




SCIENTIFIC ARTICLE

Short term olfactory memory and olfactory function after inhalation anesthetic agents: a randomized clinical trial



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KEYWORDS

Olfactory memory;
Inhalation anesthesia;
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Abstract

Background and objectives: This clinical trial aimed to evaluate the effects of two different inhalation anesthetic agents on postoperative olfactory memory and olfactory function in patients who underwent micro laryngeal surgery.

Methods: This randomized prospective controlled study consisted of 102 consecutive patients with a voice disorder. The patients underwent micro laryngeal surgery for voice disorders under general anesthesia. Patients who did not meet inclusion criteria and/or declined to participate ($n = 34$) were excluded from the study. Patients were divided into two groups. Four patients from Group 1 and four patients from Group 2 were lost to follow-up. Group 1 ($n = 30$) received sevoflurane, and Group 2 ($n = 30$) received desflurane during anesthesia. We compared the results by performing the pre-op and post-op Connecticut Chemosensory Clinical Research Center Olfactory test.

Results: Thirty-three patients (55%) were male and 27 (45%) were female. The mean age was 48.18 ± 13.88 years (range: 19–70 years). Preoperative and postoperative olfactory functions did not show a significant difference within the groups postoperatively ($p > 0.05$). Preoperative and postoperative olfactory memory showed a significant decrease 3 hours after the surgery ($p < 0.05$).

Conclusions: Olfactory functions and memory were not affected by desflurane in the early postoperative period. Although sevoflurane did not affect olfactory functions, it had a temporary negative effect on olfactory memory in the early postoperative period.

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PALAVRAS CHAVE

Memória olfativa;
Anestesia inalatória;
Desflurano;
Sevoflurano

Memória olfativa de curta duração e função olfativa após anestésicos inalatórios: estudo clínico randomizado**Resumo**

Introdução e objetivos: O estudo avaliou o efeito pós-operatório de dois agentes anestésicos inalatórios distinto na memória olfativa de curta duração e na função olfativa em pacientes submetidos à microcirurgia de laringe.

Método: O estudo prospectivo controlado randomizado avaliou, consecutivamente, 102 pacientes com alteração vocal submetidos à microcirurgia de laringe sob anestesia geral. Trinta e quatro pacientes não obedeceram aos critérios de inclusão e/ou não aceitaram participar do estudo e foram excluídos. Os pacientes foram divididos em dois grupos. Quatro pacientes do Grupo 1 e quatro do Grupo 2 foram perdidos durante o seguimento. O Grupo 1 (n = 30) recebeu sevoflurano e o Grupo 2 (n = 30) desflurano durante a anestesia. Comparamos resultados pré e pós-operatórios de memória olfativa e funções olfativas, realizando o Connecticut Chemosensory Clinical Research Center Olfactory test.

Resultados: Foram incluídos um total de 33 (55%) homens e 27 (45% mulheres. A idade média foi $48,18 \pm 13,88$ anos variação: 19–70 anos). As funções olfativas pré e pós-operatórias não apresentaram diferença estatisticamente significativa dentro dos grupos no pós-operatório ($p > 0,05$). A memória olfativa pré e pós-operatória não mostrou diminuição estatisticamente significativa quando avaliada três horas após a cirurgia ($p < 0,05$).

Conclusões: Memória e funções olfativas não foram alteradas pelo desflurano no pós-operatório imediato. Embora o sevoflurano não tenha alterado as funções olfativas, causou efeito temporário negativo na memória olfativa no pós-operatório imediato.

