Cukurova Medical Journal
ÇUKUROVA ÜNİVERSİTESİ TIP FAKÜLTESİ

Cukurova Med J 2023;48(1):11-19
DOI: 10.17826/cumj.1133058

RESEARCH

Comparison of the effects of TIVA and inhalation anesthetic techniques on olfactory functions and olfactory memory: a randomized prospective study

TİVA ile inhalasyon anestezi yöntemlerinin koku fonksiyonlarına ve koku hafızası üzerine etkisinin karşılaştırılması: randomize prospektif bir çalışma

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Abstract

Purpose: This study aimed to investigate the effects of different general anesthesia procedures on postoperative olfactory functions and olfactory memory.

Materials and Methods: This prospective study was conducted with 97 patients. Patients were divided into three groups based on anesthesia induction and maintenance technique: Group P (induction and maintenance with propofol), Group PS (induction with propofol, maintenance with sevoflurane), and Group S (induction with sevoflurane, maintenance with sevoflurane). Butanol threshold and olfactory identification tests were administered 30 minutes (min) before the operation (T_1) and 30 min (T_2), 8 hours (h) (T_3) and 24 h (T_4) after the operation.

Results: Butanol threshold values were increased at the T_2 time point compared to baseline in all groups, which returned to baseline values at T_3 only in Group P. There was a significant difference between Group P and Group S in terms of butanol threshold values at all time points except T_1. When olfactory identification increased at T_3 and T_4 compared to baseline in Group P, there was a significant difference between T_2, T_3, and T_4 time points in Group S, and between T_2 and T_3 time points in Group PS as compared to Group P.

Conclusion: Propofol only causes a temporary impairment in olfactory functions in the early period and does not alter olfactory memory.

Keywords:. Olfactory functions, propofol, sevoflurane, olfactory memory

Öz

Amaç: Bu çalışmada, farklı genel anestezi uygulamalarının postoperatif koku fonksiyonları ve koku hafızası üzerine olan etkilerinin araştırılması amaçlanmıştır.

Gereç ve Yöntem: Bu çalışma prospektif olarak 97 hasta ile yapıldı. Hastalar anestezi indüksiyonu ve idame yöntemine göre üç gruba ayrıldı; Grup P (propofol ile indüksiyon ve idame), Grup PS (propofol ile indüksiyon, sevofluran ile idame), Grup S (sevofluran ile indüksiyon ve idame). Butanol eşik ve koku identifikasyon testleri ameliyattan 30 dakika (dk) önce (bazal=T_1), ameliyattan 30 dk (T_2), 8 saat (s) (T_3) ve 24 s sonra (T_4) uygulandı.

Bulgular: Tüm gruplarda butanol eşik testi değerlerinin bazale göre T_2 zamanında arttığı ve bu artışın sadece Grup P'de T_3'te bazale döndüğü gözlendi. Butanol eşik testi değerleri açısından Grup P ile Grup S arasında, T_1 hariç tüm zamanlarda anlamlı farklılık saptandı. Koku identifikasyonunun Grup P'de bazale göre T_3 ve T_4'de arttığı, Grup P ile karşılaştırıldığında ise; Grup S'de T_2, T_3 ve T_4, Grup PS'de ise T_2 ve T_3 arasında anlamlı farklılık olduğu gözlendi.

Sonuç: Propofolün sadece erken dönemde koku fonksiyonlarında geçici bir bozukluğa sebep olur.

Anahtar kelimeler: Koku işlevi, propofol, sevofluran, koku hafızası

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Received: 20.06.2022 Accepted: 22.12.2022

INTRODUCTION

Olfactory system mediates many vital functions from safety and survival to reproductive functions and affects the quality of life[1]. Olfactory disorders are common and affect about one-fifth of the general population, with most of them being not aware of their condition[2]. Disorders of senses where subjective aspects are at the forefront, such as smell, pose great challenges for both diagnosis and treatment[3].

