as an FGF of about 1 L/min.[20] The concentrations of sevoflurane degradation products increase during anesthesia using a low-flow system,[21] and the potential toxicity of these degradation products has led to questions regarding the safety of sevoflurane administration using a low-flow system.[22] According to our results, cognitive function is not affected by the FGF rate. Low-flow and medium-flow sevoflurane anesthesia is associated with cognitive impairment in three and two patients, respectively, in the postoperative first hour. In our study, early recovery time and MMSE scores were similar in the two groups. In our opinion, the rate of FGF during anesthesia does not affect recovery. Nevertheless, the rate of FGF during wakefulness may affect recovery. We applied 6 L/min FGF during wakefulness in both groups. Therefore, the decrement times of sevoflurane in the groups were similar. There are no data related to the relationship between FGF during wakefulness with recovery and POCD. Therefore it is not possible to make further comments.

Our other finding has important practical consequences as it shows that there was no correlation between the consumption of sevoflurane and MMSE scores, although less sevoflurane was consumed in low-flow anesthesia than in medium-flow anesthesia. This result shows that the POCD is not associated with the consumption of sevoflurane.

Limitations: This study has several limitations, such as the anesthesia time being less than 90 minutes. Cognitive functions and recovery times may vary when applied to long-term anesthesia. Secondly, pediatric patients were excluded from our study so that the results are not interpreted for pediatric patients.

CONCLUSION

In conclusion, sevoflurane anesthesia, either low-flow or medium-flow, seemed to have no significant effect on cognitive function or early recovery in patients undergoing laparoscopic cholecystectomy; however, sevoflurane was less with low-flow than middle-flow anesthesia.

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