

# The comparison of effects of thiopental and ketofol on emergence agitation in patients with nasal surgery: A prospective, single-blind, randomized clinical trial

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## Abstract

**Aim:** Emergence agitation (EA) is a postanesthetic phenomenon that is common in patients who undergo nasal surgery with general anesthesia, which manifests itself with confusion and violent behaviors and may cause serious problems such as bleeding in the surgical site, unplanned removal of catheter or endotracheal tube. In this study, we aimed to compare the effect of thiopental and ketofol on EA formation after nasal surgery.

**Material and Methods:** This study was performed as a prospective, randomized, single-blind, clinical trial in 80 patients undergoing nasal surgery. The patients were randomly divided into two groups as thiopental (group P:40) and ketofol (group K:40). As the primary outcome; Riker Sedation Agitation Scale (RSAS) was used in order to evaluate EA at the 5th minute after extubation. As the secondary outcome; we aimed to evaluate predisposing factors causing EA.

**Results:** The mean age of the patients was  $38.55 \pm 13.12$  in Group P, while it was  $40.68 \pm 11.88$  in Group K. The incidence of emergence agitation (EA) was significantly higher in Group P than in Group K. There was a statistically significant difference between the two groups (Group P:12 cases (30%), Group K:1 case (2.5%),  $P < 0.001$ ). Residual sedation values in PACU were similar in both groups ( $P < 0.248$ ). The duration of stay in PACU was significantly lower in Group P ( $P < 0.001$ ). Duration of anesthesia, duration of surgery, time to extubation and time to verbal response times were similar in both groups. There was no statistically significant difference between the groups.

**Conclusion:** In patients who underwent nasal surgery under general anesthesia; using ketofol instead of thiopental can significantly reduce EA.

**Keywords:** Thiopental; ketofol; emergence agitation

## INTRODUCTION

Emergence Agitation (EA), is a postanesthetic phenomenon manifested by agitation, confusion, disorientation, and violent behavior during the early stage of general anesthesia recovery (1). It may cause serious problems such as bleeding in the surgical site, unplanned removal of the catheter or endotracheal tube, prolongation of recovery and discharge time (2). The incidence in adults was reported to be between 4.7%-21.3% (3).

Young age, smoking, sevoflurane and desflurane anesthesia, duration of anesthesia, postoperative pain  $\geq 5$  on a numerical rating scale (NRS), and presence of endotracheal tube and urinary catheter were shown to be

significantly related with the occurrence of EA (4,5).

Different scales are used to determine the degree of postoperative agitation of the patient. Among these, the Ricker Sedation-Agitation Scale (RSAS) provides a quick and easy assessment of the patient and has a wide range of use in terms of agitation-sedation rating (6).

Ketofol; It is a mixture of ketamine and propofol in different ratios and is used in many areas of anesthesia practice (7). The complementary effects of the mixture make it attractive to use. By this means, when they are used in combination, it is possible to use a dose lower than the dose to be given and to avoid side effects that may occur with the increasing doses (8).

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The effects of many anesthetic agents on EA in septal surgeries have been studied (2,9). However, studies comparing the effects of ketofol and thiopental sodium on EA are limited.

In this study, as the primary outcome, we aimed to compare the effects of ketofol and thiopental sodium on EA in adult patients undergoing nasal surgery; and as the secondary outcome; we aimed to evaluate predisposing factors causing EA.

## MATERIAL and METHODS

This study was conducted as a prospective, randomized, single-blind and controlled clinical trial in 80 patients who were ASA (American Society of Anesthesiologists) group I-II patients, aged between 18-65 years, and who were planned for elective nasal surgery, after obtaining permission from Malatya Clinical Research Ethics Committee (2019/109) and written informed consents of the patients. The patients were randomly divided into two groups as thiopental (group P:40) and ketofol (group K:40). MedCalc version-16 statistical software (medcalc.com) for Windows was used for randomization. Patients who had known allergy to drugs used in the study, body mass index  $\geq 30$  kg m<sup>2</sup>, ASA $\geq 3$ , neuromuscular disorder and cognitive disorder and who were pregnant were excluded from the study.