Reduction in the ability to identify odors is defined as anosmia (total loss of smell) and hyposmia (reduced sense of smell)[3]. Some studies have accused general anesthesia of postoperative olfactory dysfunction, but the cause of hyposmia or anosmia has not been clearly proven[4-6]. There is no clear correlation between sevoflurane and olfactory dysfunction; however, it may directly affect olfactory epithelium, causing peripheral dysfunction[4]. The effect of using sevoflurane for inhalation induction with a nasal mask on olfactory functions is unknown. Though postoperative anosmia is rare, it may disrupt the quality of life of the patient, with social and medical consequences[7]. Disrupted olfactory functions in individuals who make their living from or in relation to reliable olfactory evaluation such as chefs, firemen, wine traders, and perfumers may lead to negative results that affect life. Olfactory-related morbidity that may result from general anesthesia not only lowers the quality of life but may also cause a reduction in feeding and awareness of dangerous stimuli like gas leaks[8,9].

The primary aim of this study is to investigate the effect of different general anesthesia procedures on postoperative olfactory functions and memory and the secondary aim is to investigate the effect of inhalation induction of sevoflurane on olfactory functions and memory.

MATERIALS AND METHODS

This prospective randomized study was approved by the Clinical Research Ethics Committee of Zonguldak Bulent Ecevit University (protocol number: 2013/02, Clinical Trials. Gov Identifier: NCT05499845) and was conducted at the Department of Anesthesiology and Reanimation, Faculty of Medicine in Zonguldak Bülent Ecevit University of Hospital between January and June 2013. All participants provided written informed consent.

Sample

The study included 120 patients aged 18-60 years with an American Society of Anesthesiologists (ASA) score of I-II who were operated selectively under general anesthesia requiring intubation, with an operative time of 40-180 minutes. Patients requiring intracranial, endocrine, or nasal surgery, pregnant women, those with a history of respiratory tract diseases and psychiatric disease, disorders of odor reception and perception, smokers and chronic alcohol users, those requiring a nasogastric tube, and those who failed in the threshold test were not included in the study.

Measures

Butanol threshold test

The solution of 4% butanol was diluted to 50% with distilled water. Nine separate butanol bottles were prepared by repeated 50% dilutions. The highest concentration was in bottle number nine, while the lowest concentration was in bottle number one. Patients were asked to smell the bottles from a three-five cm distance beginning with the lowest dilution. Patients who identified the smell in bottle number five or at smaller numbers were included in the study. The preoperative butanol threshold test values of patients were recorded.

Olfactory identification test

Because of the possibility of being identified by individuals from all sociocultural groups, assessed as significant for the Turkish population with identification rates above 65%, strawberry, banana, rose, mint, cloves, cinnamon, lemon, orange, lavender, and garlic odors were chosen[10]. Aromatic oils (20 ml) were obtained from herbalists. Ten empty, roll-on glass bottles were supplied for the preparation of the olfactory identification test. The bottles were washed and sterilized with ethylene oxide. Ten ml of aromatic oil was placed in each bottle and the caps were closed with roll-on stoppers. The bottles were numbered from 1 to 10. Blotting paper was prepared in the dimensions of 5 x 10 cm. The aromatic oil to be tested was administered 3 times to the inner surface of the doubled blotter papers by means of a roll-on stopper. Subsequently, the paper was closed on itself. Aromatic blotter papers were inhaled for 1-2 minutes by gently moving the paper from a distance of 3-5 cm from patients' noses.

During smelling, the individual was made to concentrate on the smell. With eyes closed, all attention was focused on the smell. After each odor was smelled, a 1-2 min break was given. The olfactory test was performed in an odor-free environment. The mean room temperature was 20-25°C. The first test was recorded as T1. For each odor, a total of six-choice word tests were prepared. These word tests were presented with the correct answer for the odor included in the first four choices. The fifth choice was "I don't recognize the odor" and the sixth choice was "I don't smell anything." Odors identified by patients were noted. The tests were performed by the same anesthesiologist (Ü.S).

Administration of general anesthesia and monitoring

Demographic data (age, gender, weight) and ASA status of all patients were recorded. After patients had the first butanol threshold test and olfactory identification tests, they were administered IV midazolam at a dose of 0.01 mg kg^{-1}. Upon arrival in the operating room, IV access was established and normal saline was initiated. Patients were connected to a multichannel monitor, which recorded the heart rate (HR), noninvasive blood pressure, and peripheral oxygen saturation (SpO_2).

