The Effects of a Subhypnotic Dose of Ketamine on Neuromuscular Block Characteristics of Rocuronium and Intubation Quality

Subhipnotik Dozda Ketaminin Rokuronyumun Nöromusküler Blok Özellikleri ve Entübasyon Kalitesine Etkileri

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ABSTRACT Objective: In this study, we aimed to examine the effects of a subhypnotic dose of ketamine on the neuromuscular block characteristics of rocuronium and intubation quality. **Material and Methods:** Sixty patients in ASA I-II risk group were included in the study. Group S received 5 mL of 0.9% saline and Group K received 0.5 mg.kg^{-1} ketamine in 5 mL volume, one minute before induction. Both groups had anesthesia induction with a propofol dose of 2.5 mg.kg^{-1} (Propofol 1%, Fresenius Kabi). This was considered as anesthesia start time. After 1 min, a control single twitch stimulus (0.1 Hz) was applied and recorded. All patients were given 0.6 mg.kg^{-1} rocuronium (Esmeron® 50 mg.5 ml^{-1} N.V. Organon, Oss, Holland) in 5 sec. When the single twitch response was depressed 100%, the patient was intubated and the full depression time (onset time) was noted. Anesthesia maintenance was achieved with O_2/N_2O and sevoflurane. Following the intubation, the application of train-of - four (TOF) stimulation was started. When the TOF ratio reached to 20%, rocuronium was repeated at a dose of 0.2 mg.kg^{-1}. Clinical duration (T25), recovery index (T25-75) and spontaneous recovery time to TOF > 0.9 were recorded. Intubation conditions were assessed by using the scale of Fuchs-Buder. The additional drugs used during the operation and neuromuscular blocker amounts were recorded. The hemodynamic values of both groups were recorded throughout the study. Postoperative recovery times, visual analogue pain scores (VAS) and Ramsay sedation scores were also recorded. **Results:** The time for 100% depression of single twitch in Group K was shorter than that of Group S ($p<0.05$). The clinical duration, recovery index and spontaneous recovery duration of the first dose of rocuronium were longer in Group K compared to Group S ($p<0.05$). There was no difference between the total neuromuscular blocker amounts of the study groups. There was no significant difference between the groups according to intubation scores ($p>0.05$), recovery times ($p>0.05$), VAS scores, Ramsay sedation scores or mean arterial pressure values. When the mean heart rate values of the groups were compared, all values of Group K were higher than those of Group S except control and 60th min values ($p<0.001$). **Conclusion:** According to our findings, ketamine in a subhypnotic dose shortens the onset time of rocuronium block and extends the clinical duration of first dose of rocuronium without improving the intubation quality.

Key Words: Ketamine; propofol; rocuronium

ÖZET Amaç: Bu çalışmada subhipnotik doz ketaminin rokuronyumun nöromusküler blok özellikleri ve entübasyon kalitesi üzerindeki etkilerini incelemeyi amaçladık. **Gereç ve Yöntemler:** ASA I-II risk grubundaki 60 hasta çalışmaya alındı. Grup S'ye 5 mL %0,9 serum fizyolojik verildi, Grup K'ya indüksiyondan bir dakika önce 5 mL 0,5 mg.kg^{-1} ketamin verildi. Her iki gruba 2.5 mg.kg^{-1} (Propofol %1, Fresenius Kabi) propofol ile anestezi indüksiyonu yapıldı. Bu anestezinin başlama zamanı olarak alındı. Bir dakikalık bekleme zamanından sonra kontrol kasılma uyarısı (0,1 Hz) uygulandı ve kaydedildi. Tüm hastalara beş saniyede 0,6 mg.kg^{-1} rokuronyum (Esmeron® 50 mg.5 ml^{-1} N.V. Organon, Oss, Hollanda) verildi. Tek kasılma yanıtı %100 baskılandığında entübasyon yapıldı ve tam depresyon zamanı (başlangıç zamanı) belirtildi. Anestezi idamesi O_2/N_2O ve sevofluranla sağlandı. Entübasyondan sonra dörtlü uyarıya (TOF) başlandı. TOF oranı %20'ye ulaşınca rokuronyum 0,2 mg.kg^{-1} dozunda tekrarlandı. Klinik süre (T25), derlenme indeksi (T25-75) ve TOF> 0,9'a ulaşma süresi spontan derlenme zamanı olarak kaydedildi. Ameliyat sırasında kullanılan ilave ilaçlar ve nöromuskuler bloke edicilerin miktarları kaydedildi. Entübasyon şartları Fuchs-Buder skalasına göre değerlendirildi. Her iki grubun hemodinamik değerleri çalışma boyunca kaydedildi. Postoperatif derlenme süreleri, vizüel analog skala (VAS) skorları ve Ramsay sedasyon skalası skorları da kaydedildi. **Bulgular:** Tek kasılmanın %100 depresyonu için gereken zaman Grup K'da Grup S'ye göre daha kısaydı ($p<0,05$). Rokuronyumun ilk dozunun klinik süresi, derlenme indeksi ve spontan derlenme süresi Grup K'da Grup S'den daha uzundu ($p<0,05$). Çalışma gruplarının toplam nöromuskuler bloke edici miktarları arasında fark yoktu. Gruplar arasında entübasyon skorları ($p>0,05$), derlenme süreleri ($p>0,05$), VAS skorları, Ramsay sedasyon skorları ve ortalama arteriyel kan basınçları açısından fark yoktu. Grupların ortalama kalp atım hızları karşılaştırıldığında Grup K'nın tüm değerleri, kontrol ve 60. dakika değerleri hariç, Grup S'den yüksekti ($p<0,001$). **Sonuç:** Bulgularımıza göre; subhipnotik doz ketaminin, entübasyon koşullarında iyileşme yapmadan rokuronyum bloğunun etki başlangıç zamanını kısalttığı ve rokuronyumun ilk dozunun klinik etki süresini uzattığı kanısına varılmıştır.