Noninvasive blood pressure (NIBP), pulse oximetry (SpO<sub>2</sub>), electrocardiogram (ECG) and end-tidal carbon dioxide (EtCO<sub>2</sub>) standard monitoring were applied to the patients who were admitted to the operation room. Then, preoperative oxygenation was performed with 80% oxygen for 3 minutes.

In Group K anesthesia induction was prepared/performed? by supplementing with ketofol 1 mg.kg<sup>-1</sup> IV (ketamine-propofol mixture at 1:1 ratio); ketofol solution of 100 mg ketamine; 2 cc (Ketalar 50 mg/ml, Pfizer, Zentiva, Luleburgaz, Turkey), 100 mg of propofol; 5 cc (% 2 propofol; Fresenius Kabi GmbH, Austria) and 3 cc of physiological saline solution. The mixture was prepared to include 10 mg/ml of ketamine and 10 mg/ml of propofol. In Group P, anesthesia induction was performed with thiopental 5 mg.kg<sup>-1</sup> IV. Fentanyl 1 µg.kg<sup>-1</sup> IV and rocuronium 0.5 mg.kg<sup>-1</sup> IV were used in both groups. Intubation was performed by an anesthesiologist who had at least 5 years of experience in endotracheal tube placement with a success rate of over 90% after the patients lost consciousness and jaw laxity was sufficiently formed. Sevoflurane at 1 MAC in a 50% O<sub>2</sub>/N<sub>2</sub>O mixture was used for the maintenance of anesthesia. Patients in both groups were intraoperatively ventilated with tidal volume of 8 ml/kg and respiration rate was adjusted to keep EtCO<sub>2</sub> values between 35-45 mm-Hg. Mean arterial pressure (MAP), heart rate (HR), (SpO<sub>2</sub>) were recorded just before the induction of anesthesia, at 5-30 minutes after or during the surgery and 5 minutes after extubation. Demographic data, smoking, surgical duration, duration of total anesthesia, duration of extubation, the first response to

verbal stimuli, cough, and laryngospasm were evaluated.

After the surgical procedure was completed, atropine 0.01 mg.kg<sup>-1</sup> and neostigmine 0.02 mg.kg<sup>-1</sup> I.V. were used to restore neuromuscular function. The patients who opened their eyes with stimuli, whose spontaneous breathing was regular, whose respiratory rate was 12-20/minute and whose oxygen saturation was greater than 95% were extubated and taken to the recovery room. Cases with a Modified Aldrete's score of 9 were transferred to the relevant service (10).

At 5 minutes after extubation, EA was evaluated by Riker Sedation-Agitation Score Scale (RSAS); (7: Dangerous Agitation; the patient pulls at ET tube, tries to remove catheters, climbs over bedrail, strikes at staff, thrashes side-to-side. 6: Very agitated ET; the patient bites, does not calm down despite frequent verbal warnings, requires physical intervention. 5: Agitated; the patient is anxious or slightly agitated, tries to sit down, calms down with verbal warnings. 4: Calm and cooperative; the patient wakes up easily, obeys orders. 3: Sedated; the patient wakes up with verbal stimuli or slight shaking, sleeps again, follows simple orders. 2: Very sedated; the patient wakes up with physical stimuli but cannot communicate, cannot follow orders. 1: Unarousable; the patient gives minimal or no response to stimuli, does not communicate, does not obey orders) (6). Cases with an RSAS score  $\geq 5$  were accepted as agitated. Patients who could not be controlled with verbal stimuli were treated with midazolam 0.05 mg.kg<sup>-1</sup> I.V.

The duration of anesthesia is the time from anesthesia induction to the extubation. Surgical time is the time from the first surgical incision to the last suture. Extubation time is the time from end of the surgery when anesthetic drugs are discontinued, to the extubation. The duration of stay in the post-anesthetic care unit (PACU) is time from admission to the recovery room to transferring to the relevant service. Verbal response time is a meaningful response to simple verbal commands given after extubation (open your eyes etc.).

Laryngospasm was defined as an airway obstruction due to muscle rigidity in the chest and abdomen, and desaturation was defined as (SpO<sub>2</sub>  $\leq 94$ ) (11).

In the recovery room; residual sedation (RSAS 3), pain; postoperative pain on a numerical rating scale (NRS) (on a 0-10 scale (0-1: mild, 2-4: moderate, 5-7: moderate, 8-10 severe) were evaluated by a blinded anesthetist. Patients with NRS  $\geq 5$  received 15 mg.kg<sup>-1</sup> IV paracetamol.