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Introduction

Olfactory dysfunction occurs in approximately 5% of the general population.^{1,2} It has been reported that patients with smelling disorders have also serious problems regarding safety, eating, and personal hygiene.³ Olfactory disorders are frequently seen in the general population, and they have a negative effect on the patients' quality of life.⁴ The main causes of olfactory disorders are upper respiratory infections, systemic disorders, nasal disorders (e.g. sinusitis, nasal polyps), head trauma, neurodegenerative diseases and medical drugs.⁵

Olfactory memory is a crucial cerebral function in mammals. Its purposes include defense, reproduction, foraging, and infant-mother bonding.⁶ Postoperative cognitive dysfunction is a clinically recognized phenomenon following surgery; it is related to problems in daily performance and improved morbidity and mortality.⁷ General anesthesia causes a reversible decrease in short-term memory, which is quickly resolved following the cessation of anesthetic drug action.⁸

Inhalational anesthetics are commonly used for all types of surgical procedures. Anesthetic drugs have been blamed for postoperative olfactory dysfunction, but they have not been shown to cause hyposmia or anosmia.¹ There have been several scientific studies about the negative effects of anesthetic drugs on olfactory function in animals.⁹ However, the effect of inhalational anesthetics on early postoperative olfactory functions has not been properly explored.

The aim of this study was to examine the effects of two different inhalational anesthetics on post-operative

olfactory memory and olfactory function in patients who had undergone microlaryngeal surgery.

Methods

This study was carried out at a tertiary hospital on 102 patients who had undergone microlaryngeal surgery with a voice disorder diagnosis. All study protocols and informed consent forms were approved and collected by the institutional review board. The data retrieved from the medical records included patient age, sex and presenting complaints.

Patients who had benign vocal lesions were accepted for the study. Exclusion criteria included nasal septal deviation, previous nasal surgery, tonsillectomy, nasal polyposis, preexisting sinus disease, nasal allergies, preexisting subjective olfactory disturbance such as intranasal drug abusers, systemic diseases such as diabetes mellitus, rheumatologic disorders and oncological diseases. The patients who did not meet the inclusion criteria and/or declined to participate (n = 34) were excluded from this study. A randomization program generated a random allocation sequence.¹⁰ Patients were divided into two groups. Four patients from Group 1 and four patients from Group 2 were lost during the follow-up. Group 1 (n = 30) received sevoflurane agent, and Group 2 (n = 30) received desflurane agent during the anesthesia. An assistant doctor who was blinded to the study enrolled the data of the participants.

The patients underwent microlaryngeal surgery for their voice disorders under general anesthesia. All patients had a

complete ear nose and throat examination. The day before the operation, a flexible nasopharyngoscope and stroboscope were used to evaluate their vocal cord lesions and nasal pathologies. In addition, the patients who decided on surgery received a preoperative evaluation at the anesthesia clinic.

Anesthesia procedure

All patients underwent surgery under general anesthesia with endotracheal intubation. Patients without any premedication were taken into the operation room and demographic data was recorded. Standard electrocardiography, peripheral oxygen saturation, and non-invasive blood pressure monitoring were performed. After peripheral venous cannulation, anesthesia induction was achieved with 2 $\mu\text{g}\cdot\text{kg}^{-1}$ fentanyl, 2 $\text{mg}\cdot\text{kg}^{-1}$ propofol, and 0.6 $\text{mg}\cdot\text{kg}^{-1}$ rocuronium via endotracheal intubation, and intermittent positive pressure ventilation was initiated. The tidal volume was set to 8 $\text{ml}\cdot\text{kg}^{-1}$, and the frequency was set to be end-tidal carbon dioxide 35 ± 5 mmHg. Anesthesia was performed by giving sevoflurane to the first group and desflurane to the second group. The doses of inhaled anesthetic agents were adjusted to achieve 1 MAC end tidal reading of the agent (e.g. 2% for sevoflurane and 6% for desflurane). It was continued with a 40% O_2 /air mixture and 0.15–0.25 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ remifentanyl infusion. All cases were treated with paracetamol 10 $\text{mg}\cdot\text{kg}^{-1}$ and 1 $\text{mg}\cdot\text{kg}^{-1}$ tramadol hydrochloric acid intravenously for postoperative analgesia about 15 minutes before the end of the operation. Finally, a muscle relaxant effect was antagonized with 0.04 $\text{mg}\cdot\text{kg}^{-1}$ neostigmine and 0.02 $\text{mg}\cdot\text{kg}^{-1}$ atropine. Vasoconstrictor agents were not applied to the surgical area. Cases with adequate muscle strength were transported to the postoperative collection unit by the standard procedure, and the intubation was done when the modified Aldrete score was 9 or greater. All the surgeries lasted between 40–60 minutes. There was no side effect and complication related to anesthetic agents on patients.

