

ORIGINAL INVESTIGATION

Comparison of minimal-flow sevoflurane versus desflurane anesthesia: randomized clinical trial



Berna Ayanoglu Taş, Ceren Şanlı Karip, Süheyla Abitağaoğlu *, Mehmet Celal Öztürk, Dilek Erdoğan Arı

University of Health Sciences Fatih Sultan Mehmet Health Research and Application Center, Anesthesiology and Reanimation Department, Istanbul, Turkey

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Abstract

Background and objectives: Minimal-flow anesthesia provides various advantages, such as reduced environmental pollution, proper humidification and warming of anesthetic gases, and reduced costs. The aim of this study was to compare the cost-effectiveness of minimal-flow sevoflurane and desflurane anesthesia and their effects on hemodynamics, postoperative recovery, respiratory parameters, and liver and kidney functions.

Methods: A total of 60 ASA I–II patients aged 18–70 years who underwent posterior spinal instrumentation were included in the study. The patients were divided into Group S (sevoflurane) and Group D (desflurane). After anesthesia induction, the gas flow was initiated at a rate of 4 L.min⁻¹ using a concentration of 8% in Group D and 3.5% in Group S, and the time to reach 0.8 MAC was recorded. The gas flow was then switched to minimal flow. Patient hemodynamic and respiratory parameters, body temperatures and arterial blood gas levels were recorded. The integrated pulmonary index (IPI) was monitored postoperatively. Biochemical findings were recorded 12 hours after the operation. The amount of bleeding and blood transfused, and the costs involved were calculated.

Results: The patients' demographic characteristics, duration of surgery, hemodynamic parameters, IPI values, body temperatures, and arterial blood gas levels were similar at all time points. Biochemical findings, amount of bleeding and amount of blood transfused were similar between the two groups. The mean cost was lower in Group S than in Group D ($p = 0.007$).

Conclusion: The study found no significant difference in terms of reliability between minimal-flow sevoflurane and desflurane anesthesia. Furthermore, the procedure was found to be more cost-effective for Group S than for Group D.

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* Corresponding author.

E-mail: suheylaatay81@gmail.com (S. Abitağaoğlu).

Introduction

Modern anesthesia machines possess advanced rebreathers and gas analyzers. Using an anesthesia system equipped with a rebreather, it is possible to reutilize the gas mixture exhaled by the patient after eliminating the carbon dioxide and ensure a flow of fresh oxygen to meet the metabolic requirements of the body, along with a flow of volatile anesthetics. The low-flow anesthesia developed for this purpose is defined as the administration of at least 50% of exhaled gases to the patient through a rebreather system following the elimination of carbon dioxide.¹

Low-flow anesthesia (1 L.min⁻¹) provides important advantages, such as reduced anesthetic gas consumption, reduced environmental pollution, and proper humidification and warming of anesthetic gases. Moreover, it minimizes the concentration of waste gases and the level of chronic exposure to volatile anesthetics and reduces costs. Minimal-flow anesthesia, which involves decreasing the flow of fresh gas to 500 mL.min⁻¹ (0.5 L.min⁻¹), further increases these advantages.² Owing to their low solubility, sevoflurane and desflurane rapidly attain sufficient alveolar concentration and can be used safely in minimal-flow anesthesia.^{3,4}

The aim of our study was to compare the effect of minimal-flow sevoflurane versus desflurane anesthesia during posterior spinal instrumentation on the patient's hemodynamics, blood gas levels, postoperative recovery, respiratory system, liver and kidney functions, and costs.

Methods

This prospective randomized controlled study was approved by the Ethics Committee of the Fatih Sultan Mehmet Health Application and Research Center (FSM EAH 2016/11) and was conducted according to the ethical principles of the second Helsinki Declaration.

A total of 60 American Society of Anesthesiologists (ASA) physical status I-II patients aged 18–70 years who underwent posterior spinal instrumentation planned between June 2016 and March 2017 for spinal stenosis or spondylolisthesis were included in the study. Informed consent was obtained from all patients. The patients were randomized using the closed envelope method and divided into two groups: Group S (sevoflurane) (n = 30) and Group D (desflurane) (n = 30). The patients were not informed about the group they belonged to. Patients who require surgery under emergency conditions, patients with malignant hyperthermia history, patients addicted to alcohol or other drugs, patients with chronic obstructive pulmonary disease, coronary heart disease, congestive heart failure, or kidney disease and obese patients were excluded from the study.