Nausea and vomiting were evaluated with a 0-3 scale (0 = no nausea, 1 = mild nausea, 2 = severe nausea, 3 = retching, vomiting, or both). In cases of severe nausea, ondansetron 50 µg kg<sup>-1</sup> I.V. was administered as an antiemetic.

### Sample Size

The minimum sample size required to detect a significant difference using this test should be at least 26 in each

group (52 in total), considering type I error (alpha) of 0.05, power (1-beta) of 0.8, the effect size of 0.81, and the two-sided alternative hypothesis (H1).

**Statistical Analysis**

The data were expressed as mean (standard deviation, SD) or the frequency with the percentage depending upon overall variable distribution. Normality was assessed using the Shapiro Wilk test. Qualitative data were analyzed with the Pearson chi-square test, Yates corrected chi-square test, and Fisher's Exact test where appropriate. Quantitative data were analyzed by independent samples t-test. P<0.05 values were considered as significant. IBM SPSS Statistics version 26.0 for Windows (Armonk, NY: IBM Corp.) was used for all the statistical analyses.

**RESULTS**

Eighty patients undergoing nasal surgery were included in the study. Mean age of the patients was 38.55±13.12 in Group P, while it was 40.68±11.88 in Group K. Weight of the patients was 69.60±13.73 in Group P, while it was 71.95±11.08 in Group K. Mallampati, ASA, smoking, gender, and weight values were similar in both groups. There was no statistically significant difference between the groups in terms of demographic characteristics (Table 1).

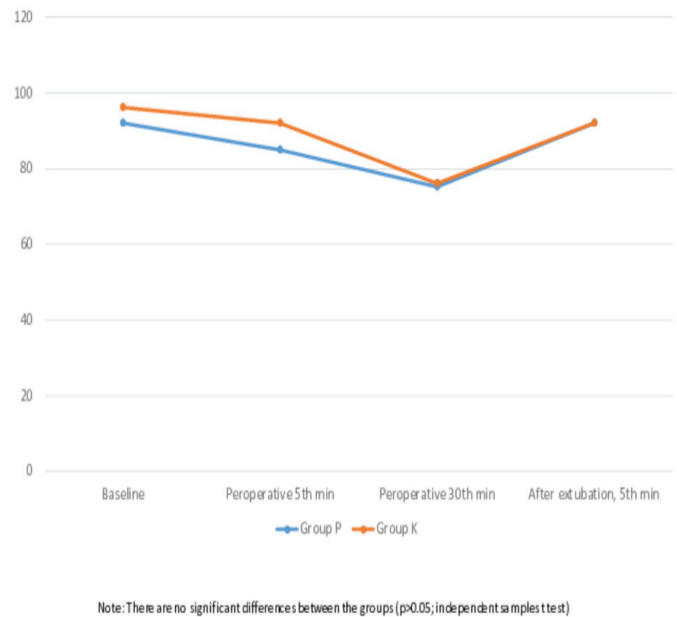
Table 1. Characteristics of the groups			
Variable	Group P (n=40)	Group K (n=40)	p value
	Mean ± SD or n(%)	Mean ± SD or n(%)	
Age, years			
Gender, male/female	14/1	7/3	10.7±7.79
Height, cm	161.5	162.6	13.4±9.44
Weight, kg			
ASA, n	43	22.4	8.8±6.12
1	34	17.7	14.7±9.30
2	27	14.1	13.9±5.62
Mallampati Score	88	45.8	10.7±9.04
1			
2	38	19.8	13.57±11.10
Smoking, n (%)	14/6	7/6	11.10±7.40

ASA: American Society of Anesthesiology; cm: centimeter; kg: kilogram; min: minutes; n: number, SD: Standard Deviation; a: independent samples t test; b: Yates' corrected chi-square test