Olfactory functions were assessed preoperatively and postoperatively using the Connecticut Chemosensory Clinical Research Center (CCCRC) smell test. The CCCRC test includes a butanol threshold test for olfactory function and a smell identification test for olfactory memory. A special diet program was not applied to all patients.

Olfactory memory test

The CCCRC test was conducted in an odorless room under standard conditions using a commercially available smell-test kit. For both parts of the test, each nostril was tested separately by having the subject occlude the opposite nostril. There were seven olfactory stimuli (baby powder, chocolate, cinnamon, coffee, mothballs, peanut butter and soap) and one stimulus (Vicks VapoRub, Eczacıbaşı Drug Company, Turkey) used to test trigeminal nerve sensory function. The capability to sense Vicks shows intact trigeminal nerve function. It was recognized by all subjects and was not involved in the final score. Olfactory tests were conducted individually and were scored out of 7 (0: worst olfaction, 7: best olfaction).

Olfactory function test

For every trial, two glass bottles were presented to the patient. One of them contained water and the other a dilute concentration of butanol. The bottles were identical in appearance and were presented simultaneously. Subjects were asked to keep one nostril obstructed while sniffing the bottle with their other nostril. Patients were asked if there was anything other than water in the bottles. If their selection was wrong, a stronger concentration of butanol was given alongside the bottle containing only water. If the subject correctly identified the same butanol concentration five times back to back, the score was documented for that nostril. The other nostril was then tested separately, and the scores for both nostrils were averaged to get to the final score. The strongest butanol concentration (bottle 0) was 4% butanol in deionized water. Each following dilution (bottles 1–9) was a 1:3 dilution with deionized water. Possible scores ranged from 0 to 9, but all scores 7 and greater were scored as 7 by the CCCRC test.^{11,12}

For the evaluation of olfactory memory and function, the CCCRC olfactory test scores measured the day before the surgery were considered as a baseline and compared with the scores 3 hours and 5 weeks after surgery.

Data analysis

Statistical analysis of the data were conducted using IBM SPSS Statistics 22 (IBM SPSS, Turkey). The data were analyzed using descriptive statistical methods (mean and standard deviation), and the Shapiro Wilks test was used to assess the normal distribution of the parameters. Student's *t*-test was used for the comparison of quantitative data showing the parameters of the normal distribution, and Chi-squared test was used for the comparison of the qualitative data. Repeated ANOVA tests were used to compare parametric dependent groups. Mauchly's sphericity test was used to evaluate the assumption of sphericity for the repeated data and "sphericity assumed" *p*-value was reported. Post-Hoc Bonferroni correction test was used to compare the differences. Results were evaluated using the 95% Confidence Intervals (CI), and the level of significance was set at *p* < 0.05.

Results

The study group comprised 60 consecutive patients. Thirty-three of them (55%) were male and 27 (45%) were female. The mean age was 48.18 ± 13.88 years (range: 19–70 years). No significant difference was observed regarding age and gender between groups (*p* = 0.162; *p* = 0.795); (Tables 1 and 2).

Preoperative and postoperative olfactory functions were compared between and within the groups. Neither Group 1 nor Group 2 showed a significant difference within the group postoperatively (*p* = 0.508; *p* = 0.715). Postoperative three hours and first week measurements did not show any difference between the groups (*p* = 0.494; *p* = 0.431); (Table 3).

Preoperative and postoperative olfactory memory was compared between and within the groups. There was a sig-

Table 1 Descriptive statistics of age and sex between the groups.

