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ORIGINAL ARTICLE

# Comparison of effects of propofol and ketamine–propofol mixture (ketofol) on laryngeal mask airway insertion conditions and hemodynamics in elderly patients: a randomized, prospective, double-blind trial

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**Abstract**
*Purpose* The objective of this study was to compare the effects of ketamine–propofol mixture (ketofol) and propofol on ProSeal laryngeal mask airway (PLMA) insertion conditions and hemodynamics in elderly patients.
*Methods* Eighty elderly patients, American Society of Anesthesiologists (ASA) physical status I and II, were randomly divided into two groups to receive either propofol 0.15 ml/kg ($n = 40$), or ketofol (using a 1:1 single-syringe mixture of 5 mg/ml ketamine and 5 mg/ml propofol) ($n = 40$) before induction of anesthesia. Sixty seconds after induction, the PLMA was inserted. Heart rate and arterial blood pressure (systolic [S] BP) were recorded prior to the induction of anesthesia, immediately following induction, immediately after PLMA insertion, and 5 and 10 min after PLMA insertion. PLMA insertion conditions were scored according to mouth opening, swallowing, coughing, head and body motion, laryngospasm, and ease of PLMA insertion by the same experienced anesthesiologist, who did not know which agents were used.
*Results* There were no differences in PLMA insertion conditions between the groups. The number of patients in need of ephedrine ($P = 0.043$) and the total dose of ephedrine ($P = 0.022$) were significantly lower, and apnea duration ($P < 0.001$) was significantly higher in the ketofol group compared with the propofol group. SBP was significantly higher in the ketofol group than in the propofol group immediately after PLMA insertion and 5 min after PLMA insertion.
*Conclusions* The same PLMA insertion conditions were found with ketofol and propofol. The number of patients in need of ephedrine and the total ephedrine dose were lower and apnea duration was increased in the ketofol group.

**Keywords** Propofol · Ketamine · Laryngeal mask airway · Elderly patients

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## Introduction

Propofol is a sedative-hypnotic agent with a short onset, duration, and recovery time [1]. These properties make propofol an ideal agent for ambulatory anesthesia. However, propofol can cause cardiorespiratory instability and depression at the doses used for laryngeal mask airway (LMA) insertion, especially in elderly and high-risk patients [2–4].

The anesthetic agent ketamine stimulates the sympathetic nervous system and increases blood pressure along with increasing the heart rate. It has been reported that intraoperative hemodynamics is more stable in studies where ketamine and propofol were combined [5, 6].

A ketamine-propofol mixture (ketofol) is obtained in a 20 ml syringe with a 1:1 mixture of ketamine 10 mg/ml with propofol 10 mg/ml [7]. It is known that the mixture of ketamine and propofol in a polypropylene syringe is chemically stable, the agents are physically compatible, and the mixture can be stored at room temperature with exposure to light [8]. With the use of the propofol and ketamine mixture, the dose of both agents is decreased and their undesired effects are minimized [9]. Ketofol is used

for sedation and analgesic purposes in pediatric oncological procedures [10], emergencies [7, 11–13], and during regional anesthesia [9, 14].

There has been no reported study showing the use of ketofol during ProSeal laryngeal mask airway (PLMA) insertion in elderly patients. The objective of this study was to compare the effects of ketofol and propofol on PLMA insertion conditions and hemodynamics in elderly patients.

## Methods

Following approval provided by the Ethics Committee of Inonu University Turgut Ozal Medical Centre (Ethics Committee No. 2011/134, 06 September 2011, President M. Genc), Malatya, Turkey, and the provision of written informed consent from the patients and/or legal guardians, 80 male patients scheduled for elective urological surgery were included in the study between September 2011 and February 2012. Patients had American Society of Anesthesiologists (ASA) physical status I–II, and were aged 65 years or older. Patients with risk of aspiration, allergy to the drugs to be used, upper respiratory tract infection, asthma history, or anticipated difficult airway were excluded.

No premedication was prescribed. In the operation room, standard anesthetic monitoring was applied with noninvasive blood pressure (NIBP), electrocardiograph (ECG), and peripheral oxygen saturation ($SpO_2$) with a pulse oximeter. Peripheral venous access was obtained using a 20-G intravenous (i.v.) catheter from the dorsal surface of the hand, and Ringer's lactate infusion was started.

