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The effects of anaesthesia induction with propofol or ketofol on cerebral oxygenation in patients above 60 years of age

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Abstract

Side effects such as hypotension and cerebral perfusion disorder may be encountered after anaesthesia induction, especially in elderly patients. Some studies have attempted to determine whether hypotension during induction and associated organ perfusion disorders can be prevented when propofol is used in combination with ketamine. However, no study has come to light investigating the effects of ketamine added to propofol on cerebral oximetry. The present study aimed to compare the effects of anaesthesia induction with propofol or propofol+ketamine (ketofol) on haemodynamic changes and cerebral oximetry in elderly patients undergoing anaesthesia induction. A total of 40 patients were randomly divided into two groups. Cerebral oximetry sensors were placed in the right and left of the frontal region. Patients in Group P were treated with 1.5 mg/kg propofol IV induction and patients in Group K were treated with the 0.2 ml/kg ketofol IV. The patients in both groups received 0.5 mg/kg lidocaine, 0.6 mg/kg rocuronium and a 0.1 mcg/kg/min infusion of remifentanil. Heart rate (HR), systolic, diastolic and mean arterial pressure (SBP, DBP, MAP) and cerebral oxygen saturation (RSO_2) values before and 1, 3, 5, 10, 30 and 60 minutes after induction were recorded.SBP, DBP and MAP values were significantly lower in the propofol group at 1, 3 and 5 minutes after induction ($p < 0.05$). The right-side RSO_2 values were significantly lower at 3 and 5 minutes after induction in the propofol group compared to the ketofol group and the left-side RSO_2 values were similarly significantly lower after 1, 3 and 5 minutes ($p < 0.05$). Ketofol used in anaesthesia induction has less effect than propofol on mean arterial pressure and cerebral oxygen saturation values. Therefore, ketofol appears to be a good choice for use in anaesthesia induction in elderly patients.

Keywords: Propofol, ketamine, cerebral oximeter, elderly patients

Introduction

Elderly patients' sensitivity to drugs used in anaesthesia induction is increased [1]. As a result, hypotension and consequently decreased brain blood flow may occur after anaesthesia induction [2]. This reduction in brain blood flow becomes more evident by the fact that propofol causes more myocardial depression and hypotension, especially in elderly patients.[3,4] Ketamine activates the sympathetic nervous system to increase heart rate and blood pressure, and consequently elevation of cerebral blood flow[5-7].

Cerebral oxygen saturation values are affected by hypotension and the decreased cerebral blood flow that may follow the hypotension. Propofol reportedly causes a temporary decrease in cerebral oxygen saturation in both young and old patients with a decrease in the mean arterial pressure following anaesthesia induction [4]. Undesired haemodynamic side effects can be reduced with the use of propofol and ketamine together [8-13]. However, to the best of our knowledge, there has been no study investigating how the combined use of propofol and ketamine affects cerebral oxygenation in elderly patients.

Therefore, the aim of the present study was to compare the effects of propofol or ketofol (ketamine+propofol) on haemodynamic changes and brain oxygenation in anaesthesia induction in elderly patients.

Materials and Method

The study was carried out between January 2016 and June 2016 in the hospital operating theatre, after obtaining the approval of the ethics committee of Ondokuz Mayıs University (Year: 2015 Number: B.30.2.0DM.0.20.08/2120). All patients were informed about the study before the procedure and their voluntary informed consent was obtained.

A total of 40 patients classified as ASA 1 or 2 and above 60 years of age who underwent elective laparotomy were included in our study. Patients with cerebrovascular disease, coronary artery

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disease, a diagnosis of carotid artery stenosis, liver or kidney failure and allergies to prescribed drugs were not included in the study.

In order to determine a sufficient number of patients for the study, power analysis was performed. According to a power analysis with 85% power and a 95% confidence interval ($\alpha = 0.05$, $\beta = 0.95$), a study with 34 individuals in each group has 80.6% power.