Routine hemodynamic monitoring together with BIS and body temperature monitoring was performed. Anesthesia was induced with sodium thiopental 5–7 mg.kg⁻¹, fentanyl 2 mcg.kg⁻¹, and rocuronium 0.6 mg.kg⁻¹ to maintain BIS < 60. Invasive arterial monitoring was performed after anesthesia induction to measure arterial blood gas levels at baseline. Prior to the delivery of anesthetic gas, the age and weight of the patients were entered into a Dräger Primus (Lübeck, Germany) device. Gas flow was then initiated at a rate of

4 L.min⁻¹ (40% oxygen + 60% air) using a concentration of 8% in Group D and 3.5% in Group S, and the time to reach 0.8 MAC was recorded. The flow rate was then reduced to 0.5 L.min⁻¹ (40% oxygen + 60% air) to ensure a minimal flow. Group S received 2–4% sevoflurane, and Group D received 5–7% desflurane to maintain BIS values between 40 and 60 to maintain anesthesia. The patients in both groups received fentanyl infusion at a rate of 1 mcg.kg⁻¹.h⁻¹. Then, patients were followed by a second anesthesiologist who was blinded to the study groups was assigned to the patient. During the follow-up patients were ventilated with a tidal volume of 6–8 mL.kg⁻¹ of ideal body weight, which was corrected according to Devine's formula (for male: 50 kg + 2.3 × [(height (cm)/2,54) - 60] and for female: 45.5 kg + 2.3 × [(height (cm)/2,54) - 60]). And the patients were ventilated with a frequency of 12–16 breaths.min⁻¹ to maintain ETCO₂ concentrations at 30–35 mmHg. The lower limit alarm for oxygen was set at 28%. The soda-lime (Intersorb-PlusREF:2179000) was changed when the inspiratory CO₂ was > 1 mmHg after excluding other reasons for an increase in inspiratory CO₂. The hemodynamic and respiratory parameters and body temperatures of the patients were recorded every 5 minutes during the first 20 minutes, then at the 30th minutes and at 30-min intervals. Arterial blood gas levels were recorded at 1 hour and 2 hours after induction. In the case of prolonged surgery, the monitoring of arterial blood gases was continued at 1-h intervals.

Thirty minutes prior to the end of surgery, paracetamol 1 g, tramadol 2 mg.kg⁻¹, and ondansetron 8 mg were administered intravenously, and the infusion of fentanyl was stopped, whereas the administration of anesthetic gases was discontinued 10 minutes before the end of surgery. At the end of surgery, the air flow rate was changed to 4 L.min⁻¹ with 80% oxygen + 20% air. Atropine 0.02 mg.kg⁻¹ and neostigmine 0.05 mg were applied intravenously to reverse of neuromuscular blockage. When the BIS values were > 90, the patients were extubated and moved to the postoperative recovery room. In the recovery room, integrated pulmonary index (IPI) monitoring (Capnostream 20p/Covidien-Origion Medical) was performed to track the adequacy of the patients' respiration, and the IPI values were recorded 1, 5, 10, 20, and 30 minutes after the operation. IPI values between 7 and 10 were considered normal respiration. Postoperative evaluation was performed by the anesthesiologist blinded to the groups. The arterial blood gas levels of the patients were checked at 30 minutes after the operation, and patients with Aldrete scores of nine and above were moved to the regular ward. The amount of intraoperative bleeding and blood transfused were calculated, and ALT, AST, BUN, and creatinine levels were recorded 12 hours after the operation. The amount of anesthetic agent consumed was calculated (anesthetic agent consumption [mL.h⁻¹] = 3 × fresh gas L.min⁻¹ × concentration [%]), and the cost of anesthetic gas was determined accordingly (based on the hospital medication costs for 2017).

Statistical analysis

Power analysis was performed using the Power and Sample Size software according to cost at a flow rate of 0,8 L.min⁻¹ as indicated in a previous study about low-flow anesthesia.⁵

Table 1 Demographic characteristics of the patients.