The patients were randomly divided into two groups (ketofol group and propofol group) using a computer-generated random number table (Fig. 1). For the ketofol group, a ketofol solution (total 20 ml) was prepared, with the agents in the same syringe, using ketamine 100 mg (Ketalar® 50 mg/ml Pfizer) and propofol 100 mg (1 % propofol® Fresenius); the ketofol syringes contained ketamine 2 ml (100 mg), propofol 1 % 10 ml (100 mg), and saline 8 ml. The concentrations of these drugs were thus 5 mg/ml ketamine and 5 mg/ml propofol, and there was no interaction between these drugs in the mixture. A 20-ml syringe of propofol 1 % (10 mg/ml) was used for the propofol group.

Following 3-min preoxygenation, fentanyl 1 μg/kg was administered in 30 s, and ketofol 0.15 ml/kg (0.75 mg/kg ketamine + 0.75 mg/kg propofol) for the ketofol group and propofol 0.15 ml/kg for the propofol group were administered in 20 s. If required, further increments of drugs (ketofol or propofol), at 0.05 ml/kg, were given every 30 s until loss of consciousness and loss of eyelash reflex. At 60 s after the induction of anesthesia, a PLMA (Laryngeal Mask Co, Henley-on-Thames, UK) was inserted, using the Brain method [15], by the same experienced anesthesiologist, who did not know which of the agents were given. PLMA insertion conditions were scored according to mouth opening (1 = full, 2 = partial, 3 = none), swallowing (1 = nil, 2 = mild, 3 = severe), coughing (1 = nil, 2 = mild, 3 = severe), head and body motion (1 = nil, 2 = mild, 3 = severe), laryngospasm (1 = none, 2 = mild, 3 = severe), and ease of LMA insertion (1 = easy, 2 = difficult, 2 = impossible).

Following successful PLMA insertion, the position of the PLMA was checked by observing respiratory movements, chest expansion, and capnography. Cessation of respiration for 30 s was accepted as apnea, and the apnea times were recorded after PLMA insertion.

In cases of failure of PLMA insertion, an additional dose of 0.05 ml/kg ketofol or propofol was applied. At most, 3 failed attempts were allowed. The number of attempts for successful insertion was noted; however, the first insertion condition was evaluated.

Following successful PLMA insertion, anesthesia was maintained using sevoflurane 1–2 % and nitrous oxide 60 % in oxygen.

After the PLMA insertion, the patients were manually ventilated to maintain $SpO_2$ at >95 % and an end-tidal $CO_2$ concentration of 4.6–5.9 kPa until the return of spontaneous ventilation.

Heart rate (HR), mean blood pressure (MBP), systolic blood pressure (SBP), diastolic blood pressure (DBP), and $SpO_2$ were recorded prior to the induction of anesthesia ($t_0$), immediately following induction ($t_1$), immediately after PLMA insertion ($t_2$), and 5 ($t_3$) and 10 min after PLMA insertion ($t_4$). Complications such as bradycardia, muscle rigidity, and excessive secretion were monitored. If SAP or HR decreased below 80 mmHg or 45 beats/min, respectively, ephedrine 5 mg or atropine 0.5 mg was administered.

An appropriate power analysis suggested that the study design would have more than 90 % power to detect a significant difference in the hemodynamic response between groups (change of > 20 % in systolic blood pressure). Statistical analyses were done using SSPS 16.0 version via Windows computer software (SSPS, Chicago, IL, USA). Within the groups, normality of variables was measured using the Shapiro–Wilk test. Differences between groups were evaluated using an independent sample *t*-test and the Mann–Whitney *U*-test. When appropriate, paired sample *t*-tests and the Wilcoxon test were used for intergroup repeating tests. Yates corrected $\chi^2$ test was used for category changes in the groups (ephedrine need). Differences between the groups in the doses of ephedrine used were determined using Fisher's exact test.