Total (n = 60)		Group 1 (Sevoflurane) (n = 30)	Group 2 (Desflurane) (n = 30)	<i>p</i>	
Age	Min–Max (Median)	19–70 (50)	19–70 (54)	19–70 (47)	t: –1.416
	Mean ± Sd	48.18 ± 13.88	50.70 ± 14.15	45.66 ± 13.36	0.162 ^a
Gender	Female	27 (45.0)	13 (43.3)	14 (46.7)	χ ² : 0.067
	Male	33 (55.0)	17 (56.7)	16 (53.3)	0.795 ^b

^a Student *t*-Test.^b Chi-Square Test.**Table 2** Descriptive statistics of age by sex.

Sex	Age	
	Min–Max	Mean ± SD/%
Female	16–65	47.35 ± 12.66
Male	19–70	48.51 ± 14.47

nificant difference among the results of Group 1 ($p = 0.019$). A post-hoc Bonferonni was used to compare the differences. There was a significant decrease three hours after the operation (0.001). However, there was no difference between preoperative and first week results ($p > 0.05$). Group 2 did not show significant differences within the group postoperatively ($p = 0.804$). Postoperative three hours and first week measurements did not show any difference between the groups ($p = 0.943$; $p = 0.967$); (Table 4).

Discussion

Olfactory memory is important for the maintenance of daily physiological functions and contributes greatly to the quality of life.¹³ In this study, we investigated the effects of desflurane and sevoflurane on early postoperative olfactory memory and olfactory function in patients who underwent microlaryngeal surgery under general anesthesia.

Olfactory impulses are detected in the olfactory region of the nose. Smell molecules dissolve in the mucus on the

olfactory epithelium and connect with olfactory receptor cells. In this way, chemical information from the smell molecules causes an action potential in smell receptor cells. These impulses are then carried to the bulbus olfactorius in the brain. After that, they are carried via the tractus olfactorius and stria olfactorius to the olfactory cortex.¹⁴ Olfactory memory is found in the piriform cortex, the amygdala and entorhinal cortex.¹⁵ Smell is the only one of the five senses that is carried directly into the cortical regions of the brain without passing through the thalamus.¹⁶ The related neurotransmission systems (adrenergic and gamma-aminobutyric acid) are known targets of anesthetic drugs.¹⁷

Volatile anesthetic agents are commonly used in anesthesia and are generally well-tolerated by patients without systemic diseases, but very rarely unplanned complications can be seen. Sevoflurane, isoflurane and desflurane now constitute the fundamental halogenated volatile anesthetics used in developed countries.¹⁸ Post-anesthesia anosmia cases have been little reported in the literature. Konstantinidis et al. reported the presence of anosmia in a 60 year-old female patient who had undergone urological surgery.¹⁹ The patient was given general anesthesia using fentanyl, propofol and sevoflurane; it was thought that the development of anosmia might originate from the direct effect of sevoflurane on the olfactory epithelium with resultant peripheral-type olfactory dysfunction.^{19,20} Various scientific studies have indicated that among general anesthetic drugs, fentanyl and propofol depressed olfactory

Table 3 Comparison of the preoperative and postoperative olfactory function (butanol threshold test) between groups and within groups.

Olfactory function (Butanol Threshold Test)	¹ Preop	² Postop 3 rd hour	³ Postop 1 week	First-last change	Post-hoc Bonferroni test
	Mean ± SD (CI 95%)	Mean ± SD (CI 95%)	Mean ± SD (CI 95%)	<i>p</i> ^b	<i>p</i> ^c
Group 1 (Sevoflurane)	8.30 ± 2.95 (7.9–9.40)	8.20 ± 2.76 (7.17–9.23)	8.10 ± 2.56 (7.15–9.05)	0.508	1–2 <i>p</i> :1.000 1–3 <i>p</i> :1.000 2–3 <i>p</i> :1.000
Group 2 (Desflurane)	8.33 ± 2.90 (7.75–9.92)	8.7 ± 2.87 (7.63–9.77)	8.63 ± 2.66 (7.64–9.63)	0.715	1–2 <i>p</i> :1.000 1–3 <i>p</i> :1.000 2–3 <i>p</i> :1.000
<i>p</i> ^a	0.483	0.494	0.431		

^a Student *t*-test.^b Repeated Measures ANOVA test.^c Adjustment for multiple comparisons: Bonferroni test $p < 0.05$.

