The Comparison of the Effects of Remifentanil in Combination with Sevoflurane, Desflurane or Propofol on Cognitive Functions in Elective Surgical Procedures

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Abstract
Objectives: Cognitive functions are affected by varying degrees after general anaesthesia. We aimed to compare the effects of remifentanil in combination with sevoflurane, desflurane or propofol on haemodynamic variables, post anaesthesia recovery and cognitive functions in patients for whom head and neck surgery were planned.

Methods: This clinical research was performed on 60 patients, ASA I-II, aged 20-60 years with at least 8 years of education who would undergo elective surgical operations under general anaesthesia.

Anaesthesia induction was realized with remifentanil 0.5 µg/kg/min infusion,1 mg/kg propofol until verbal response disappeared and then 0.15 mg/kg cisatracurium was given. After intubation, the remifentanil dose was reduced by 50 % in all of the three groups. Anesthesia was maintained in Group P (n=20) with 50 % O_2 + 50 % air and 6 mg/kg/hr propofol infusion, in Group S (n=20) with 50 % O_2 + 50 % air and 1% sevoflurane and in Group D with 50 % O_2 + 50 % air and 3% desflurane.

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Mean arterial pressure and heart rate were recorded before induction, after induction, 15 minutes after intubation and at every 30 minutes after operation. At the end of the operation spontaneous eye opening time and time for Aldrete score ≥ 9, as well as postoperative side effects and cognitive functions were evaluated. Trieger Dot Test and Digit Substitution Test were performed on the day before surgery and at 15^{th}, 60^{th} and 120^{th} minutes after the surgery.

Results: The demographic data and duration of surgery were similar in all the groups. A statistically significant difference was determined in mean arterial pressure at the first minute after induction between Group P and Group D (p<0.05). Aldrete recovery scores were completed in all groups at the 15^{th} minutes (>9). There were no difference between groups in terms of side effects, DSST and TDT scores.

Conclusion: We concluded that all three methods may be used as alternatives to each other with similar satisfactory results.

Keywords: *remifentanil, sevoflurane, desflurane, propofol, postanaesthesia recovery, cognitive function*

Elektif Cerrahi Girişimlerde Sevofluran, Desfluran veya Propofol ile Kombine Edilmiş Remifentanilin Kognitif Fonksiyonlar Üzerine Etkisi

Özet

Amaç: Genel anestezi uygulamalarından sonra kognitif fonksiyonlar değişik derecelerde etkilenmektedir. Çalışmamızın amacı baş ve boyun cerrahisi planlanan hastalarda remifentanil ile birlikte sevofluran, desfluran veya propofol kullanımının hemodinami, derlenme ve kognitif fonksiyonlar üzerine etkisini araştırmaktır.

Yöntem: Çalışma; ASA I-II grubu, 20–60 yaş arası, en az 8 yıl eğitim almış, genel anestezi altında elektif cerrahi girişim planlanan, 60 olgu üzerinde gerçekleştirildi.

Anestezi indüksiyonu 0.5 µg kg-1 dak-1 remifentanil infüzyonu, verbal uyarıya cevap kayboluncaya kadar 1 mg kg-^{1} propofol ve 0.15 mg kg-1 cisatrakuryum ile sağlandı. Entübasyon sonrasında remifentanil dozu tüm gruplarda % 50 azaltıldı. Anestezi idamesi; Grup P'de (n=20) % 50 O2 + % 50 hava ve 6 mg kg-1 saat-1 propofol infüzyonuyla, Grup S'de (n=20) % 50 O2 + % 50 hava ve % 1 sevofluran ile, Grup D'de (n=20) ise % 50 O2 + % 50 hava ve % 3 desfluran ile sağlandı. İndüksiyon öncesi, indüksiyon sonrası ve entubasyon sonrası 1 ve 15. dk. ve ameliyat süresince 30 dk aralıklarla ortalama arter basıncı (OAB), kalp tepe atımı (KTA) kaydedildi. Ameliyat bitimini takiben spontan göz açma zamanı, Aldrete skoru ≥ 9 süresi, yan etkiler ve kognitif fonksiyonlar değerlendirildi. Operasyondan bir gün önce ve operasyon sonrası 15. 60. ve 120. dakikalarda TDT ve DSST uygulandı.