A total of 40 patients included in the study were randomly divided into two groups of 20, Group P (propofol administered) and Group K (ketofol administered). The patients were evaluated in the preoperative anaesthesia outpatient clinic on the day before the operation, when their height, weight, age, sex and ASA scores were recorded. Patients were not premedicated. The study was carried out in patients who underwent laparotomy in the operating theatre of the General Surgery, Obstetrics and Gynaecology departments.

The study protocol was conducted as double-blind for both groups. Systolic (SBP), diastolic (DBP) and mean arterial pressure (MAP), ECG monitoring, heart rate (HR) and peripheral oxygen saturation (SPO_2) were monitored in patients. Then, right and left cerebral oxygen saturation ($rRSO_2$ and $lRSO_2$) monitoring (INVOS™ 5100 Somatic/Cerebral Oximeter; Medtronic, UK) was performed. Before induction, the cerebral oximetry sensors were placed at least 2 cm above the eyebrows and 3 cm away from the midline, right and left, according to the manufacturer's instructions. The patient's forehead was cleansed with acetone and alcohol before the sensor pads were mounted. The sensor pads were wrapped with a bandage to prevent them from being affected by the ambient light and movement.

Preparation of ketofol: 2 ml of 50 mg/ml (total 100 mg) ketamine, 10 ml of 10 mg/ml (total 100 mg) propofol and 8 ml saline were loaded to a 20 ml syringe.

After preoxygenation, the induction was applied to the patients in Group P with 0.5–1 mg/kg lidocaine IV and 1.5 mg/kg propofol IV. The patients in Group K received 0.5–1 mg/kg lidocaine IV and 0.2 ml/kg ketofol IV. The patients who received 0.6 mg/kg rocuronium IV for neuromuscular blockade were intubated after 3 minutes. Anaesthesia was maintained with desflurane (4%) in the O2/air mixture (FIO_2 0.40) and IV remifentanyl infusion (0.2 mcg/kg/min) in both groups.

Mean arterial pressure (MAP) and left and right cerebral oxygen saturation (RSO_2) were measured and basal values were determined (T1). The values immediately after induction of anaesthesia (T2) and values at 1, 3, 5, 10, 30 and 60 minutes after the intubation (T3, T4, T5, T6, T7, T8) were recorded.

Patients who had difficult intubation, difficult ventilation, chest wall rigidity, arrhythmia or allergic reactions were excluded from the study. An increase of 20% in the measured MAP value was considered as hypertension after 1 minute. In this case, topical anaesthesia findings were evaluated. The patients who underwent topical anaesthesia were treated with 0.05 ml/kg propofol or ketofol. After 1 minute, if hypertension persisted, esmolol 10 mg was applied to patients with a CAH value above 100 and perlinganit 100 μg to patients with a CAH value below 100. Hypotension was accepted as a 20% decrease in baseline after 1 minute. In this case, 5 mg ephedrine IV was administered to the patient. The presence of a CAH value of < 45 was accepted as bradycardia. Atropine was administered at 0.5 mg IV. The presence of CAH > 100 was considered as tachycardia. If there were no signs of topical anaesthesia, 10 mg esmolol IV was administered.

Data were analysed using the IBM SPSS v23 (Chicago, USA) program. The Shapiro–Wilk test was used to test the normality of data from the quantitative variables. An independent sample t-test was used to compare means of groups for the variables with a normal distribution. The Mann–Whitney U-test was used to compare the means of the parameters deviating from the normal distribution. The Wilcoxon test was used for intragroup comparisons. The mean ± standard deviation of the quantitative variables with normal distributions was reported, whereas the median (minimum–maximum) were reported for the non-normal variables. The significance level was accepted as $p < 0.05$.