Anahtar Kelimeler: Ketamin; propofol; rokuronyum

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In clinical practice, achieving a rapid and good intubation quality has many advantages mostly in emergency and full-stomach conditions. As succinylcholine has many side effects, shortening of the onset times of nondepolarizing neoromuscular blocker agents is very important. Although rocuronium is the most advantageous nondepolarizing agent with its relatively short onset time when used in high doses, there are few studies about the enhancement of this advantage of rocuronium.

Numerous previous studies have concluded that ketamine enhances the effects of neuromuscular agents.[1-6] The effects of ketamine on the neuromuscular junction was attributed to the blockade of the open conformations of acetylcholine-dependent ion channels in motor end plates in vitro, but this explanation was not clarified in vivo conditions.[7,8]

Propofol is found to be effective in improvement of intubation conditions.[9] A combination of a subhypnotic dose of ketamine with propofol during induction may be advantageous for additional good intubation success and prevention of hypotension and bradicardia due to propofol. We hypothesized that combining ketamine in a subhypnotic dose with propofol during induction might shorten the onset time of rocuronium and improve the intubation conditions of rocuronium block with an advantage of preventing the hypotensive effect of propofol. Therefore, in this study, we aimed to examine the effects of ketamine in a subanesthetic dose on neuromuscular characteristics of rocuronium and intubation quality by observing the hemodynamic changes due to propofol induction.

MATERIAL AND METHOD

ETHICS

Ethical approval for this study (Ethical Committee N° 2009/05-15) was provided by the Ethical Committee of Karaelmas University Hospitals, Zonguldak, Turkey (President Assoc. Prof. BD. Gun) on April 16, 2009.

This prospective and randomized study was conducted between in years 2009 and 2010 in the Department of Anesthesiology and Reanimation in Zonguldak Karaelmas University, Faculty of Medicine. This study was conducted in accordance with the principles of the Helsinki Declaration of 2008.

A total of 60 patients aged between 18-60 years, in ASA risk groups I-II and scheduled for elective operations longer than one hour were enrolled in the study after providing their informed consents. Exclusion criteria included egg, propofol and ketamine allergy; previous history of neurological disorders and trauma in the concerned hand, high intracranial pressure, uncontrolled hypertension, heart failure, ischemic heart disease, diabetes mellitus and neuromuscular disease, body temperature <35° C or >38° C, sepsis or bacterial infection, electrolyte and acid-base imbalance, body mass index >30, use of an analgesic drug within the last 24 hours, use of aminoglycoside antibiotics or calcium channel blockers, thyroid malfunction, pregnancy or nursing.

All patients were administered 0.07 $mg.kg^{-1}$ IM midazolam (Dormicum®, Roche, 5 $mg.mL^{-1}$, Fontenay-sous-Bois, France) as a premedication 45 minutes before their arrival to the operating room. Mean arterial blood pressure (MAP), heart rate (HR), peripheral oxygen saturation (SpO_2) and peripheral temperature values were recorded before induction, before intubation and after intubation. Peroperative end-tidal carcon dioxide ($ETCO_2$) and inspired sevoflurane (Fi_{sevo}) were recorded with 5 min intervals during surgery. TOF-WATCH® SX (Organon Teknika B V Netherlans) device was used to monitor neuromuscular transmission. The skin was cleaned with alcohol,dried, and a distal electrode (Neotrode® Neonatal ECG Electrode, USA) was placed on the ulnar nerve trace one centimeter above the wrist joint in the volar wrist, adjacent to the ulnar artery. The proximal electrode was placed on the skin 2-3 cm proximal to the distal electrode. An acceleration transducer was mounted on the thumb and the hand was plastered on the operation table with leaving the thumb free. Patients were covered fully and it was ensured that the thenar region skin temperature did not fall below 32°C.[9] The surgery room temperature was set to 20-25°C.