Bulgular: Demografik veriler ve cerrahi süresi üç grupta da benzer bulundu. İndüksiyon sonrasındaki birinci dakikada ölçülen OAB değerlerinde Grup D ve Grup P arasında istatiksel olarak anlamlı fark olduğu görüldü($p<0.05$). Aldrete derlenme skoru (>9) her üç grupta da 15. dakikada tamamlandı. Yan etkiler, DSST ve TDT skorları açısından gruplar arasında fark yoktu.

Sonuç: Her üç yöntemin de güvenle kullanılarak birbirine alternatif olabileceği kanısına vardık.

Anahtar Kelimeler: *remifentanil, sevofluran, desfluran, propofol, anesteziden derlenme, kognitif fonksiyon*

Introduction

In general anesthesia, the aim is to remove the patient's cognitive functions temporarily and to provide suitable conditions for the operation. Thus, agents that effect rapidly and recover cognitive functions in a short time after operation are preferred.

Although anesthetic agents have effects on all organs and systems, their main effects are on the nervous system. This causes cognitive functions of the brain to be affected in different levels after anesthesia. Postoperative cognitive functions are evaluated by investigation of mental changes caused by anesthetics and surgical intervention or by determining the level of recovery and by evaluating the residual effects of anesthetics[1-4].

Postoperative cognitive disorders can be examined in two main groups[5] :
a) Postoperative delirium and
b) Neurocognitive disorder (Postoperative cognitive disfunction)

a) Postoperative delirium:
Postoperative delirium is characterized with acute disorders in consciousness and cognitive functions. It is a syndrome that delays the healing, extends the duration of hospital stay, increases morbidity and mortality in geriatric patients. In the cognitive functions of orientation, speaking, learning and memory disorders are seen. Emotional disturbance, anxiety, rage and depression may also be seen. Postoperative delirium fluctuates during the day. The most common delirium type after the operation is interval delirium, seen at the postoperative 2nd and 7th days. Emergence delirium is seen right after the operation in all age groups and is a temporary disorder.

b) Postoperative Cognitive Disfunction (POCD)
It is characterized with the insufficiency of memory and concentration. It is often seen in older patients who had undergone a major surgery. In addition to general anesthesia, the predisposition of the patient, the type of the operation, postoperative factors (such as opioid analgesics) can cause cognitive function disorders in older patients. The pathogenesis of postoperative cognitive dysfunction is not clear, but it is claimed that age, alcohol addiction, low basal cognitive status, hypoxia, hypotension and the type of the surgery contribute to the development of this problem.

Postoperative cognitive state can be affected by the anesthetic medicine used, because the volatile residual levels of anesthetics may cause changes in the Central Nervous System (CNS) activity. Therefore, use of anesthetics with fast elimination and low metabolism ratio can be advantageous.

It is shown that the deterioration in postoperative cognitive function and psychomotor abilities are frequently short term and temporary and can follow even short surgical procedures. Although post-operative long term cognitive and psychomotor disorder is rare, if it develops, it creates a serious problem[3,4,6-9]. In the experimental studies among animals, it is proven that anesthetics are effective on cognitive functions[10-11]. It is known that post-anesthesia recovery and recovery of cognitive function disorders are directly proportional to the anesthetic agent used and blood/

gas solubility coefficient. It is advantageous to use short-term anesthetics such as sevoflurane, desflurane and propofol in same-day cases. Selection of a short-acting opioid provides good per-operative analgesia and hemodynamic stability[12] and shortens the time for the recovery of the collective and cognitive functions[13].

The purpose of this study is to measure the cognitive functions with the Digit symbol substitution test (DSST) and Trieger Dot test (TDT) post general anesthesia maintained by sevoflurane , desflurane or propofol added remifentanil whilst monitoring mean arterial pressure (MAP) and heart rate (HR) parameters that are thought to affect per-operative cognitive functions.

Material and Procedure

This study was carried on 60 patients who were planned to have an elective neck-head surgery (ASA I-II), aged between 20-60 Aim was to compare the effects of anesthesia provided by sevoflurane, desflurane and propofol combined with remifentanil, on per-operative hemodynamics and early postoperative cognitive functions. After the hospital ethical committee's approval, each patient was informed about the study and informed consent was obtained.

The patients with neurological and psychiatric illnesses that affect CNS and cognitive functions, patients who were using medicine that can affect CNS and cognitive functions and the ones who were drinking alcohol once or twice a week or with any kind of drug addiction were not included in the study.