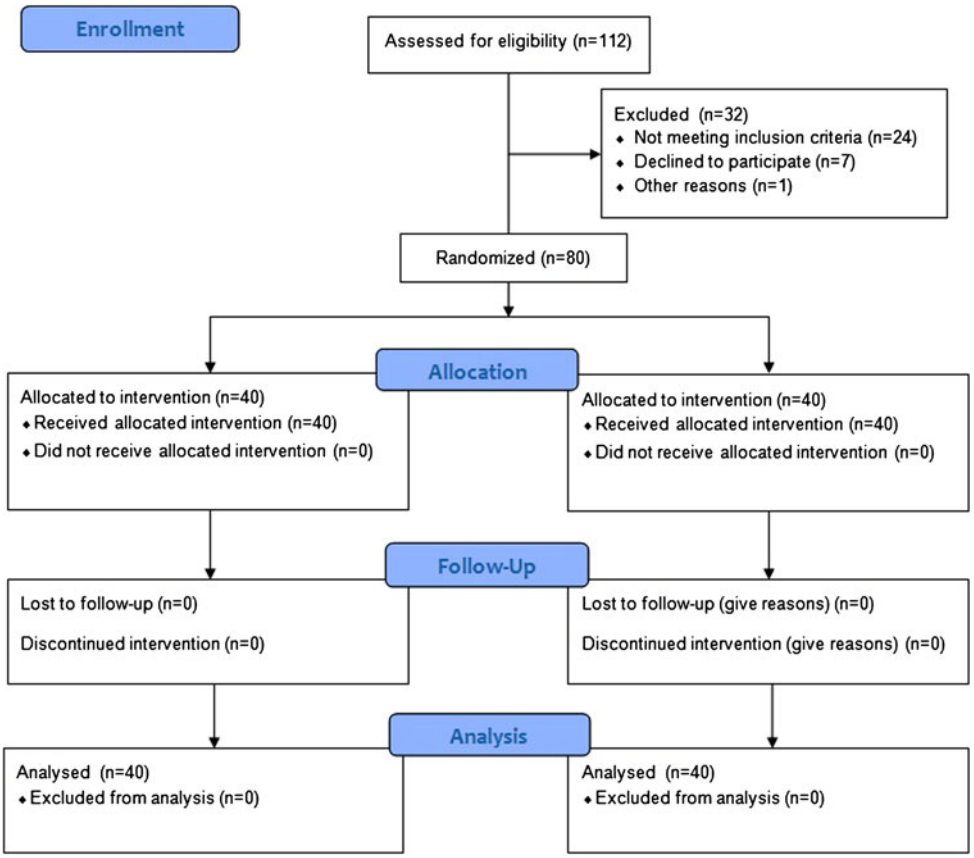


**Fig. 1** Flow chart of the study

A $P$ value of less than 0.05 was considered to be statistically significant. Data are expressed as mean values ± SD or numbers ($n$).

## Results

The demographic data of the patients in the two groups were similar (Table 1).

There were no differences in PLMA insertion conditions between the groups (Table 2).

Systolic blood pressure (SBP) was significantly higher in the ketofol group compared with the propofol group at $t_2$ ($P < 0.05$) and $t_3$ ($P < 0.05$). There were statistically significant decreases in SBP when compared with baseline measurements for both groups at all times (Fig. 2).

Although HR was higher at all measurement times in the ketofol group compared with the propofol group, the increases in the HR were statistically significant only at $t_1$ and $t_4$ (Fig. 3).

The number of patients in need of ephedrine ($P = 0.043$) and the total dose of ephedrine ($P = 0.022$) were significantly lower, and apnea duration ($P < 0.001$) was significantly higher in the ketofol group compared with the propofol group (Table 3).

No adverse effects, such as excessive secretion, bradycardia, or muscular rigidity were observed in any patients.

**Table 1** Demographic data

| | Ketofol group ($n = 40$) | Propofol group ($n = 40$) |
|---|---|---|
| Age (years) | 71.67 ± 7.10 | 70.85 ± 5.95 |
| Body weight (kg) | 71.05 ± 9.37 | 71.32 ± 9.58 |
| ASA grade (I/II) | 12/28 | 14/26 |

Values are presented as means ± SD or numbers of patients

*ASA* American Society of Anesthesiologists

## Discussion

Our study has shown that ketofol is a better alternative to propofol in providing acceptable PLMA insertion conditions causing less hemodynamic alteration in elderly patients, with a lower number of patients in need of ephedrine and lower total ephedrine consumption.