Results

There was no statistically significant difference between the two groups, P and K, in terms of age, height or weight ($p = 0.869$). The duration of anaesthesia and surgery was similar in both groups. The demographic characteristics of the groups are presented in Table 1

Table 1. Demographic characteristics of groups

	K group	P group
Age**	67.8 ± 6.9	68.2 ± 6.7
Height**	166.2 ± 7.9	162.9 ± 6.3
Weight **	78.7 ± 10.0	77.1 ± 10.4
ASA*	2 (1 – 3)	2 (1 – 3)
Anesthesia Time *	115 (75 - 150)	105 (80 - 260)
Surgery Duration *	100 (65 - 130)	95 (70 - 240)

***Median (min-max), ** mean ± standard deviation**

Table 2. Right-side RSO2 values of groups.

Time	K group	P group
T1	68 (51 - 74)	66.5 (55 - 76)
T2	65 (51 - 70)	66 (54 - 75)
T3	64 (48 - 69)	58 (47 - 70)*
T4	64.5 (51 - 70)	59 (47 - 71)*
T5	65 (52 - 70)	60.5 (46 - 71)*
T6	66 (60 - 71)	64 (55 - 82)
T7	66 (57 - 70)	66 (50 - 76)
T8	64.5 (51 - 71)	66 (52 - 70)

Median (min-max),
*: significant difference from the preoperative value at the corresponding measurement time in intra-group comparison ($p<0.05$)

When the groups were compared in terms of right-side RSO_2 measurements, the values in the propofol group were significantly lower than in the ketofol group at 3 and 5 minutes (T4, T5) after intubation. The right-side RSO_2 values and comparison between the two groups and within groups are shown in Table 2 and Figure 1.

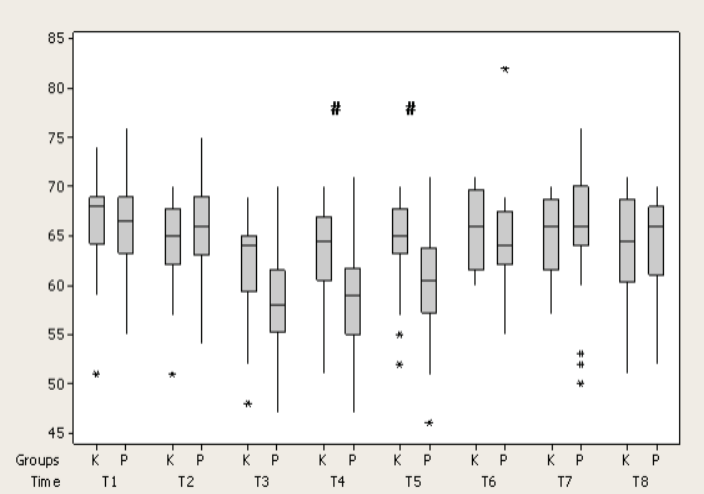

Figure 1. Comparison of the right-side RSO_2 values of groups.
: significant difference between groups at the corresponding measurement time

Left-side RSO_2 measurements revealed that the values at 1, 3 and 5 minutes (T3, T4, T5) in the propofol group were significantly lower than in the ketofol group. The left-side RSO_2 values of the groups and their comparison are shown in Table 3 and Figure 2.

Table 3. Left-side RSO_2 values of the groups.

Time	K group	P group
T1	65 (49 - 72)	64.5 (54 - 74)
T2	65 (50 - 70)	64 (51 - 73)
T3	63 (48 - 70)	58.5 (45 - 73)*
T4	63.5 (48 - 69)	59 (46 - 69)*
T5	64 (50 - 68)	59 (45 - 75)*
T6	66 (60 - 70)	64 (54 - 84)
T7	64 (59 - 73)	64 (50 - 79)
T8	63 (53 - 72)	63 (48 - 71)

Median (min-max),
*: significant difference from the preoperative value at the corresponding measurement time in intra-group comparison ($p<0.05$).