Normal cognitive function levels of the patients were detected by DSST and TDT tests performed a day before the operation (Fig.1,2). In TDT test, the patients were given a paper with a shape formed of dots on it and were asked to draw following the dots. The number of the dots they missed, were recorded and the percentage was obtained for statistical evaluation. In DSST, the patients were asked to match the numbers with shapes in a minute. The correct number of matches was recorded and the percentage was obtained for statistical evaluation. The patients were randomly divided into three groups. They were not given any premedication in order not to affect their cognitive functions. In the operation room, vascular access was applied with 16 or 18 gauge cannula to the patients and 500 cc of 0.9% NaCl solution was administered till anesthetic induction. Electrocardiogram (ECG), peripheric oxygen saturation (SpO_2) and arterial pressure monitorization (NIBP) were monitored. In the operation room before induction, 3 minutes of pre-oxygenation (100% O_2) was administered to the patients. The demographic data, MAP and HR were recorded 1 minute before and 1 minute after induction, at the first and 15th minutes after intubation and every 30 minutes until the operation was ended.

During the operation, the anesthetic and analgesic requirement was adjusted to maintain MAP and HR values within ± 20% of basal value. A 20% increase in MAP from the basal value and/or HR being > 90 pulse/minute was accepted as insufficient anesthesia and dose of remifentanil was increased by 25%. A 20% decrease from the basal value of MAP and/or HR being < 50 pulse/minute was accepted as deep anesthesia and remifentanil dose was decreased by 25%. Atropin was used when bradycardia occurred lasting for 2 minutes.

In all the groups; 0,5 µg kg^{-1} $min.^{-1}$ of remifentanil infusion was started intravenously for anesthesia induction to the patients. After 2 minutes, 1 mg kg^{-1}propofol and 0,15 mg kg^{-1} cis-atracurium as muscle relaxant were administered and 3 minutes later, mechanical ventilation support was applied by orotracheal intubation.

The maintenance of anesthesia was provided with 50% O_2 + 50% air together with 3% desflurane and 0.25 µg $kg^{-1}min^{-1}$ remifentanil infusion in Group D (Desflurane) (n=20).

In Group S (Sevoflurane) (n=20), the maintenance was provided with 50% O_2 + 50% air together with 1% sevoflurane and 0.25 µg $kg^{-1}min^{-1}$ remifentanil infusion.

In Group P (Propofol) (n=20), the maintenance was provided with 50% O_2 + 50% air together with 6 mg kg^{-1} $hour^{-1}$ propofol infusion and 0.25 µg $kg^{-1}min^{-1}$ remifentanil infusion.

Ventilation was provided in all patients with 30-35 mm Hg of $ETCO_2$ value, 8 mL kg^{-1} of tidal volume and 10-14/minute of respiration rate.

The remifentanil infusion was stopped when the skin was started to be closed towards the end of the operation and the general anesthetic agent and the air was stopped when the skin was completely closed. Following the antagonization of neuromuscular block with 0.01 mg kg^{-1} atropine and 0.03 mg kg^{-1} neostigmine, the patients were extubated when their spontaneous respiration reached to a sufficient level. 1000 mg of paracetamol was administered intravenously for postoperative analgesia to all patients in the three groups.

Spontaneous eye opening time, at post extubation, at the 2nd and 5th minutes were recorded (Aldrete Recovery Scores -Table1). When the Aldrete Recovery Scores hit 9, the patients were transferred from postoperative care unit to the ward. They were followed up for any side effects (nausea, vomiting, chest rigidity in induction).

15, 60 and 120 minutes after anesthesia recovery, cognitive functions were evaluated via DSST and TDT tests. NCSS (Number Cruncher Statistical System) 2007&PASS 2008 Statistical Software (Utah, USA) was used for statistical analysis to evaluate the findings of the study. Methods of descriptive statistics (Mean, Standard deviation) were used in evaluation of the study data and in comparison of quantitative data. One way Anova test was used in comparing the groups in which the parameters are displayed in normal distribution and Tukey HSD test was used to determine the group causing the difference. In comparison between groups of parameters that do not display in normal distribution, Kruskal Wallis test was used. When comparing qualitative data, Ki-Square test was used. Significance level was accepted when p was <0.05.