All patients were randomly assigned to the 3 groups using the sealed envelope technique. Group P (n=40) (Propofol), Group PS (n=40) (Propofol-Sevoflurane), and Group S (n=40) (Sevoflurane). Anesthesia was performed by a different anesthesiologist. Patients were given 4 L min^{-1} oxygen (O_2) through a face mask and preoxygenation was started. Then, anesthesia induction was provided by 2-2.5 mg kg^{-1} propofol and 1 µg kg^{-1} remifentanil in Group P and Group PS, while 7% concentration sevoflurane through a mask and 1 µg kg^{-1} remifentanil were administered in Group S. All groups were given 0.6 mg kg^{-1} rocuronium and intubated. For anesthesia maintenance, Group P had 10 mg $kg^{-1}h^{-1}$ for the first 10 min and 8 mg $kg^{-1}h^{-1}$ for the following 10 min with 6 mg $kg^{-1}h^{-1}$ propofol for the remaining time and 0.2 µg $kg^{-1}min^{-1}$ remifentanil infusion with 50%/50% O_2-air administered at 4 L min^{-1}. Group PS and Group S had 1 MAC sevoflurane with 50%:50% O_2-air administered at 4 L min^{-1}, fresh gas, and 0.2 µg kg^{-1} min^{-1} remifentanil infusion. During the operation, all groups had tidal volume and frequency set so that end-tidal carbon dioxide was 35-40 mmHg. All three groups had 0.1 mg kg^{-1} rocuronium IV bolus for maintenance of muscle relaxation.

Ephedrine 5 mg iv bolus was administered when hypotension (decrease in systolic pressure >25% from baseline, or an absolute systolic value<90 mmHg) could not be controlled within 3 min by increasing the fluid infusion and decreasing gas concentrations, and atropine 0.5 mg IV bolus was given for bradycardia (HR<50).

The operative times of all patients were recorded. At the end of the operation, 0.02 mg kg^{-1} atropine and 0.05 mg kg^{-1} neostigmine was used to antagonize residual block and inhalation anesthesia was terminated. After antagonizing the muscle relaxant, patients were extubated. In the last skin suture, 1 mg kg^{-1} tramadol and 10 mg metoclopramide were administered to all patients. Olfactory identification tests were re-administered to all patients at postoperative 30 min (T_2), 8 hour (T_3) and 24 hour (T_4), and the results were recorded.

Statistical analysis

The approximate sample size was calculated using the PASS 11 Sample Size Software prior to the study. In the sample size analysis performed with reference to type 1 error of 0.05, type 2 error of 0.2, d=0.8 power (group 1: 8.03 ± 1.50, group 2: 6.75 ± 1.70)[11], the minimum number of patients per group was found to be 26. Within the scope of the study, data were uploaded and analyzed in the SPSS (Statistical Package for Social Sciences) for Windows 16.0 software. Analysis results for quantitative data are shown as mean + standard deviation and median (minimum-maximum). ANOVA test was used in independent groups with a normal distribution (3 groups), and the Kruskal-Wallis test was applied to independent groups that did not follow a normal distribution (3 groups). A p-value <0.05 was considered a statistically significant difference.

RESULTS

The Consolidated Standards of Reporting Trials (CONSORT) flow diagram was used for patient enrollment (Figure 1) (12). A total of 23 patients were excluded from the study. Two patients were excluded from the study due to an operative time longer than 180 min, 12 patients due to the requirement for additional intraoperative medication use, and 9 due to postoperative nausea-vomiting complaints.