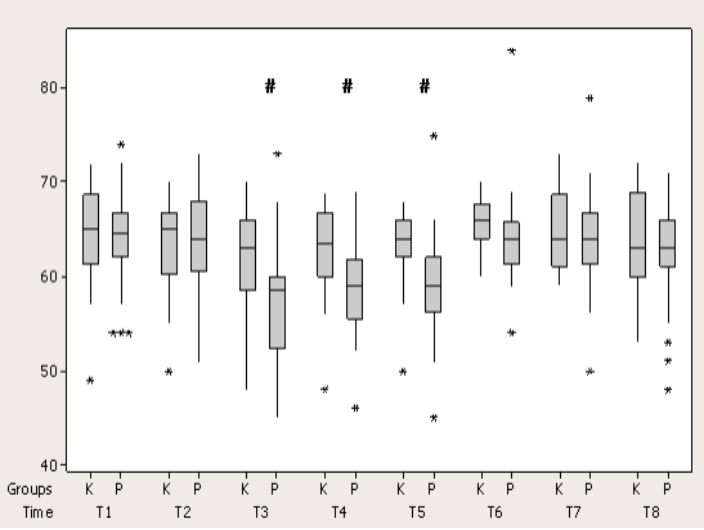

Figure 2. Comparison of the left-side RSO_2 values of groups.
#: significant difference between groups at the corresponding measurement time

When the recorded values of the RSO_2 in terms of time were compared to the preoperative values within the propofol group, RSO_2 was found to be significantly lower after 1, 3 and 5 minutes (T3, T4, T5) after intubation in both the right and left sides. The RSO_2 value decreased from the 10th minute (T6) to the same level as the initial value and no significant difference was found between the values at 30 and 60 (T7, T8) minutes after intubation and the value at the preoperative period.

When the values of the RSO_2 measured at various times were compared to the preoperative values in the ketofol group, no statistically significant difference was observed.

Comparison of the mean arterial pressure values in the groups revealed that the values of MAP at 3 and 5 minutes (T4, T5) were significantly lower in the propofol group than in the ketofol group. MAP values and comparison of the groups are shown in Table 4

Table 4. MAP values of groups

Time	K group	P group
T1	97 (82 - 101)	97.5 (86 - 149)
T2	96 (83 - 101)	97.5 (88 - 130)
T3	93 (75 - 104)	80 (66 - 141)
T4	92 (72 - 107)	77 (68 – 101)
T5	89.5 (79 - 108)	75 (67 - 142)
T6	95 (70 - 102)	83.5 (71 - 184)
T7	96 (68 - 99)	89.5 (65 - 115)
T8	90.5 (71 - 106)	92 (73 - 116)

*: significant difference between group at the corresponding measurement time

Discussion

The effect of different anesthetic drugs on cerebral oxygenation has been investigated in a variety of surgical prosedures. In this study, we investigated the changes in vital signs after anaesthesia induction with propofol and ketofol in patients over 60 years of age and the effects of these changes on cerebral oxygen saturation.

In terms of vital signs, the MAP values were lower in the propofol group compared to the ketofol group at 1, 3 and 5 minutes after induction. The possible explanation for the lower values for group P could be myocardial depression and decrease in peripheral vascular resistance caused by propofol. In the ketofol group, sympathetic stimulation by ketamine may have limited these effects. Aydoğan et al. [14] compared propofol and ketofol in the induction of anaesthesia in elderly patients. They concluded that while propofol use decreases MAP the combination of propofol and ketamine causes minimal hemodynamic changes. These results seem to be consistent with our findings. Kwok et al. [3] also coherently with our results reported that when propofol is used alone in patients older than 55 years causes hypotension for the 5 minutes after induction and that the addition of phenylephrine may prevent the development of hypotension by causing vasoconstriction. Likewise Özgül et al. [15] found that patients administered propofol had significantly lower MAP values after induction than those with ketofol.