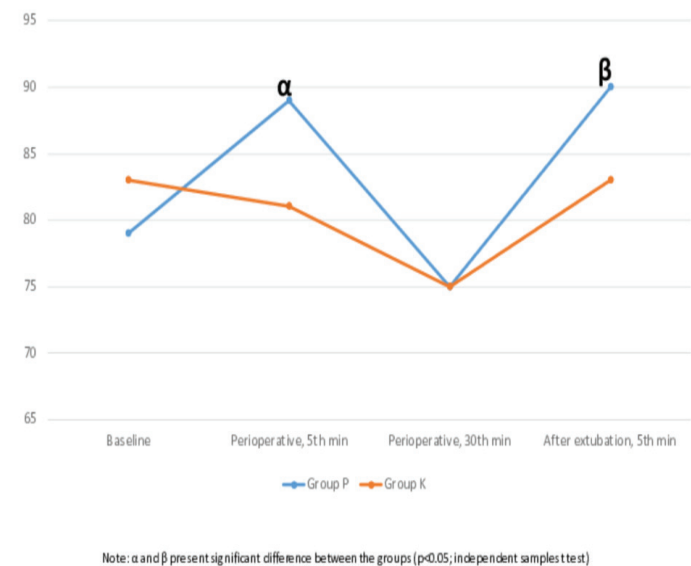
The incidence of emergence agitation (EA) was significantly higher in Group P than in Group K (Group P=12 cases (30%), Group K:1 case (2.5%), P=0.001). Residual sedation values in PACU were similar in both groups (P=0.248). Duration of stay in PACU was significantly lower in Group P (P<0.001). While the duration of anesthesia, duration of surgery,

length of stay in PACU and time to verbal response times were different in both groups, time to extubation was not statistically significant between the groups (Table 2). The incidence of laryngospasm was similar in both groups. There was no significant difference between the groups.

Hemodynamic parameters of the cases; perioperative 5th minute and post-extubation 5th minute HR values in group K were significantly lower than in Group P, which were statistically significant difference between the groups (P=0.024 and P=0.012). When the MAP values of both groups were compared, there was no significant difference between the groups (figures 1 and 2).



**Figure 1.** Heart rate of the patients at various timepoints in two groups



**Figure 2.** Mean arterial pressure of the patients at various timepoints in two groups

**Table 2. Incidence of emergence agitation and recovery characteristics**

Variable	Group P (n=40)	Group K (n=40)	p value
<b>RSAS</b>			
1			
2	5 (12.5%)	0 (0%)	10.7±7.79
3	13 (32.5%)	12 (30%)	13.4±9.44
4	10 (25%)	27 (67.5%)	
5	9 (22.5%)	1 (2.5%)	
6	2 (5%)	0 (0%)	
7	1 (2.5%)	0 (0%)	
Emergence agitation (EA)	12 (30%)	1 (2.5%)	0.001 <sup>a</sup>
Residual sedation	22 (55%)	28 (70%)	0.248 <sup>c</sup>
Time to verbal response, min	6.250±2.400	4.780±2.423	0.008 <sup>d</sup>
Time to extubation, min	8.900±3.550	7.980±3.958	0.275 <sup>d</sup>
Length of stay in PACU, min	17.200±6.065	22.600±6.961	<0.001 <sup>d</sup>
Duration of Anesthesia, min	89.50±34.69	113.13±36.50	0.004 <sup>d</sup>
Duration of Surgery, min	75.200±32.379	95.480±36.568	0.01 <sup>d</sup>

ASA: American Society of Anesthesiology; cm: centimeter; kg: kilogram; min: minutes; n: number, SD: Standard Deviation; a: independent samples t test; b: Yates' corrected chi-square test

In PACU; postoperative NRS was similar in both groups in terms of pain intensity assessment, and there was no statistically significant difference (P=0.114). The incidence of rescuing analgesics was higher in group P (6 cases; 15%). This rate was 4 (10%) in Group K. However, there was no statistically significant difference between the groups. Postoperative vomiting was seen in 2 (5%)

cases in Group P and 4 (10%) cases in Group K. There was no statistically significant difference (P=0.262). The incidence of using anti-emetic drugs was lower in group P (2 cases; 5%). In Group K, they were used in 4 cases (10%). There was no statistically significant difference between the groups (Table 3).

