



## Influence of Different Doses of Ketamine on Intubating Conditions during a Rapid Sequence Induction and Intubation Model

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**Objective:** This prospective, randomized, double-blinded study aimed to compare the effects of three different doses of ketamine or lidocaine on intubating conditions and haemodynamics in a rapid-sequence induction model with 3 mg kg<sup>-1</sup> propofol and 0.6 mg kg<sup>-1</sup> rocuronium.

**Methods:** A total of 128 ASA I–III patients who were scheduled for elective surgery were randomized in the following five groups: Group 1 (n=24), 1 mg kg<sup>-1</sup> lidocaine+3 mg kg<sup>-1</sup> propofol+0.6 mg kg<sup>-1</sup> rocuronium; Group 2 (n=23), 0.1 mg kg<sup>-1</sup> ketamine+3 mg kg<sup>-1</sup> propofol+0.6 mg kg<sup>-1</sup> rocuronium; Group 3 (n=29), 0.3 mg kg<sup>-1</sup> ketamine+3 mg kg<sup>-1</sup> propofol+0.6 mg kg<sup>-1</sup> rocuronium; Group 4 (n=26), 0.5 mg kg<sup>-1</sup> ketamine+3 mg kg<sup>-1</sup> propofol+0.6 mg kg<sup>-1</sup> rocuronium and Group 5 (n=26), 3 mg kg<sup>-1</sup> propofol+0.6 mg kg<sup>-1</sup> rocuronium+saline as placebo. After preoxygenation, induction was performed with the assigned combination, and intubation was initiated after 60 s. The time to intubation, intubation score (Viby–Mogensen score) and haemodynamic data were recorded. Postoperative hoarseness, sore throat and hallucination incidences were followed up.

**Results:** Demographic, time to intubation and haemodynamic data were comparable among groups. Group 4 [13.5 (4–14)] revealed a higher intubation score than groups 1, 2 and 5 [12 (3–14), 11 (2–14) and 9.5 (0–13) and p=0.026, p=0.001 and p=0.000001, respectively]. Groups 3 [13 (4–14)] and 4 [13.5 (4–14)] had similar intubation scores. Side effects were comparable among all groups.

**Conclusion:** The combination of 0.5 mg kg<sup>-1</sup> ketamine and 0.6 mg kg<sup>-1</sup> rocuronium along with propofol improves intubation conditions in a stimulated rapid-sequence induction model.

**Keywords:** Intubation, rapid-sequence induction, ketamine

### Introduction

Rapid sequence intubation is an intervention that is applied for rapidly establishing a secure airway in situations defined as risky for the airway, such as cases with a high risk of aspiration or airway loss (trauma and burns) (1).

Rapid sequence induction and intubation is a standard and accepted method in the administration of general anaesthesia in patients with aspiration risk. Thus, the goal is first to ensure a secure airway and then to administer general anaesthesia (2). For this aim, after applying preoxygenation to patients through an oxygen mask for a length of time, a hypnotic agent and neuromuscular blocker are given. Rapid relaxation and intubation of the patient are targeted.

Rocuronium bromide is an agent with quite a short action time among the non-depolarizing neuromuscular blocking agents commercially available, but its action time is dose-dependent and high doses applied for obtaining rapid action cause a prolonged action time of the agent. These factors limit its use in short-term procedures (3).

In the literature, various drug combinations and methods are defined for reducing the action time of rocuronium without increasing the dose (4–8). In these studies, the effects of added drugs on the occurrence of the actions of neuromuscular blockers have been investigated independently of the usual induction doses.

In light of this information, it was aimed to clinically evaluate the effects of the combinations of different ketamine doses with 0.6 mg kg<sup>-1</sup> rocuronium on the quality of intubation and on the haemodynamic parameters and to compare the effects of these combinations with those of the lidocaine-rocuronium combination in this study.

## Methods

After receiving approval from the Clinical Research Ethics Committee of the Faculty of Medicine in Ankara University (Decision no: 153-4864), Turkey, and written informed consent from the patients, 128 adult patients between the ages of 18 and 65 years and who presented with ASA I-III and who were planned to undergo elective surgery under general anaesthesia, were included in this prospective randomized study. On the other hand, patients who had a neuromuscular disease, an allergy to the drugs to be applied in the study, a likelihood of difficult intubation (Mallampati score  $\geq 3$ ) or a body mass index  $30 \text{ kg m}^{-2}$  or over, who were planned to undergo an emergency medical intervention and who were not fasted were excluded from the study.