RESULTS

Study was carried out in Okmeydanı Training and Research Hospital, Anesthesiology and Reanimation Clinic (n=60; 30 male and 30 female). The ages of the patients were between 20 and 60 with an average of 35.98±10.75. When the demographic data of the patients were compared no significant difference was found (Table 2). While there was no statistically significant difference between MAP levels at the first minute before induction and 15, 45, 75 and 105 minutes after intubation with respect to groups , there was no significant difference between MAP levels of the groups at the first minute after induction (p>0.05) (Figure 3). The

MAP levels of the propofol group at the first minute after induction was significantly higher than that of the desflurane group ($p:0.046$; $p<0.05$) (Figure 3).

There was no statistically significant difference between HR levels at the first minute before induction, first minute after induction and 15, 45, 75 and 105 minutes after intubation with respect to groups (Figure 4).

The mean time for spontaneous eye opening was 18.95±3.67 min, 17.50±3.27 min and 16.85±3.16 min for Groups P, S and D respectively (Table 3, Fig 5).

There was no statistically significant difference between the groups in terms of measurements of DSST collected a day before and at 15,60 and 120 minutes after recovery (Table 4, Fig.6).

There was no statistically significant difference between groups in terms of measurements of TDT measured a day before and at 15, 60 and 120 minutes after recovery (Table 5, Fig.7).

There was no statistically significant difference between groups in terms of additive analgesics need, nausea and bronkospasm (Table 6, Fig. 8).

DISCUSSION

In determining the time of post-anesthetic exposure, not only the effects of agents on respiratory and circulation systems are important but also the effects on the memory, other cognitive functions and psychomotor abilities as well.

The patients are regarded as completely recovered when they return to their preoperative physiologic and psychomotor conditions; recovery time, eye opening to a verbal stimulant, person-place-time orientation are often examined[14]. When evaluating early recovery; the stability of vital symptoms, the recovery of the patient from anesthesia, gaining his/her protective reflexes, returning of the motor activities and the criteria of following the commands are evaluated[15]. A common score used widely is Alderate Score for recovery[16]. In the middle term recovery, the patients are first made to sit up and then stand up. Liquid intake starts, post-operative nausea-vomiting are followed and the process of discharging starts. The prolonged early and middle term recoveries raise the cost of the surgery. To keep the psychomotor and cognitive incompetence to a minimum level, the conditions of discharge must be evaluated carefully and the patient's cooperation must be assured, following a safe anesthetic application[17].

Short and safe postoperative recovery period; especially the returning time of physiologic and cognitive functions are extremely important after general anesthesia. After being exposed to anesthetic substances, there is a disruption in psychomotor and cognitive functions for 10-12 hours, and in advanced tests it is seen that this disruption can last for 1-2 days[6]. Long lasting psychomotor and cognitive disruption is very rare after anesthesia, but when happens it is a serious problem. Postoperative disruption in cognitive functions and psychomotor abilities is often short-term and temporary[18]. It is shown that these symptoms can be followed by very short acting anesthetic applications.

The post anesthesia cognitive function disruptions are not only dependent on surgical effects but also on an illness that needs surgery and post-operative treatment. After using anesthetic agent, the recovery of cognitive functions is generally fast changing between a few hours to a few days. However, postoperative treatment (providing analgesia with long term effective opiods) can affect cognitive functions. Temporary post-operative delirium (1-3 days), can be seen in some risky (major surgery, old patient, brain sensitivity or sepsis) patients[19]. Postoperative delirium is an acute picture that ranges from light confusion to a psychotic disruption. Dementia that was present before, water electrolyte balance disorder, hypoxia, hypocapnia, insomnia, medicine are believed to have caused this[20]. However, the reasons behind post-operative cognitive function disorders (POCD) are not entirely enlightened. Biedler et al [21] have studied 1218 patients over 60 and have detected cognitive dysfunctions of 25% in 1 month and 9.9% in 3 months; as early term POCD risk factors which they had identified are old age, duration of anesthesia, low education level, second operation, development of post-operative infection, respiratory complications; as late term POCD risk factor is age. They stated that the long term cognitive dysfunction is seen in old patients, after a major surgery with general anesthesia.

In the last years, one of the most significant changes in health services is the tendency from long lasting hospital caring surgeries to outpatient surgeries. For these, anesthetic agents which have fast effect, provide intra-operative amnesia, analgesia, have a short recovery time and do not have side effects are preferred.