The superiority of propofol in inhibiting upper airway reflexes has made it the primary choice among all other agents for LMA insertion [16]. Propofol doses required for

**Table 2** Insertion conditions of ProSeal laryngeal mask airway (PLMA; numbers of patients)

| | Ketofol group ($n = 40$) | Propofol group ($n = 40$) |
|---|---|---|
| Mouth opening | | |
| Full/partial/nil | 37/3/0 | 38/2/0 |
| Gagging or coughing | | |
| Nil/mild/severe | 40/0/0 | 40/0/0 |
| Swallowing | | |
| Nil/partial/full | 37/3/0 | 37/3/0 |
| Movement | | |
| Nil/partial/complete | 37/3/0 | 35/5/0 |
| Larygospasm | | |
| Nil/partial/complete | 38/2/0 | 40/0/0 |
| Ease of PLMA insertion | | |
| Easy/difficult/ımpossible | 37/3/0 | 33/6/1 |
| Insertion conditions summed | | |
| Score | 6 (range 6–8) | 6 (range 6–9) |

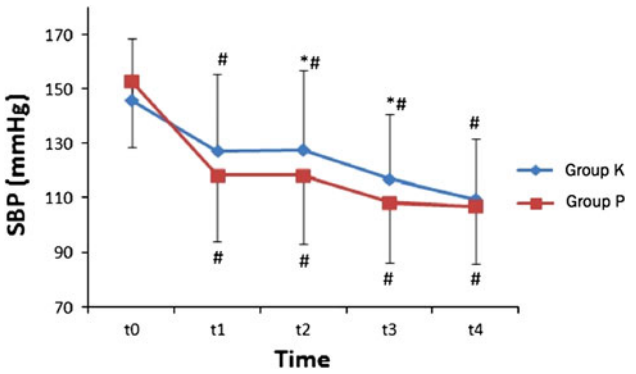


**Fig. 2** Changes in systolic blood pressure (*SBP*). $^{*}P < 0.05$ differences between groups. $^{\#}P < 0.05$ compared with baseline values. *Group K* ketofol group, *Group P* propofol group

laryngeal mask insertion (administered during induction) frequently cause a significant decrease in blood pressure. This rarely has clinical importance for young and healthy patients, but it is very important for the elderly [17]. Hypotension that can be caused by propofol may reduce tissue perfusion and oxygenation [18]. Various agents, such as nitrous oxide [19], clonidine [20], opioids [21], and low-dose ketamine [22] have been used in order to reduce the propofol concentration required for LMA insertion.

Goh et al. [18] used ketamine, fentanyl, or saline during LMA insertion prior to propofol induction, and showed higher systolic blood pressures (SBPs) in the ketamine group in comparison to those in the fentanyl and saline groups. Even though there was no significant difference in the heart rates (HRs), there was a slight tendency to an increase in the ketamine group. Gupta et al. [23], who compared ketamine, fentanyl, and butorphanol before

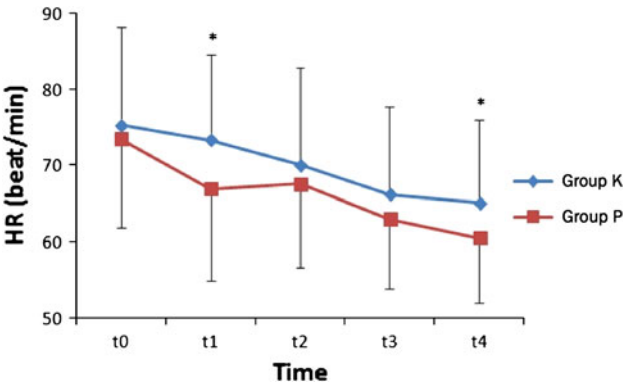


**Fig. 3** Changes in heart rate (*HR*). $^{*}P < 0.05$ differences between groups. For time (*t*) definitions, please see the 'Methods' section in the text

**Table 3** The numbers of patients who received ephedrine, the total dose of ephedrine, and the apnea duration

| | Ketofol group ($n = 40$) | Propofol group ($n = 40$) | *P* value |
|---|---|---|---|
| The total dose of ephedrine (mg) | 3 ± 4.77 | 6.87 ± 8.44 | 0.022 |
| The number of patients in need of ephedrine (*n*) | 14 | 23 | 0.043 |
| Apnea duration (min) | 5.85 ± 2.8 | 3.45 ± 2.20 | <0.001 |

propofol induction in LMA insertion also found higher systolic and diastolic BPs in the ketamine group. In our study, the SBP and HR were higher in the ketofol group; however, the differences between the groups in SBP and HR reached statistically significant levels only at $t_2$ and $t_3$ and $t_1$ and $t_4$, respectively.