The patients were taken into the operating room and then intravenous (iv) vascular access was established in the arm following routine monitorization (ECG, non-invasive blood pressure and peripheral oxygen saturation).

Before beginning anaesthesia induction, the patients were given 100% oxygen through a mask for 3 min. Midazolam, at a dose of  $0.03 \text{ mg kg}^{-1}$  for premedication, and a study drug according to the group of each patient was administered intravenously for 30 s. Three  $\text{mg kg}^{-1}$  propofol was applied for anaesthesia induction and  $0.6 \text{ mg kg}^{-1}$  rocuronium was given as a neuromuscular blocker for 5 s.

As the study drug,  $1 \text{ mg kg}^{-1}$  lidocaine was given to Group 1 and  $0.1 \text{ mg kg}^{-1}$ ,  $0.3 \text{ mg kg}^{-1}$  and  $0.5 \text{ mg kg}^{-1}$  ketamine were given to Groups 2, 3 and 4, respectively. Group 5 was applied saline. Randomization of the patients was performed via a sealed envelope technique.

Laryngoscopy was performed at the 60<sup>th</sup> second following anaesthesia induction and neuromuscular blocker administration and intubation was tried. All the intubation procedures were carried out by an experienced anaesthetist blind to the study drug (BCM), and the intubation conditions were assessed. For this aim, the intubation time and intubation score (according to the Viby–Mogensen scale) were noted (9, 10).

The intubation conditions were evaluated considering seven parameters, including easiness of laryngoscopy, relaxation of the jaw, resistance to the blade, position and movements of the vocal cords, cough to intubation and/or extremity movements. All these parameters were scored as perfect (2 points), good (1 point) or poor (0 point). This evaluation is shown in Table 1. A total score of 12 or above was accepted as a perfect condition (11).

On the other hand, the haemodynamic data (mean arterial pressure and heart rate values before the induction, after the induction and at the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup> and 10<sup>th</sup> minutes) of the patients were recorded. In the case of an increase above

20% in blood pressure or in heart rate,  $0.5 \text{ mg kg}^{-1}$  esmolol was used. On the other hand, in case of a decrease above 20%,  $5 \text{ mg}$  ephedrine was applied.

In the postoperative period, the incidences of hoarseness, sore throat and hallucinations were assessed in patients in the recovery unit.

## Statistical analysis

The data were summarized as the mean  $\pm$  standard deviation or median (minimum-maximum) for the variables obtained through measurement and as the frequency (percentage) for the categorical variables. Independent groups more than two were compared using the one-way analysis of variance or Kruskal–Wallis test for the variables obtained by measurements and the chi-square test for the categorical variables. The Bonferroni post hoc test was employed in the study. The value of  $p < 0.05$  was accepted to be statistically significant in the evaluations.

## Results

A total of 130 patients were included in the study. Two of the patients were excluded from the study because difficult intubation was predicted. The data of 128 patients were analysed (Figure 1). No statistically significant difference was detected among the demographic data, the Mallampati scores and the Cormack and Lehane scores of these patients (Table 2). In the comparison of intubation conditions, the intubation time was also evaluated to be similar among the patients (Table 2).

During intubation, no statistically significant difference was found among the haemodynamic data (Figure 2, 3). Additional drug administration due to the changes in blood pressure and heart rate was not needed in any patient.

Table 1. Evaluation of intubation conditions (Viby–Mogensen score) (8)

Variables	Perfect (2 points)	Good (1 points)	Poor (0 points)
Laryngoscopy	Easy	Medium	Difficult
Relaxation of the jaw	Relaxed	Not completely relaxed	Poor relaxation
Resistance to the blade	None	Mild	Active
<b>Vocal cords:</b>			
Position	In abduction	In the middle	Closed
Movement	None	Moving	Closing
<b>Reaction to the insertion of tracheal tube and/or inflation of the:</b>			
Movement in the extremities	None	Mild	Many
Cough	None	Diaphragm movement	Cough longer than 10 s

Table 2. Demographic data, Mallampati score, Cormack–Lehane score and intubation-related features