	Group S (n = 30)	Group D (n = 30)	p
Age (years) <i>Mean±SD</i>	50.57 ± 11.08	49.93 ± 14.53	0.850 ^a
Gender <i>n,%</i>	Male	10 (33.3%)	0.595 ^b
	Female	20 (66.7%)	
BMI <i>Mean±SD</i>	27.79 ± 3.46	28.51 ± 3.96	0.456 ^a
ASA <i>n,%</i>	I	9 (30%)	0.116 ^b
	II	21 (70%)	

^a Student's t-test.^b Yates's Correction for Continuity.**Table 2** Evaluation of operation data and amount of bleeding and blood transfused.

	Group S (n = 30)	Group D (n = 30)	p
Duration of anesthesia (h) <i>Mean±SD</i>	3.44 ± 1.15	3.24 ± 1.08	0.492 ^a
Duration of surgery (h) <i>Mean±SD</i>	3.23 ± 1.15	3.07 ± 1.03	0.574 ^a
MAC 0.8 duration (min) <i>Mean±SD</i>	2.37 ± 1.06	3.55 ± 2.08	0.008 ^{a, b}
Amount of bleeding (mL) <i>Mean±SD</i>	943.33 ± 630.64	991.67 ± 531.44	0.749 ^a
Amount of blood transfused (mL) <i>Mean±SD(median)</i>	245 ± 333.31 (0)	175 ± 238.8 (0)	0.500 ^c

Min, minute.

^a Student's t-test.^b $p < 0.05$.^c Mann-Whitney U Test.**Table 3** Evaluation of HR values in both groups.

HR	Group S (n = 30) Mean ± SD	Group D (n = 30) Mean ± SD	p
Baseline	77.73 ± 17.34	86.07 ± 15.3	0.055
Induction	85.17 ± 14.05 ^a	90.77 ± 17.64	0.179
1st min, 4 lt.min ⁻¹ flow	80.47 ± 10.87	87.2 ± 15.55	0.057
10th min, 4 lt.min ⁻¹ flow	76.77 ± 13.06	86.93 ± 17.45	0.013 ^b
1st min, 0.5 lt.min ⁻¹ flow	74.23 ± 12.49	83.33 ± 15.84	0.016 ^b
20th min, 0.5 lt.min ⁻¹ flow	72.5 ± 11.53	81.63 ± 16.32	0.015 ^b
30th min, 0.5 lt.min ⁻¹ flow	68.53 ± 11.73 ^a	77.5 ± 14.48 ^a	0.011 ^b
60th min, 0.5 lt.min ⁻¹ flow	63.2 ± 8.98 ^a	70.13 ± 13.52 ^a	0.023 ^b
90th min, 0.5 lt.min ⁻¹ flow	61.77 ± 9.57 ^a	68.37 ± 15.11 ^a	0.049 ^b
120th min, 0.5 lt.min ⁻¹ flow	64.14 ± 11.01 ^a	67.35 ± 15.01 ^a	0.367
150th min, 0.5 lt.min ⁻¹ flow	66.05 ± 11.22 ^a	68.83 ± 13.24 ^a	0.453
180th min, 0.5 lt.min ⁻¹ flow	63.21 ± 8.83 ^a	68.68 ± 13.98 ^a	0.159
End of surgery	64,6 ± 12.21 ^a	71.4 ± 14.1 ^a	0.049 ^b
Extubation	79.17 ± 16.3	90.17 ± 17.45	0.014 ^b
Postoperative 5th min	73.33 ± 14.34	85.97 ± 14.62	0.001 ^b

Min, minute.

Student's t-test.

^a Paired samples t-test, $p < 0.05$ when compared to baseline.^b $p < 0.05$.

In this analysis, according to the cost analysis, the values of Δ :1,32 and SD:1,5 were taken for the assessment, and the number of subjects in each group was calculated as 22 with a power of 0.80 and an α of 0.05.

The study data were analyzed using the IBM SPSS Statistics 22 (IBM SPSS, Turkey) software package. The data's fit to a normal distribution was assessed using the Shapiro-Wilk test. In addition to using descriptive statistics (means, stan-

dard deviations, and frequency) when evaluating the study data, quantitative data were compared using Student's *t*-test for the comparison of parameters with a normal distribution, whereas the Mann-Whitney U test was used for the comparison of parameters without normal distribution. Qualitative data were compared using Yates's correction for continuity. Intragroup evaluation of parameters with a normal distribution was performed using the paired samples

t-test, whereas that without a normal distribution was performed using the Wilcoxon signed-rank test. $P < 0.05$ was considered statistically significant.