Ketamine increases the HR, arterial BP, and cardiac outflow. These cardiovascular effects depend on the stimulation of the sympathetic nervous system and the inhibition of norepinephrine reuptake. The main effect of propofol on the cardiovascular system is a decrease in BP due to a reduction in systemic vascular resistance, cardiac contractility, and preload [24]. Some studies have demonstrated that the coadministration of propofol and ketamine is more favorable than propofol alone, due to the stabilizing hemodynamics, given that the arterial pressure and HR effects of the individual agents tend to cancel one another out [22].

Ephedrine has both $\alpha$ and $\beta$ adrenergic properties and is helpful in hypotension treatment; however, it can cause tachycardia [25] and arrhythmia [26]. The vasoconstrictor and hypertensive effect of ephedrine is a potential problem. Cardiovascular complications and tachycardia are observed more frequently in elderly patients and can cause serious cardiovascular risks. Age-related changes in the density of

$\alpha_1$-adrenoceptors could be one possible cause of the augmented pressor response to ephedrine in the elderly [25]. So a decrease in the ephedrine requirement is clinically beneficial in a geriatric population. Although the smallest effective dose of i.v. ephedrine for reducing the incidence of hypotension was found to be 10 or 20 mg, this dose did not completely eliminate hypotension and caused reactive hypertension [27]. Small doses of ephedrine ranging from 0.07 to 0.1 mg/kg before propofol anesthesia were associated with fewer hypotensive episodes, less need for rescue vasopressors, fewer ischemic episodes, and minimal changes in HR during valve surgery [28]. We think these cardiovascular side effects can be minimized, if not totally eliminated, by careful titration of ephedrine. In our study, the ketofol group needed less ephedrine than the propofol group. Thus, the use of ephedrine can be decreased and the negative effects caused by ephedrine may be prevented when ketofol is used.

Correct positioning and smooth insertion of an LMA requires sufficient depth of anesthesia. Nowadays, propofol is the most preferred agent in LMA insertion. To improve LMA insertion conditions, lidocaine [29], midozalam [30], opioids [31], or low-dose muscle relaxants [32] have been combined with propofol. In the present study, the PLMA insertion conditions for both the ketofol and propofol groups were similar.

In the present study it was observed that the apnea duration in the ketofol group was longer than that in the propofol group. It has been shown in various animal and human studies that bolus-dose ketamine depresses the respiratory response to $CO_2$, similar to opioids. Similarly, there are studies stating that hypoxemia and apnea have been observed following the administration of i.v. ketamine [33, 34]. The use of opioids during LMA insertion also increases the apnea duration [35]. The increase of apnea duration in the ketofol group in our study may have been due to the use of fentanyl (although it was used in both groups) and the aforementioned effects of ketamine.

Ketamine can increase airway secretions. This hypersalivation is clinically important in children; however, in adults it occurs less frequently and is rarely of clinical significance [36]. The combination of ketamine and propofol has not been shown to cause excessive secretions when an LMA or a tracheal tube is used in airway management [18, 22, 37]. It has been reported that propofol could be effective in eliminating the side effects of a subanesthetic dose of ketamine in humans [38]. In the present study, excessive secretions were not observed in either of the two groups.

Another concern limiting the use of ketamine is the possibility of an increase in intracranial pressure and the emergence of psychotomimetic reactions. Because of these adverse effects, ketofol may be contraindicated in patients with an open eye injury or other ophthalmologic disorder; psychiatric disease, such as schizophrenia; a history of adverse reaction to ketamine; or patients with vascular aneurysms [39].

The limitations of our study are that the anesthetic depth could not be measured, and the lack of evaluation of injection pain during induction of anesthesia in both groups.

The bispectral index (BIS) is a processed electroencephalography (EEG) variable that is widely used to guide the administration of hypnotic drugs. Several studies have reported an increase in BIS values, despite a deepening level of hypnosis, when ketamine 0.5 mg kg was administered as a rapid bolus during general anesthesia [40, 41]. Therefore, we did not use BIS for assessment of the level of hypnosis during induction.

It was concluded, from our study in elderly patients, that although ketofol increased the apnea duration, it provided PLMA insertion conditions similar to those for propofol, with a decreased ephedrine requirement. Ketofol is a good choice of induction agent when using a ProSeal LMA in elderly patients, except in those patients for whom the use of ketamine is contraindicated.

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