Variables	Group 1 (n=24)	Group 2 (n=23)	Group 3 (n=29)	Group 4 (n=26)	Group 5 (n=26)	p
Age (year)	44±12	40±11	43±18	40±13	37±15	AD
Body weight (kg)	73±13	71±13	73±13	69±9	62±9	NS
Gender (F/M)	6/18	5/18	13/16	6/20	4/22	NS
Mallampati score	1 (1–3)	2 (1–4)	1 (1–3)	2 (1–3)	2 (1–3)	NS
Cormack–Lehane score	2 (1–4)	1 (1–4)	2 (1–4)	1 (1–4)	2 (1–3)	NS
Intubation time	72.2±13	72.6±11	68.2±11	74.3±30	72.8±13	NS

F: female; M: male; NS: not significant. Data are presented as the mean±standard deviation and median (minimum-maximum). These analyses were performed using chi-square, one-way analysis of variance and Kruskal–Wallis tests.

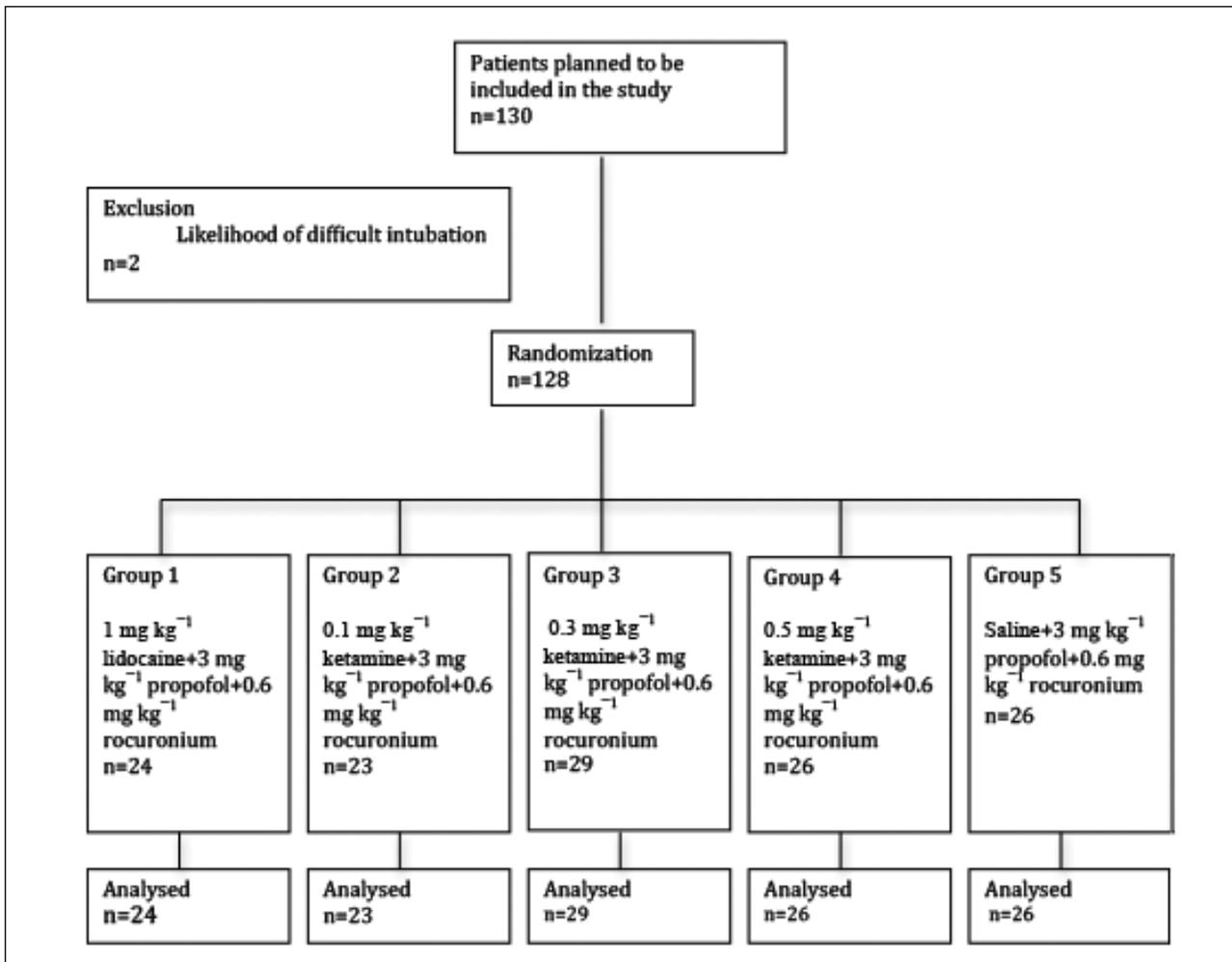


Figure 1. Consort flow diagram

When the intubation scores were evaluated, it was found that the scores of patients given an additional 0.5 mg kg<sup>-1</sup> ketamine were significantly higher than those of patients given additional lidocaine, 0.1 mg kg<sup>-1</sup> ketamine and saline (p=0.026, p=0.001, and p=0.000001, respectively) (Table 3). On the other hand, although the mean intubation score of the group given 0.3 mg kg<sup>-1</sup> ketamine was significantly higher than that of the group given saline, it was similar to

the mean scores of the groups given additional lidocaine, 0.1 mg kg<sup>-1</sup> ketamine and 0.5 mg kg<sup>-1</sup> ketamine. Among all the groups, the scores of patients given 0.3 mg kg<sup>-1</sup> and 0.5 mg kg<sup>-1</sup> ketamine were evaluated as perfect because they were above 12.