Results

A total of 60 patients (30 per group, aged 22–70 years) were included in the study. Of these patients, 23 (38.3%) were male and 37 (6.7%) were female. There was no significant difference in the demographic characteristics of the patients between the groups with respect to ASA risk classification (Table 1).

The duration of anesthesia and surgery were similar between the patients. The time needed to reach 0.8 MAC was longer in the desflurane group. There were no differences between the groups in the amount of bleeding and blood transfused (Table 2).

The hemodynamics of the patients were within normal limits during the study. The mean arterial blood pressure (MABP) was similar between groups except for the values for Group S at 60 minutes, which were found to be significantly lower than those in Group D. The baseline heart rates (HR) of the patients were similar. After the first minute of the induction, except the period between 120, 150, and 180 min, the HR values were higher in Group D (Table 3). No significant differences in SpO₂ were observed between the groups.

No active warming methods were used, and no significant difference in body temperature was identified between the groups. Body temperatures were at normothermic levels. A decrease in the body temperature from baseline was observed after 120 minutes in both groups.

Arterial blood gas levels were monitored during surgery and in the recovery room. These values were within the normal physiological range, and there was no difference between the groups. The IPI values monitored in the recovery room were found to be similar between the groups (Table 4).

There were no significant differences between groups in the serum levels of ALT, BUN and creatinine measured in the pre- and postoperative periods and all markers were within normal ranges. In an intragroup analysis, postoperative BUN and creatinine serum levels were lower than preoperative levels in both groups. In Group D, preoperative AST serum levels ($26.2 \pm 22 \text{ U.L}^{-1}$) were higher than Group S ($17.9 \pm 5 \text{ U.L}^{-1}$); but postoperative AST levels were similar between groups ($p = 0.004$ and $p = 0.066$, respectively).

The mean amount of volatile anesthetic used was $14.3 \pm 4.91 \text{ mL/patient}$ in Groups S and $32.57 \pm 13.12 \text{ mL/patient}$ in Group D ($p = 0.001$). In Group S volatile anesthetic cost was $5.13 \pm 1.76 \text{ \$/patient}$ and it was $6.7 \pm 2.27 \text{ \$/patient}$ in Group D ($p = 0.007$).

Discussion

The aim of our study was to compare minimal-flow sevoflurane versus desflurane anesthesia in terms of reliability and cost-effectiveness and their effects on liver and renal functions and postoperative respiration in patients undergoing posterior spinal instrumentation. We found that the two volatile anesthetics shared similar reliability profiles and had similar effects on organ functions, respiratory param-

eters, and blood gas levels. The amount and cost of the volatile anesthetic consumed were higher in the minimal-flow desflurane group.

The increasing use of inhalation anesthetic agents with low solubility for anesthesia has overruled many concerns regarding the use of the low-flow approach and has increased the importance of low-flow applications.^{3,4} More efficient use of resources should not be questioned in a world that faces a dramatic increase in population.⁶ It is important to note that organic anesthetic gases remain in the atmosphere for long periods and can produce a greenhouse effect.⁷⁻⁹ Therefore, it is imperative that we increase the use of minimal-flow anesthesia techniques to reduce the amount of waste inhalation agents generated through the use of the lowest flow of fresh gas possible. However, low-flow anesthesia also has some disadvantages and risks. First, low-flow anesthesia requires modern equipment and monitors and requires close monitoring for hypoxia and hypercapnia. Frequent replacement of soda-lime to prevent carbon monoxide toxicity and compound A increase is essential.³ In the present study, we compared the effects of sevoflurane and desflurane when used in minimal-flow anesthesia.

In addition to its positive effects on lung physiology, minimal-flow anesthesia is also known to maintain body temperature.^{3,4} Although no warming method was used for the patients in our study, body temperatures remained at normothermic levels during the 2-h period, and no significant difference was identified between the groups. Although a decrease in body temperature compared with that at baseline was observed in both groups after 120 minutes, the lowest temperatures were observed at the time of extubation, which were $35.95 \pm 0.73 \text{ }^\circ\text{C}$ in Group S and $34.79 \pm 5.98 \text{ }^\circ\text{C}$ in Group D, and the difference between the groups was not significant.