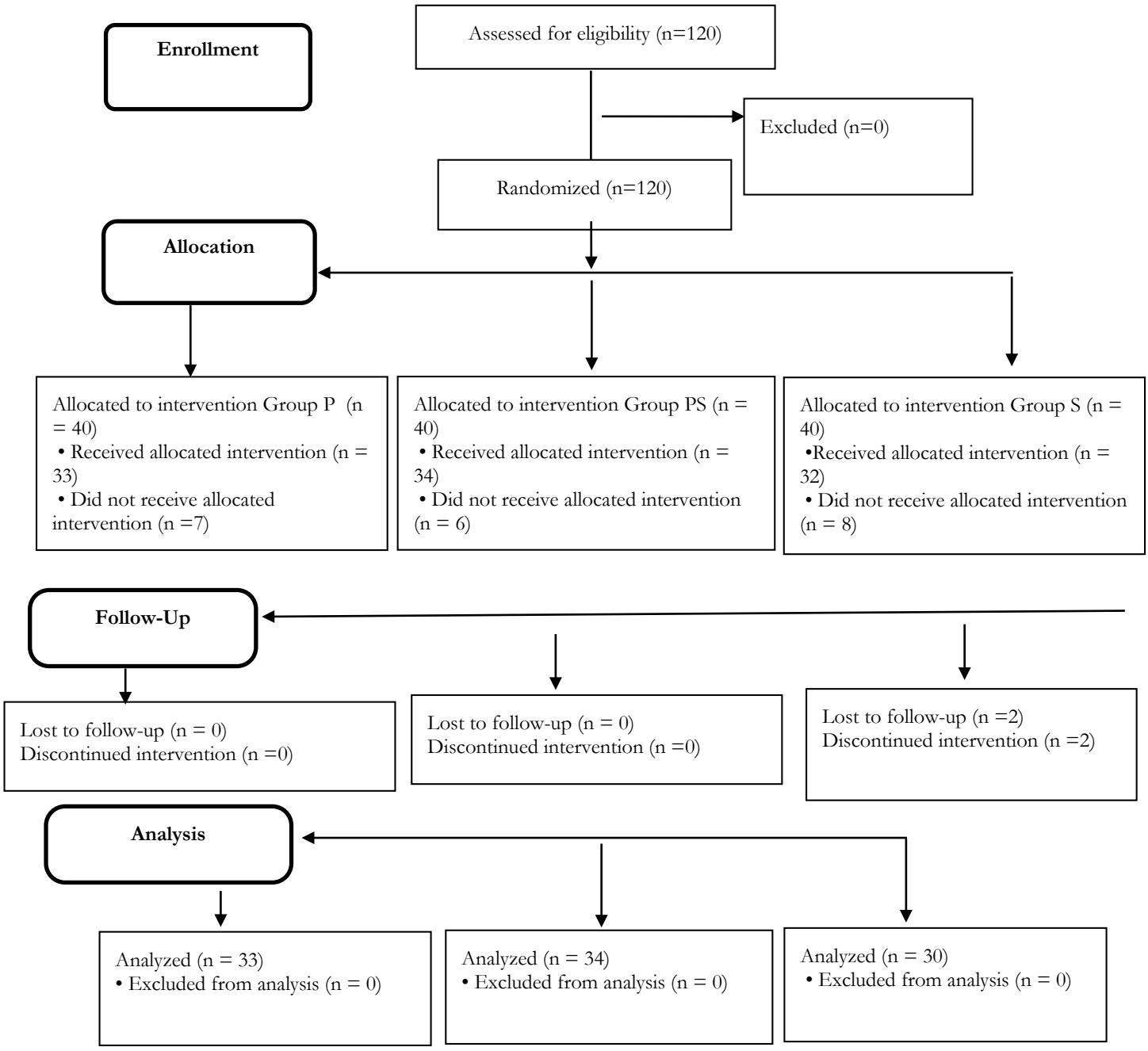

Fig.1 CONSORT flow diagram of the study.

The study included a total of 97 patients. There was no significant difference in patient characteristics, ASA risk classification, and operative time between the groups ($p>0.05$) (Table1).

Table 1. Comparison of the groups' demographic characteristics, ASA risk classes and operation durations

	Group P (n=33)	Group PS (n=34)	Group S (n=30)	p
Gender (F/M)	18/15	23/11	24/6	0.099
Age (years)	38.84±10.82	40.00±10.42	38.20±10.89	0.792
Height (cm)	167.84±7.83	165.02±20.21	166.30±5.78	0.684
Body weight (kg)	75.24±14.42	75.55±12.31	73.53±15.62	0.831
ASA (I/II)	24/9	24/10	17/13	0.344
Surgery time (min)	86.8±19.8	83.7±24.6	86.0±21.4	0.082

Data are presented (mean±SD) F: Female, M: Male, ASA: American society of anesthesiologists. Min: Minute

There were no significant differences between the groups when compared in terms of T1 butanol threshold values (p=0.416). The comparison of the butanol threshold values of the groups at T2 showed a difference between the groups (p<0.001), with the mean butanol threshold value in Group P being lower compared to Group PS (p<0.001) and Group S (p<0.001). The comparison of the butanol threshold values at T3 between the study groups revealed a difference between the groups (p=0.017), with the mean butanol threshold value in Group P being lower compared to Group S (p=0.009). The comparison of the butanol threshold values at T4 between the groups showed a difference between the groups (p=0.024), with the mean butanol threshold value in Group P being lower compared to Group S (p=0.008) (Table 2).