In the evaluation of the side effects associated with postoperative administration of intubation and ketamine, no statis-

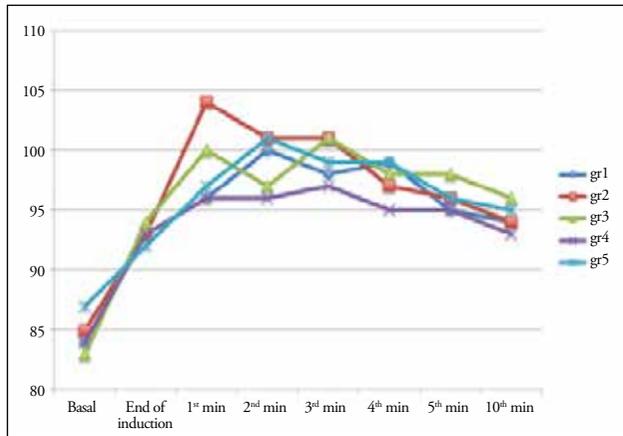


Figure 2. Mean heart rate values at the basal level, at the end of induction and during the first 10 min.

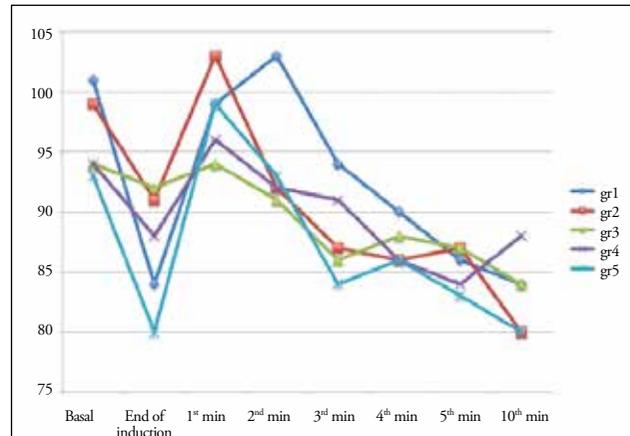


Figure 3. Mean blood pressure values at the basal level, at the end of induction and during the first 10 min.

Table 3. Intubation scores

Variables	Group 1 (n=24)	Group 2 (n=23)	Group 3 (n=29)	Group 4 (n=26)	Group 5 (n=26)	p
Intubation score	12 (3–14)	11 (2–14)	13 (4–14)	13.5 (5–14)	9.5 (0–13)	0.006

Data are presented as the median (minimum-maximum). The significant difference among the groups is due to the difference of Group 4 from Groups 1-2 and 5 and the difference of Group 3 from Group 5. These analyses were performed using the Kruskal-Wallis test.

Table 4. Complications associated with intubation and the drug

Variables	Group 1 (n=24)	Group 2 (n=23)	Group 3 (n=29)	Group 4 (n=26)	Group 5 (n=26)	p
Hoarseness	3	4	9	3	2	NS
Sore throat (while swallowing)	8	12	12	10	10	NS
Hallucinations	0	2	0	1	0	NS

Data are presented as the numbers of patients. NS: not significant. These analyses were performed using the chi-square test.

tically significant difference was detected in terms of the incidence of hoarseness, sore throat and hallucinations (Table 4).