High fresh gas flow is required during the induction and cessation of anesthesia because it requires a longer time to attain the desired concentrations in minimal-flow anesthesia. Minimal alveolar concentrations are known to reflect the anesthetic potential of the anesthetic agent in a state of equilibrium. A previous study compared 18% desflurane and 6% sevoflurane with a fresh gas flow of either 0.5 L.min^{-1} or 1.0 L.min^{-1} and demonstrated that the time required to reach 1 MAC was $8.5 \pm 1.7 \text{ min}$ with desflurane at 0.5 L.min^{-1} , $3.7 \pm 0.7 \text{ min}$ with desflurane at 1.0 L.min^{-1} , $15.2 \pm 2.4 \text{ min}$ with sevoflurane at 0.5 L.min^{-1} and $6.2 \pm 1.3 \text{ min}$ with sevoflurane at 1.0 L.min^{-1} . The study thus showed that 18% desflurane reached 1 MAC within a shorter period at both gas flow levels.¹⁰ We monitored the depth of anesthesia in our study using the BIS and the time to reach 0.8 MAC was $3.56 \pm 2.1 \text{ min}$ in Group D and $2.38 \pm 1.06 \text{ min}$ in Group S. The main reason for the different values observed in our study is the higher flow and lower concentrations of inhalation agents delivered at the start of the surgery. As indicated in previous studies, the time to reach the desired MAC depends on the rate of fresh gas flow and the concentrations of inhalation agents.

In an earlier study, it was reported that no significant increases in COHb levels under closed circuit anesthesia without carbon monoxide (CO) elimination during laparoscopic surgery and constant renewal of intraperitoneal gas in adult patients prevented CO intoxication during electro-

Table 4 Evaluation of IPI levels in both groups.

IPI	Group S (n = 30) Mean ± SD (median)	Group D (n = 30) Mean ± SD (median)	p
Recovery 1 st min	8.5 ± 1.46 (8.5)	8.17 ± 2.57 (10)	0.691
Recovery 5 th min	8.93 ± 1.51 (10)	8.73 ± 1.91 (9.5)	0.728
Recovery 10 th min	9.3 ± 1.09 (10) ^a	8.73 ± 1.53 (9)	0.083
Recovery 20 th min	9.37 ± 1.35 (10) ^a	8.77 ± 1.5 (9.5)	0.055
Recovery 30 th min	9.2 ± 1.24 (10) ^a	8.93 ± 1.48 (10) ^a	0.465

Min, minute.

Mann–Whitney U test.

^a Wilcoxon signed-rank test, $p < 0.05$ when compared to baseline.

cautery use.¹¹ In a previous study on laparoscopic surgeries lasting for > 6 hours, the authors reported that COHb levels remained within normal physiological limits.² In our study, COHb and other blood gas levels were also within normal physiological limits, which was consistent with previous studies.^{12,13}

Assessments of the respiratory functions of patients are frequently based on measurements of peripheral oxygen saturation (SpO₂), end-tidal carbon dioxide (ETCO₂), respiratory rate (RR), and heart rate (HR). Integrated pulmonary index (IPI) monitorization can offer a single value for easy evaluation of ventilation and oxygenation. This method combines the SpO₂, ETCO₂, RR and HR values in a mathematical model to obtain the IPI.^{14,15} The IPI value was considered a useful marker in a clinical setting.¹⁶ In our study, we used the IPI monitor to assess respiratory sufficiency during the postoperative period. Previous studies on low-flow anesthesia evaluated respiratory parameters and heart rate separately during postoperative recovery. A combined evaluation of these parameters provides effective and rapid monitoring of the respiratory situation of the patient. To the best of our knowledge, there are no studies in the literature using IPI monitoring after low-flow anesthesia. In all follow-ups involving IPI assessment, the IPI values of both groups remained similar and within normal limits at all time points. It was therefore concluded that minimal-flow sevoflurane and desflurane anesthesia had no negative effects on respiration during the postoperative period and had similar effects on respiratory recovery.