Table 4 Comparison of the preoperative and postoperative olfactory memory (identification test) between groups and within groups.

Olfactory memory (Identification Test)	¹ Preop	² Postop 3 ^d hour	³ Postop 1 week	First-last change	Post-hoc Bonferroni test
	Mean ± SD (95% CI)	Mean ± SD (95% CI)	Mean ± SD (95% CI)	<i>p</i> ^b	<i>p</i> ^c
Group 1 (Sevoflurane)	7.70 ± 3.44 (6.41–8.98)	6.57 ± 1.25 (6.10–7.03)	7.57 ± 2.98 (6.45–8.67)	0.019*	1–2 <i>p</i> :0.001 1–3 <i>p</i> :1.000 2–3 <i>p</i> :0.129
Group 2 (Desflurane)	7.37 ± 3.37 (6.10–8.562)	7.63 ± 3.53 (6.31–8.95)	7.53 ± 3.19 (6.34–8.72)	0.804	1–2 <i>p</i> :1.000 1–3 <i>p</i> :1.000 2–3 <i>p</i> :1.000
<i>p</i> ^a	0.706	0.943	0.967		

^a Student *t*-test.

^b Repeated Measures ANOVA test.

^c Adjustment for multiple comparisons: Bonferroni test **p* < 0.05.

response.⁷ However, in our study we did not encounter anosmia in the postoperative period.

In the literature, limited data can be found regarding the effect of anesthetic agents and methods on olfactory memory. Several studies have shown that the popular inhalational anesthetic isoflurane may cause neurotoxicity connected with cognitive dysfunction or learning/memory impairment. Meanwhile, desflurane, another popular inhalational anesthetic, does not have these kinds of effects. On the other hand, one clinical study indicated that general anesthesia with isoflurane 1.2% has no significant effect on olfactory memory.²¹

Another study with sevoflurane performed by Kostopaniotou et al. demonstrated that sevoflurane impaired post-operative olfactory memory but olfactory function was preserved.⁸ The University of Pennsylvania Smell Identification Test (UPSIT) was used in their study within the first three hours after surgery. A CCCR test was used in our study, and two different anesthetic agents were studied. In addition to their measurement, the results after the first postoperative week were also considered. Our study showed that the negative effect of sevoflurane on olfactory memory was completely resolved by the end of the first week.

Yildiz et al. analyzed the effect of desflurane 6% on postoperative olfactory memory by Brief-Smell Identification Test TM (B-SIT).²² They found that desflurane had no effect on short-term olfactory memory. This is similar to our results regarding desflurane. In addition to their results, we added first-week data to our study and found no difference.

Michael et al. evaluated the effects of five inhalational anesthetics on the learning capabilities and memory of rats.²³ They found that larger doses of sevoflurane, halothane, and desflurane had negative effects on learning, while 0.44% desflurane had significant adverse effects on memory. Callaway et al. studied the effects of desflurane anesthesia in rats. They demonstrated that the effects of desflurane on learning and memory were age and dose-dependent.²⁴ Those studies were performed with varying dosages on animals, but our study was performed with standard therapeutic doses on human patients. Minimum

alveolar concentration was kept over 1 in our study by using sevoflurane concentration of 2% and desflurane of 6%.

The limitations of our research can be listed as a deficiency in our patient population and a lack of investigation of different doses of desflurane and sevoflurane over longer periods to determine their long-term postoperative effects.

Conclusion

Olfactory function and memory were not affected by desflurane in the early postoperative period. Although sevoflurane did not affect the olfactory functions, it had a temporary negative effect on olfactory memory in the early postoperative period. In order to make more reliable comments, further studies with larger cohorts are required.

Conflicts of interest

The authors declare no conflicts of interest.

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