Solubility of desflurane in fat, blood and water is significantly lower than the other volatile anesthetics. Therefore, the absorption, distribution and excretion from the lungs is faster than similar agents. For these reasons, desflurane anesthesia causes fast induction and recovery and it is suggested that it could be preferred in daily cases[22-26].

Low dissociation coefficient of sevoflurane in blood/gas causes fast induction, fast elimination and these features provide fast recovery[15]. Sevoflurane is preferred for its short recovery time[27-29].

In a meta-analysis, 58 controlled studies between 1966 and 2002, in which propofol, isoflurane, sevoflurane and desflurane were examined, it was stated that desflurane and sevoflurane caused faster recovery[30].

Pensado et al [31] compared the duration of spontaneous eye-opening, spontaneous onset of respiration and extubation times after desflurane, sevoflurane and isoflurane anesthesia. As a result, there was no difference between desflurane and sevoflurane but in the isoflurane group, the recovery time was longer than the others.

In the study performed by Chen et al [26], the recovery time -from the time anesthesia was completed to the time when eyes are opened-, duration of extubation, the time to following verbal orders and orientation was significantly shorter in desflurane group compared to sevoflurane group. When compared the pre-operative basal Mini Mental Test (MMT) values, the average of MMT scores in both groups have decreased in the post-operative first hour. More than 85% of the patients in both groups have returned to their pre-operative basal levels at the 6th hour post operatively. At 24th hour, all the patients (except one in sevoflurane group) have returned to their basal MMT scores. There has been no difference in the MMT scores among desflurane and sevoflurane groups in the pre-operative and post-operative first, 3rd, 6th and 24th hours.

In the study where Deepak et al [22] compared desflurane and sevoflurane in terms of eye opening, duration of extubation, the length of time of following verbal orders, orientation of place and time, the patients in the group in which desflurane was used, has recovered faster and was found in a better condition. At the 6th hour, 100% of the patients who were administered desflurane and 97% of the patients who were administered sevoflurane, has returned to their normal cognitive functions. Although fast recovery was provided with desflurane, the returning of cognitive functions were similar in both groups[22-26].

Propofol is used often because it provides fast recovery due to fast distribution and short elimination half-life and it is also used in total intravenous anesthesia (TIVA) applications for its antiemetic effect[32-34]. Heidi and Korttila[35] used Maddox Wing and DSS tests to evaluate psychomotor function in their study in which they examined the effects of desflurane combined with propofol, desflurane and ondansetron on postoperative recovery. They found the results of cognitive functions similar in all the groups at the 30th, 60th and 90th minutes. There are different studies in which propofol and desflurane are compared and recovery effects are found to be similar[32-33].

In the study where Rodino et al[36] compared sevoflurane and propofol, spontaneous eye opening time was shorter in sevoflurane group but there was no difference found in the recovery times. There are different studies where sevoflurane and propofol are compared and the recovery effects were similar[37].

In their study where Ebert et al [38] compared cognition time, response to oral stimulation and time for the first analgesic need following propofol and sevoflurane anesthesia; they found that there was no difference in the duration of cognition in sevoflurane and propofol groups whereas it was longer in isoflurane group.

Wandel et al[27] compared the characteristics of recovery in adults who had daily surgery with sevoflurane and propofol anesthesia in their study and they evaluated pre and post-operative cognitive functions with DSST and they discovered that the cognitive functions in sevoflurane group was significantly faster to reach the preoperative rates. In this study, the writers stated that sevoflurane is a better alternative than propofol in daily surgeries. In different studies where sevoflurane and propofol are compared, retrieval of cognitive functions in short time and faster recovery is provided by sevoflurane[27-28].

Using fast and short acting anesthetic and analgesics decrease the possible side effects in recovery period. In these applications opioids are widely used as sedatives and analgesics[39]. TIVA is commonly preferred in especially daily surgeries with general anesthesia due to short acting hypnotic and opioid usage. [40,41].

Remifentanil with its pharmacodynamic qualities, is a typical μ-opioid receptor agonist similar to fentanil and its derivations. Metabolization of remifentanil by nonspecific esterases gives it a different pharmacokinetic profile than the other opioids. The advantage of the drug is that its clearance is very fast and therefore the disappearance of the effect is fast [42-43].