It has been demonstrated that isoflurane, desflurane and sevoflurane do not cause any negative effects on the kidneys and liver during low-flow anesthesia applications.¹³ Another study comparing low-flow anesthesia with total intravenous anesthesia reported no significant difference in terms of renal and hepatic toxicity.¹⁷ Previously, it was shown that liver and kidney functions remained within normal limits following more than 8 hours of minimal-flow sevoflurane anesthesia and that there were no significant differences in liver and kidney function tests compared with those at baseline.¹⁸ Our study also demonstrated similar limited effects of minimal-flow desflurane and sevoflurane anesthesia on postoperative liver and kidney functions. Although within normal ranges, preoperative serum levels of AST were different between groups; this imbalance between groups may be related to the small sample size and limitations in the randomization and enrollment processes. It was reported that perioperative changes in renal function

are not associated with the anesthetic method used and that these changes might instead be caused by factors unrelated to anesthesia, such as the duration of surgery, the size and extent of the surgical site and the resulting stress, the antibiotic agents administered, pre-existing renal dysfunction and changes in perioperative arterial pressure.¹⁹ The two inhalation agents may have similar effects on renal functions, as the present study included patients undergoing a single type of surgery with a similar surgical time and the blood pressures of these patients remained within normal limits during follow-up. We concluded that postoperative decreases in BUN and creatinine levels were associated with perioperative hydration and were of no clinical significance.

One of the strengths of minimal-flow anesthesia is the ecological and economic advantage it provides by reducing anesthetic agent consumption by 75–80%. While the cost-savings from the use of minimal- and low-flow anesthesia is not notable for 1-h periods, minimal-flow anesthesia for 2-h periods is reported to provide greater cost-savings.²⁰ In a previous study, it was reported that the use of BIS monitoring could reduce the use of inhalation agents such as desflurane.²¹ During general anesthesia, one of the advantages of BIS monitoring is the prevention of the use of excessive doses of agents due to concerns of superficial anesthesia.²² In light of this evidence, in our study, we followed the depth of anesthesia with BIS monitoring.

In a study comparing the use of low-flow desflurane versus isoflurane anesthesia, the consumption of anesthetics and the costs incurred were found to be higher in the desflurane group.²³ In the mentioned study the cost of desflurane consumption for 180 minutes was reported to be 6.42 € for 0.5 L.min⁻¹ flow, which was similar to our results. In a review article, it was indicated that inhalation anesthesia with sevoflurane is the most cost-effective agent when compared with the other agents used for similar flow rates.²⁴ In our study, we maintained the BIS values at 40–60%, and the amount of inhalation agents used was lower in Group S. The costs incurred according to the market prices at the time of the study were significantly lower in Group S than in Group D.

There are some limitations in our study. First, cost analysis was performed according to volatile anesthetic consumption, and the length of hospital stay was not included in the cost analysis. It may be more accurate to take into account all in-hospital expenditures to assess the cost in detail. Further studies considering the recovery time and duration of surgery in the cost analysis must be performed

because these parameters also affect total costs. Another limitation of our study is that we cannot provide active warming to our study patients because we do not have active warming devices.