**Table 3. Incidence of adverse events and patients received rescue drugs in PACU**

Variable	Group P (n=40)	Group K (n=40)	p value
<b>NRS for pain</b>			
1	24(60%)	33(82.5%)	
2	10(25%)	3(7.5%)	
3	5(12.5%)	3(7.5%)	0.114 <sup>a</sup>
4	1(2.5%)	1(2.5%)	
<b>Vomiting and nausea</b>			
1	30(75%)	33(82.5%)	
2	8(20%)	3(7.5%)	
3	-	-	0.262 <sup>a</sup>
4	2(5%)	4(10%)	
Analgesics	6 (15%)	4 (10%)	0.737 <sup>b</sup>
Antiemetics	2 (5%)	4 (10%)	0.675 <sup>b</sup>

The data are presented as frequency (percentage); NRS: numerical rating scale (0=no sense of pain, 10=worst imaginable sense of pain); a: Pearson Chi square test, b: Fisher's exact test

## DISCUSSION

In this study; the effects of thiopental and ketofol on EA in adult nasal surgery patients were compared. It was found that EA was less common in the ketofol group, and that the duration of anesthesia, duration of surgery, length of stay in PACU and time to verbal response times were different in both groups, time to extubation was not statistically significant between the groups. In the postoperative period, the need for rescue analgesic use was higher in group P, although not statistically significant.

Although EA is more common in children after general anesthesia, it is also a problem seen in adults (12). The incidence of EA in adults has been reported as between 4.7% and 21.3% (3).

The patient may cause harm to himself or the people around him/her due to EA. If the patient is not taken under control; he/she may lead to self-extubation, uncontrolled removal of urinary catheters and other catheters. This situation causes many undesirable complications such as bleeding hypoxia, reoperations, and prolongation of length of hospital stay.

Risk factors in the development of EA have not been fully explained. Type of surgery, gender, age, smoking status, pain, volatile anesthetics, duration of surgery and anesthetic procedure, tracheal tube, and presence of a urinary catheter are the leading risk factors (12, 2).

Although various anesthetic techniques and agents (TIVA, Inhalation anesthetics) have been used to prevent EA, the ideal method has not been fully described. Ear, nose, and throat procedures are among the most common surgical procedures in which EA may occur. EA is especially seen in nasal surgery, possibly due to the feeling of suffocation (13).

There are no EA studies in the literature comparing thiopental and ketofol, which are commonly used in anesthesia practice. In our study, the incidence of EA in patients undergoing nasal surgery (septoplasty, rhinoplasty, and endoscopic sinus surgery) was significantly higher in group P than in Group K ( $p < 0.001$ ). The incidence of EA was 30% in group P, while 2.5% in the Ketofol group. The combination of ketamin and propofol mixture and the complementing effects of propofol and ketamine at lower doses used in our study makes the mixture more attractive. It's well known that ketamine has hallucinating effect. We consider that the use of ketamine in combination with propofol could minimize this effect in occurrence of EA. This clinical situation is supported by the literature (14). In our study; duration of surgery, time to extubation and time to verbal response times were similar in Group P and Group K, while Duration of Anesthesia ( $p = 0.004$ ), length of stay in PACU were shorter in Group P ( $p < 0.001$ ). Thiopental is a barbiturate derivative sedative-hypnotic commonly used in anesthesia practice because it provides effective sedation and rapid return when administered intravenously (15). Although propofol is a short-acting sedative agent, it is a longer-acting agent than the ketamine propofol in the ketofol mixture. As

the propofol ratio in ketofol increases, the duration of anesthesia and the length of stay in the intensive care unit are prolonged compared to thiopental. Badrinath et al. reported that discharge time was prolonged as the amount of ketamin in ketofol increased (16).

Pain is one of the risk factors for EA. Pain has been reported to increase the frequency and severity of EA (17). Radke et al. reported that high postoperative pain scores (NRS 6-10) were important risk factors for EA (4). In our study, the incidence of rescue analgesic use and pain in PACU was lower in Group K. Although it was reported by another study that the need for rescue analgesics and immediate postoperative pain intensity was not influenced by the type of anesthetic agents used (18). Steven et al., in their study, reported that the use of subanesthetic doses of ketamine reduced pain and opioid consumption in the postoperative period (19). In another study using ketofol, it was reported that ketamine decreased opioid consumption by providing effective analgesia (16). This may be explained by the potent analgesic activity of ketamine, an N-methyl-d-aspartate (NMDA) receptor antagonist (20). The results obtained in our study are also consistent with the literature.

## CONCLUSION

In patients who underwent nasal surgery under general anesthesia; the EA can be significantly reduced using ketofol instead of thiopental.

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