There has been a couple of studies which define the pharmacokinetic features of remifentanil. In the first evaluation, it has been established that remifentanil shows its effect rapidly, its distribution volume is small, redistribution is fast and half lime of terminal elimination is 8.8 to 40 minutes[42-44].

Besides providing a good pre-operative analgesics and hemodynamic stability, short acting opioids shorten recovery period of cognitive functions. The tests that evaluate the recovery time vary from simple tests like recovery of consciousness to complex psychomotor tests[4]. In this study, the cases were evaluated with regards to eye opening time. It was determined that there was no statistically significant difference among the three groups from the end of anesthesia until the time of spontaneous eye opening ($p>0.05$). Spontaneous eye opening times was 18.95±3.67 min. in propofol group, 17.50±3.27 min. in sevoflurane group and 16.85±3.16 min. in desflurane group. It was determined that there was not any significant difference among the groups in terms of eye opening times. Palazon et al [45] found out that in the groups where remifentanil was combined with sevoflurane and propofol, the eye opening time was shorter in sevoflurane group.

Larsen et al[13] compared recovery of cognitive functions post remifentanil and propofol, desflurane and sevoflurane anesthesia. The patients in the remifentanil/propofol group, showed a significantly faster recovery and awareness in early recovery phase than the patients in the desflurane or sevoflurane groups. They also had the tendency to give less false answers in TDT test when compared to desflurane and sevoflurane patients. 30 minutes after anesthesia was stopped, the patients in the remifentanil/propofol and desflurane group had given significantly more correct answers in DSST test compared with the patients in sevoflurane group. At 60th minute of remifentanil/propofol anesthesia group, the recovery of cognitive functions was significantly short, but at 90th minute, DSST results were similar in all the groups. In the study of Larsen et al, it was stated that the reason for faster recovery in remifentanil/propofol group was due to faster elimination of the medicines when compared with desflurane and sevoflurane, and because fentanyl was used in desflurane and sevoflurane group, there could be a residual effect in the recovery from anesthesia. In the study performed by Larsen et al, it was seen that remifentanil is clinically more advantageous in terms of early recovery of cognitive functions when compared to desflurane and sevoflurane anesthesia.

In this study, inhalation anesthetics were also combined with remifentanil as well as propofol and no difference was recorded among the groups in the TDT and DSST tests at the 15th, 60th, 120th minutes post surgery.

Loop et al,[40] compared the same amount of remifentanil infusion with desflurane, sevoflurane and propofol anesthesia used in this study with regards to spontaneous eye opening time, extubation time and time to tell his/her name after desflurane, sevoflurane and propofol anesthesia and they have not found no significant difference as in this study.

Per operative hemodynamic symptoms of the patient can be a risk for cognitive dysfunction. However, Biedler et al,[21] stated that hypoxemia and hypotension was not a risk factor for early or late cognitive dysfunction. In this study, it was noted that there has been times with statistically low MAP values in all three groups however all the values were within normal levels, they did not necessitate any treatment, no intraoperative hypotension was determined.

In one of the studies carried on, among surgeries with minimal trauma like disc hernia, hemodynamic stability was provided by remifentanil infusion with desflurane and sevoflurane anesthesia[12]. In another study where propofol and remifentanil combination was compared with sevoflurane and nitrous oxide combination, high HR, low MAP were determined[12]. Another study with similar results with our study in terms of nausea vomiting incidence is the study of Castagnini et al[29]. In the study where post operative nausea and vomiting was examined, Karlsen[46] et al, compared desflurane, sevoflurane and isoflurane as inhalation agents and followed patients in early post operative period and within post operative 24 hours. They did not find any significant difference among the three groups in terms of nausea and vomiting in the early post operative period. However, after 24 hours of monitoring, they have found significant differences in terms of nausea and vomiting in the groups as follows: desflurane (67%), isoflurane (22%) and sevoflurane (36%). Pensado et al, [31] found the post operative nausea and vomiting complications similar in the three groups in which desflurane, sevoflurane and isoflurane was administered. In some studies carried on among adults, it is suggested that desflurane anesthesia caused more nausea than sevoflurane and isoflurane[47] and in some studies the incidence of nausea and vomiting were found similar[12]. In this study no significant difference was found in the three groups in terms of nausea and vomiting incidence. As conclusion, we believe that all the three methods can be used safely as an alternative to each other.

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