In conclusion, the present study reports no significant difference between minimal-flow sevoflurane and desflurane anesthesia in terms of hemodynamics, organ function and blood gas levels in patients undergoing posterior spinal instrumentation. The IPI parameters in the postoperative period were similar, indicating that both agents have similar effects on postoperative respiratory function. The amount and cost of the volatile anesthetic consumed were higher in the desflurane group.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Erbay RH, Tomatır E, Hancı V, et al. Desfluran-N2O, Sevofluran-N2O Minimal Akım ve Propofol-Remifentanil Anestezilerinde Maliyetlerin Karşılaştırılması. *Türkiye Klinikleri J Anest Reanim.* 2009;7:11–8.
2. Park SY, Chung CJ, Jang JH, et al. The safety and efficacy of minimal-flow desflurane anesthesia during prolonged laparoscopic surgery. *Korean J Anesthesiol.* 2012;63:498–503.
3. Hönemann C, Hagemann O, Doll D. Inhalational anaesthesia with low fresh gas flow. *Indian J Anesthesiol.* 2013;57:345–50.
4. Nunn G. Low-flow anaesthesia. Continuing education in anaesthesia. *Crit Care Pain.* 2008;8:1–4.
5. Martelli A. Costs optimization in anaesthesia. *Acta Biomed.* 2015;86:38–44.
6. Okur O, Tekgöl ZT, Yeniay O, et al. Effect of low flow anesthesia education on short term anesthetic gas consumption. *Tepecik Eđit. ve Arařt. Hast. Dergisi.* 2016;26:146–50.
7. Langbein T, Sonntag H, Trapp D, et al. Volatile anaesthetics and the atmosphere: atmospheric lifetimes and atmospheric effects of halothane, enflurane, isoflurane, desflurane and sevoflurane. *Br J Anaesth.* 1999;82:66–73.
8. Oyaro N, Sellevag SR, Nielsen CJ. Atmospheric chemistry of hydrofluoroethers: reaction of a series of hydrofluoroethers with OH radicals and Cl atoms, atmospheric lifetimes, and global warming potentials. *J Phys Chem A.* 2005;109:337–46.
9. Ryan SM, Nielsen CJ. Global warming potential of inhaled anesthetics: application to clinical use. *Anesth Analg.* 2010;111:92–8.
10. Horwitz M, Jakobsson JG. Desflurane and sevoflurane use during low- and minimal-flow anesthesia at fixed vaporizer settings. *Minerva Anesthesiol.* 2016;82:180–5.
11. Soro M, García-Pérez ML, Ferrandis R, et al. Closed-system anaesthesia for laparoscopic surgery: is there a risk for carbon-monoxide intoxication? *Eur J Anaesthesiol.* 2004;21:483–8.
12. Ceylan A, Kırdemir P, Kabalak A, et al. Düşük Akım Desfluran ve Sevofluran Anestezisinde Karboksihemoglobin, Hemodinami ve Uyanma Kriterlerinin Karşılaştırılması. *Gulhane Med J.* 2004;46:291–7.
13. Yıldırım A, Göksu H, Toprak GÇ, et al. İzofluran, Desfluran ve Sevofluran ile Uygulanan Düşük Akımlı Anestezinin, Anestezi Kalitesi ve Güvenilirliğinin Karşılaştırılması. *Fırat Tıp Dergisi.* 2006;3:170–4.
14. Arora S, Singh PM, Goudra BG, et al. Changing trends of hemodynamic monitoring in ICU – from invasive to non-invasive methods: are we there yet? *Int J Crit Illn Inj Sci.* 2014;4:168–77.
15. Small heer BA. Technology and monitoring patients at the bedside. *Nurs Clin North Am.* 2015;50:257–68.
16. Schier R, Roozkrans M, Velzen M, et al. Opioid-induced respiratory depression: reversal by non-opioid drugs. *F1000 Prime Rep.* 2014;6:1–8.
17. Sahin SH, Cinar SO, Paksoy I, et al. Comparison between low flow sevoflurane anesthesia and total intravenous anesthesia during intermediate-duration surgery: effects on renal and hepatic toxicity. *Hippokratia.* 2011;15:69–74.
18. Choi S, Cho W, Chin Y, et al. The effects of prolonged minimal-flow sevoflurane anesthesia on postoperative hepatic and renal function. *Kor J Anesthesiol.* 2008;54:501–6.
19. Ebert TJ, Arain SR. Renal responses to low-flow desflurane, sevoflurane, and propofol in patients. *Anesthesiology.* 2000;93:1401–6.
20. Bozkurt P. Klinik uygulamada düşük akımlı anestezi. (Çeviri Editörü E Tomatır). *Düşük Akımlı Anestezi – Düşük Akımlı, Minimal Akımlı ve Kapalı Sistemle Anestezide Kuram ve Uygulama.* 1. baskı İstanbul: Nobel zTıp Kitapevleri; 2002. p. 250–3.
21. Akkaya T, Arık E, Gümüş H, et al. Comparison of desflurane and isoflurane anesthesia with bispectral index monotorization. *Türkiye Klinikleri J Anest Reanim.* 2007;5:69–78.
22. Rosow C, Manberg PJ. Bispectral index monitoring. *Anesth Clin North Am.* 2001;19:947–66.
23. Buchinger H, Kreuer S, Paxian M, et al. Desflurane and isoflurane in minimal-flow anesthesia. Consumption and costs with forced fresh gas reduction. *Anaesthesist.* 2006;55:854–60.
24. Naço M, Çeliku E, Gani H, et al. The calculated economic cost of inhalator volatile anesthetics in low flow anesthesia. *AJMHS.* 2019;51. Online publication ahead of print.