## Discussion

In this study, for the rapid sequence induction model applied with 3 mg kg<sup>-1</sup> propofol and 0.6 mg kg<sup>-1</sup> rocuronium, it was revealed that the addition of 0.5 mg kg<sup>-1</sup> ketamine into the drug combination improved intubation conditions in 60 s at a statistically significant rate compared with the lower doses of ketamine, lidocaine and a placebo.

Intubation time depends on the action time of the neuromuscular blocker, the time of the drug reaching the muscles and forming the neuromuscular block and the cardiac output. In the literature, it has been demonstrated that the action speed of rocuronium is increased with some agents such as ketamine, etomidate and ephedrine (12-14). In the study on induction with ketamine conducted by Topçuoğlu et al. (15), it was reported that the addition of low-dose ketamine to propofol was more effective than 'priming' with rocuronium and that it shortened the action time of rocuronium significantly

and improved the quality of intubation. Moreover, Ahn et al. (16) obtained similar results in their study with cisatracurium. They suggested that the use of low-dose ketamine with 'priming' with cisatracurium provided better intubation conditions and reduced the action time of the neuromuscular blocker. In another study, Munoz et al. (17) found that the action time of rocuronium was reduced by 26% with a 70 µg kg<sup>-1</sup> dose of ephedrine given at the stage of induction. The authors explained this reduction by a possible increase in cardiac output. Also, in our study, it was observed that the addition of 0.5 mg kg<sup>-1</sup> ketamine to induction increased the quality of intubation at the 60<sup>th</sup> second to the perfect level. On the other hand, it was found that 0.3 mg kg<sup>-1</sup> ketamine increased the intubation score to the perfect level, similar to the dose of 0.5 mg kg<sup>-1</sup>. Different from the recent literature, the results of our study suggest that the addition of a lower dose of ketamine to induction can also make intubation conditions perfect.

In this study, a greater decrease was observed in mean blood pressures during induction in the lidocaine and saline groups

compared with the ketamine groups, which was statistically and clinically insignificant. In a similar study conducted by Topçuoğlu et al. (15), which was performed with 0.5 mg kg<sup>-1</sup> ketamine, they defended that blood pressure was significantly higher in the ketamine group after induction, which they suggested caused the neuromuscular blocker to be carried to the targeted organ (muscles) more rapidly; thus, the effects were observed in a shorter time. Similarly, it can be suggested in our study that the maintenance of the mean blood pressure with 0.5 mg kg<sup>-1</sup> doses of ketamine can be more effective in carrying the neuromuscular blocker to the muscles, and its effect can occur more rapidly in this way. This can be explained by the perfect intubation conditions. Different from other studies, the fact that a similar effect was obtained with a lower dose of ketamine (such as 0.3 mg kg<sup>-1</sup>), although statistically insignificant, can be a subject for dose studies in future.

On the other hand, no significant difference was observed among the groups in terms of the frequency of intubation-related complications, such as hoarseness and a sore throat in our study. The incidence of hallucination, which is a side effect that can be caused by ketamine, was quite low and similar among the groups.

The use of numerous drugs is one of the limitations in this study, which made the interpretation of data more difficult. In further studies that are planned to be conducted with fewer drugs, a clearer comparison of the effect of the study drug can be targeted. In addition, other limitations of the study included that the time of action occurrence was not evaluated and neuromuscular monitorization (NMM) was not used. Further studies should be performed to reveal the neuromuscular blocker action time with NMM and to evaluate different doses of ketamine more objectively and clearly.

## Conclusion

It has been demonstrated that ketamine increases intubation conditions to the perfect level in the rapid sequence induction model, in which ketamine is combined with propofol and rocuronium at low doses of 0.5 mg kg<sup>-1</sup>. Moreover, 0.3 mg kg<sup>-1</sup> ketamine can also be a better alternative than 1 mg kg<sup>-1</sup> lidocaine and 0.1 mg kg<sup>-1</sup> ketamine for facilitating intubation conditions.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the ethics committee of Ankara University School of Medicine Clinical Trials Ethical Committee (Decision No: 153-4864).

**Informed Consent:** Written informed consent was obtained from patients who participated in this study.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept - B.C.M.; Design - B.C.M., Z.A.; Supervision - N.A., Z.A.; Data Collection and/or Processing - B.C.M., A.O.B., O.Y.; Analysis and/or Interpretation - B.C.M., Z.A.; Literature Search - A.O.M., O.Y.; Writing Manuscript - B.C.M., A.O.B.; Critical Review - N.A., Z.A.; Other - O.Y.

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