When each study group was compared in terms of butanol threshold values at different time points, a difference was observed in Group P only between the T_1 threshold value and the T_2 threshold value (p=0.001). In Group PS and Group S, there were differences between the T_1 values and the values measured at other times for within-group comparisons (p<0.001) (Table 2).

Table 2. Butanol threshold values in the groups

Time	Group P (n=33)	p^1	Group PS (n=34)	p^1	Group S (n=30)	p^1	p^2
T_1	3 (2-5)	-	3 (2-5)	-	3 (2-5)	-	0.416
T_2	4 (2-6)	0.001	5 (3-6)*	<0.001	5 (3-7)*	<0.001	<0.001
T_3	3 (2-5)	0.102	4 (3-5)	<0.001	4 (3-6)*	<0.001	0.017
T_4	3 (2-5)	0.999	4 (2-6)	0.005	4 (2-5)*	<0.000	0.024

Data are presented median (min-max) n: number

T_1: Preoperative 30th min, T_2: postoperative 30th min, T_3: postoperative 8th hour, T_4: postoperative 24th hour.

P^1: Comparison to T_1 values within groups, P^2: Comparison between groups,

*: Compared with Group P p<0.05

The comparison of the study groups in terms of olfactory identification values measured at T1 showed no significant difference between the groups (p=0.607) (Table 3). The comparison of the study groups in terms of olfactory identification values measured at T_2 and T_3 revealed differences between the groups (p<0.001). The values of Group P were observed to be higher compared to those of Group PS and Group S (p<0.005) (Table 3). When the olfactory identification values were compared between the study groups at T_4, there were differences between the groups (p=0.030), with values of Group P being higher compared to those of Group S (p=0.008) (Table 3). When each study group was compared within itself, the T_1 olfactory identification value was observed to be different from the olfactory identification values at T_3 and T_4 Group P (p<0.001) (Table 3). In Group PS and Group S, the olfactory identification value at T_1 was observed to be different from the olfactory identification values measured at T_2 and T_4 time points (p<0.05) (Table 3).

Table 3. Olfactory identification values of groups

Time	Group P (n=33)	p[1]	Group PS (n=34)	p[1]	Group S (n=30)	p[1]	p[2]
T1	9 (8-9)	-	9 (6-9)	-	8.5 (6-9)	-	0.607
T2	9 (6-10)	0.637	6 (3-9)*	<0.001	5.5 (3-9)*	<0.001	<0.001
T3	9 (8-10)	<0.001	9 (6-10)	0.181	8 (5-10) *	0.169	<0.001
T4	9 (7-10)	<0.001	9 (7-10)	<0.001	9 (6-10)*	0.033	0.030

Data are presented median (min-max) n: number
T_1: Preoperative 30th min, T_2: postoperative 30th min, T_3: postoperative 8th hour, T_4: postoperative 24th hour.
P^1: Comparison to T_1 values within groups, P^2: Comparison between groups,
*: Compared with Group P $p<0.05$.

None of the patients included in our study developed complications such as cough, desaturation, hypotension, bradycardia, laryngospasm, bronchospasm, or breath holding. No escape medications were required for any patient during the study period.

DISCUSSION

In our study investigating the effects of general anesthesia on olfactory functions, with all three anesthesia techniques, the postoperative 30-min butanol threshold values were increased compared to baseline values. In other periods, the disruption in olfactory threshold values in Group S and Group PS continued until postoperative 24 h, while the olfactory threshold values in Group P returned to baseline values from postoperative 8 h. The olfactory identification test values were observed to increase at postoperative 8 and 24 h in Group P compared to baseline values. Groups S and Group PS had a reduction in olfactory identification test values at postoperative 30 min, but the values returned to baseline at postoperative 8 h, with an increase compared to baseline values at postoperative 24 h.