We found that post-induction RSO_2 values were significantly lower in patients within the propofol group compared to baseline

values. When the groups were compared, the RSO_2 values were significantly lower in the propofol group compared with the ketofol group. Cerebral oxygenation is known to be affected by variables such as cerebral blood flow, cerebral oxygen consumption and mean arterial pressure [16]. Decreased preoperative hematocrit values, higher preoperative fluid deficit compared to young patients, cerebral fat embolism and hypotension in elderly patients after anaesthesia induction have been reported as potential causes of cerebral desaturation [17]. Anaemia or fluid deficit was not detected in the preoperative evaluation of the patients in our study. The main cause of the decrease in the RSO_2 values appears to be the reduction of brain blood flow with propofol's hypotensive effect.

We found that the RSO_2 levels were lower after 1, 3 and 5 minutes in the propofol group compared to the ketofol group. The higher RSO_2 values evident at 1, 3 and 5 minutes in the ketofol group compared to the propofol group may be due to the lower rate of decrease observed in MAP values, owing to sympathetic stimulation of ketamine. A ketamine-induced increase in the brain blood flow may have contributed to higher levels of post-induction RSO_2 values in patients in the ketofol group compared to the propofol group.

Ketamine wich we added to propofol in our study activates the sympathetic nervous system and preserves cerebral perfusion pressure. Another outcome of the sympathetic activation is the increase in arterial blood pressure. The combination of propofol and ketamine may have maintained the CBF and provided higher RSO_2 values. It is reported that propofol decreases cerebral metabolic rate of oxygen ($CMRO_2$), reduses cerebral blood flow (CBF) and intracranial pressure. Hung et al. [4] compared the effect of propofol on haemodynamic changes and cerebral oximetry between young and elderly patients. There was a statistically significant decrease in both groups in MAP and RSO_2 values after induction. Sevoflurane is known to reduce CBF less than propofol. Moreover sevoflurane can cause an increase on CBF with high concentrations. But the effects of both drugs on $CMRO_2$ are similar. Various studies tested whether RSO_2 diferred with sevoflurane or propofol anesthesia. Except for a few [18] most of them concluded that sevoflurane was associated with higher RSO_2 values [19, 20, 21]. In the study performed by Güçlü et al. [22] propofol infusion was administered to one group and sevoflurane was administered to the other group. Cerebral oxygen saturation levels were found to be statistically lower in the propofol group. Valencia et al. [23] also investigated the effect of sevoflurane and propofol on cerebral oximetry. The results of the study revealed that the RSO_2 values of the patients in the propofol group were lower than those of the sevoflurane group. There was a significant decrease in baseline RSO_2 values after induction in the propofol group.

In the present study, RSO_2 values measured in the propofol group at 5 minutes and in the ketofol group at 3 minutes were similar to the baseline values. This might be because the drugs used in the maintenance of anaesthesia after the end of the induction period did not yield any significant difference between the groups Kwok et al. reported that RSO_2 values returned to normal levels between 5 and 10 minutes after induction [3]. The aforementioned study of Hung et al. [4] reported that post-induction RSO_2 value returned to baseline in 5 minutes.

Based on the results of the study reported here, we believe that the effects of ketamine on sympathetic stimulation and cerebral blood flow are compensated by propofol, and that myocardial depression and the hypotensive effects of propofol are balanced by ketamine. Considering these aspects the temporary decrease in MAP and RSO_2 values after induction could be due to the inability to balance the effects of propofol when used alone.

Conclusions

In conclusion, 1:1 ketamine addition to propofol (ketofol) provides more stable haemodynamics for the induction of anaesthesia in elderly patients compared to the sole use of propofol. Therefore, it helps to maintain cerebral oxygen saturation. When the results are considered ketofol administration as an induction agent in elderly patients will contribute to the preservation of cerebral oxygen saturation and hence the preservation of postoperative cognitive functions. However these results need to be confirmed with larger groups in future studies.

Competing interests
The authors declare that they have no competing interests.

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Ethical approval
Ondokuz Mayıs University, Medicine Faculty Ethics committee approval was obtained with the following file number 2015 yılı Sayı: B.30.2.0DM.0.20.08/2120.

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