Anesthetic medications may affect olfactory functions by nasal vasodilatation, mucous hypersecretion, and causing damage to the olfactory neuroepithelium with toxicity at the central nervous system or at the peripheral level.[13] Salmi et al.[14] showed that sevoflurane and propofol affected subcortical and cortical ɣ-aminobutyric acid (GABA) receptor-ligand binding. GABA is the main inhibitory neurotransmitter in the human brain and is responsible for the deafferentation of plasticity in the brain. Levy et al.[15] determined that patients with phantosmia had a significant reduction in brain GABA levels. As a result, factors affecting GABA-dependent pathways may affect the transmission of olfactory stimuli to the central region of the olfactory system. Propofol and pentobarbital are known to be clear GABA-A-positive modulators in the brain. GABA-A receptors are commonly found in the central nervous system, including the olfactory and trigeminal systems. Propofol and pentobarbital cause an obvious reduction in blood supply to the cortical and subcortical regions, including the olfactory system.[16] Reduced blood supply may result in a reduced olfactory response. Similarly, in our study, induction with propofol caused a disruption in olfactory threshold values in the early recovery period; however, this was not permanent. In other periods, the olfactory threshold values returned to normal limits. We believe that this may be attributed to the short half-life of propofol.

A 60-year-old, non-smoking female patient with vaginal tape for urinary incontinence was reported to develop parosmia (disorder in distinguishing odors) and dysgeusia (disrupted taste sensation) immediately after the operation associated with propofol, fentanyl, and sevoflurane use, lasting up to 4 months.[4] There is no clear correlation between sevoflurane and olfactory dysfunction, but as this material is in the volatile form, it may directly affect olfactory epithelium. Accordingly, it is stated to be a potential risk source in terms of peripheral dysfunction.[4] The results of our study showed that sevoflurane use disrupted the butanol threshold, causing a temporary dysfunction in the olfactory identification values. This disruption was more pronounced especially in the group without propofol use (Group S) compared to the group for which no sevoflurane was used (Group P). We are of the opinion that sevoflurane induction with a mask may

affect olfactory epithelium, causing dysfunction similar to the peripheral type.

There is an interesting short case of a 77-year-old female patient who underwent an abdominal hysterectomy under general anesthesia using propofol, morphine, vecuronium, and isoflurane. On postoperative day 5, her sense of smell returned after being absent for 20 years.[17] In our study, propofol caused an increase in olfactory threshold values in the early recovery period. However, the threshold values returned to normal limits in a short time and an improvement in olfactory memory occurred similar to this case report.

There are also a few examples of contrary case reports with propofol. Farzana et al.[18] reported a case of a 58-year-old male who underwent radical nephrectomy under general anesthesia using propofol and fentanyl and who developed parosmia and dysgeusia on postoperative day 3, which recovered 15 days after surgery. Du et al.[19] described a case of anosmia and hypogeusia for 6 weeks after a uterine curettage operation in a 32-year-old woman. Propofol was the only anesthetic used during surgery and anesthesia. They stated that the underlying mechanisms may be related to the synaptic dysfunction or that impairment of sensory fibers induced by anesthetics may be the reason for long-term dysfunction of taste and smell.

Kostopanogiotou et al.[20] administered propofol, epidural, and sevoflurane anesthesia and reported higher mistaken identification rates for odors in patients in the sevoflurane group compared to those in the propofol and epidural groups. This study is the first to show postoperative changes in olfactory memory. In this study, variations in olfactory memory were not associated with elevated olfactory threshold values. They stated that the underlying mechanism may be linked to a reduction in plasma melatonin levels observed with sevoflurane anesthesia. The same study reported that it was not known when olfactory memory would return, stating that plasma melatonin levels only return to normal after 24 h. Moreover, it was reported that the short study period of only three hours was a limitation. There is another study investigating the effect of general anesthesia on plasma melatonin levels. Ram et al.[21] administered general anesthesia using thiopental, fentanyl and isoflurane to 20 patients and showed significantly low plasma melatonin levels on the night of the operation compared to baseline values and higher melatonin levels examined after 24 h compared to baseline values. They stated that the changes in melatonin levels may be associated with the anesthetic agent used. Saravan et al.[22] aimed to assess the effect of isoflurane, sevoflurane, propofol, and regional anesthesia on the olfactory threshold, olfactory identification, and endocrine regulation of associative memory in the postoperative period. They observed that sevoflurane was associated with short-term impairment in olfactory identification along with a concomitant reduction in melatonin levels, illustrating a possible humoral mechanism. In a study of 56 mice that received general anesthesia with 120 mg kg-1 propofol, Dispersyn et al.[23] observed reduced peripheral melatonin levels 4 h later, with an increase after 20 h, linking this to the melatonin circadian rhythm. In our study, propofol increased the butanol threshold value in the early period, which returned to normal values within 8 h. Propofol did not disrupt olfactory identification; in fact, it was even observed to increase it. We believe that this increase may be related to plasma melatonin levels. In a study of 18 patients with induction with 5% concentration of isoflurane and 7% concentration of sevoflurane, Arai et al.[24] stated that isoflurane increased melatonin levels, while sevoflurane reduced it. Isoflurane stimulates the sympathetic nervous system, contrary to sevoflurane, which was suggested to cause an increase in melatonin levels. A study by Fassoulaki et al.[25] investigating the effects of sevoflurane on plasma melatonin and endorphin levels in 26 patients showed no statistical significance but a reduction in melatonin levels at postoperative 0 and 4 h compared to baseline values and an increase at 24 h. In our study, the administration of sevoflurane alone, or in combination with propofol, caused a disruption in olfactory threshold value lasting for 24 h, with disrupted olfactory identification in the early period and an increase after 24 h. In light of the abovementioned studies, we are of the opinion that the decline in olfactory identification in the early period is associated with the reduction in melatonin levels by sevoflurane, while the increase after 24 h may be linked to increased melatonin levels.

One of the limitations of our study was not studying the melatonin levels. Undoubtedly, advanced-level studies are needed to identify the effects and mechanisms of specific anesthetic medications on the sense of smell. There is also a need for studies to reveal the incidence of this side effect and whether it is necessary to inform the patient when obtaining

consent and especially to gain clarity about which medications cause this side effect.

In conclusion, the use of sevoflurane for inhalation induction and maintenance of anesthesia negatively affects olfactory function, causing a temporary disruption in olfactory memory. Propofol use only causes a temporary disruption in the sense of smell in the early period, while it does not affect olfactory memory. In fact, it was concluded to improve olfactory memory. For individuals who frequently use smell for professional, livelihood, and security purposes and need to achieve significant postoperative recovery in the early period for day-case surgical interventions, we recommend that propofol be chosen for anesthesia induction and maintenance of general anesthesia if possible. Further studies with a larger sample size will be necessary to confirm our results.

Yazar Katkıları: Çalışma konsepti/Tasarımı: ÜS, RDO, HA, İÖT, FÇ; Veri toplama: ÜS, RDO, NNG, GK, BGK; Veri analizi ve yorumlama: FNA, ÜS, HA, İÖT; Yazı taslağı: ÜS, RDO, HA, GK, BGK; İçeriğin eleştirel incelenmesi: GK, BGK, ÖP, İÖT; Son onay ve sorumluluk: ÜS, RDO, HA, BGK, GK, ÖP, NNG, FNA, FÇ, IÖT; Teknik ve malzeme desteği:ÜS, RDO; Süpervizyon: RDO, HA, İÖT; Fon sağlama (mevcut ise): yok.
Etik Onay: Bu çalışma için Bülent Ecevit Üniversitesi Klinik Araştırmalar Etik Kurul Başkanlığı'nın 22.01.2013 tarih ve 2013/02 sayılı kararı ile etik onay alınmıştır.
Hakem Değerlendirmesi: Dış bağımsız.
Çıkar Çatışması: Yazarlar çıkar çatışması beyan etmemişlerdir.
Finansal Destek: Yazarlar finansal destek almadıklarını beyan etmişlerdir.

Author Contributions: Concept/Design : ÜS, RDO, HA, İÖT, FÇ; Data acquisition: ÜS, RDO, NNG, GK, BGK; Data analysis and interpretation: FNA, ÜS, HA, İÖT; Drafting manuscript: ÜS, RDO, HA, GK, BGK; Critical revision of manuscript: GK, BGK, ÖP, İÖT; Final approval and accountability: ÜS, RDO, HA, BGK, GK, ÖP, NNG, FNA, FÇ, IÖT; Technical or material support: ÜS, RDO; Supervision: RDO, HA, İÖT; Securing funding (if available): n/a.
Ethical Approval: Ethical approval was obtained for this study by the decision of the Bülent Ecevit University Clinical Research Ethics Committee dated 22.01.2013 and numbered 2013/02.
Peer-review: Externally peer-reviewed.
Conflict of Interest: Authors declared no conflict of interest.
Financial Disclosure: The authors declared that they did not receive financial support.

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