Prior to induction, 10 ml.kg^{-1} ringer lactate infusion was initiated. The patients were divided into two groups according to ''Random Samples Table''. Group S received 5 mL of 0.9% saline and Group K received 0.5 mg.kg^{-1} of ketamine (Ketalar®, Pfizer, 50 mg.mL^{-1}, Ortaköy, Istanbul, Turkey) in a volume of 5 mL. The same anesthesiologist (fourth year senior resident) performing induction and intubation was unaware of the contents of the study syringes. One minute after administration of the study drugs, both groups were injected propofol 2.5 mg.kg^{-1} (Propofol 1%, Fresenius Kabi) in 20 seconds. This was considered as anesthesia start time. Calibration of peripheral nerve stimulator was performed with Cal 2. After one minute, a control single twitch stimulus (0.1 Hz) was applied and recorded. Then, 0.6 mg.kg^{-1} of rocuronium (Esmeron® 50 mg.5 ml^{-1} N.V. Organon, Oss, Holland) was injected to all patients in five seconds. When the single twitch response was depressed by 100%, intubation was performed and the full block duration (onset time) was noted. Intubation conditions were assessed by using the scale of Fuchs-Buder et al.[10] (Table 1). Anesthesia was maintained with 2% sevoflurane in 50% O_2/N_2O (ET sevoflurane 1.7%). Throughout the study, $ETCO_2$ value was maintained between 30-35 mmHg. When the TOF ratio reached to 20%, 0.2 mg.kg^{-1} of rocuronium was injected as the repeat dose.

Following endotracheal intubation, train-of-four (TOF) was initiated. The following parameters regarding the neuromuscular blockade were recorded:

1. Onset time (sec): Time from the end of muscle relaxant injection to maximum neuromuscular blockade.

2. Clinical duration (T25) (min): Time from the end of muscle relaxant injection to 25% recovery of the neuromuscular blockade.

3. Recovery index (T75-25) (min): Time needed for the neuromuscular blockade to recover from 25% to 75%.

4. Spontaneous recovery time (TOF 90) (min): Time from administration of the drug to TOF level of 0.9.[9]

The times for restoration of spontaneous respiration (respiratory rate after ending sevoflurane breathing >8.min^{-1}, $ETCO_2$ <50 mmHg, SpO_2 >90%), and extubation were recorded.

The additional drugs and total muscle relaxant consumption were also recorded. Neuromuscular block was antagonized by using 0.05 mg.kg^{-1} neostigmine and 0.01 mg.kg^{-1} atropine, and then extubation was performed. Time between the closure of anesthetic gases and reaching an Aldrete score of 9 was recorded as recovery time. All patients received non-steroid anti-inflammatory drugs (NSAID) IM 15 minutes before the end of the surgery to achievepostoperative analgesia. Patients with VAS scores >3 were administered an additional analgesic as 1 mg.kg^{-1} of tramadol IV 30 minutes after NSAID. Postoperative additional drug use and postoperative complications were recorded. Ramsay sedation scores were recorded before the induction and 0, 5, 10, 15, 20, 25, 30, 45 and 60 minutes after surgery.

TABLE 1: Assessment of intubation conditions (according to Fuchs-Buder et al.).[10]

Variables	Excellent	Good	Poor
Ease of laryngoscopy	Easy	Fair	Difficult
	Jaw relaxed; no resistance to blade	Jaw not fully relaxed; slight resistance	Poor jaw relaxation; active resistance
Position and movement of vocal cords			
Position	Abducted	Intermediate	Closed
Movement	None	Moving	Closing
Reaction to intubation			
Moving of limbs	None	Slight	Vigorous
Coughing	None	Diaphragm	Sustained

SAMPLE SIZE CALCULATION

Our primary endpoint was the onset time of rocuronium. Sample size estimation was based on a similar study performed by Topcuoglu et al.[11] In order to detect a 10% change in onset time of rocuronium (216±20 sec in Topcuoglu et al.'s study), with an α error of 0.01 and a power of 98%, we calculated that sample size should be at least 30 patients per group. The sample size estimation was performed using Power Calculator (Department of Statistics, University of California, Los Angeles; http://www.stat.ubc.ca/_rollin/stats/ssize).

STATISTICAL ANALYSIS

The Statistical Package for the Social Sciences (SPSS) 16.0 was used for data analysis. The descriptive statistics used in the study included number and percentage frequencies, arithmetic mean ± standard deviation (SD). An analysis of distribution was performed by Kolmogorov-Smirnov test. Two-way analysis of variance and Bonferroni test were used used to compare parametric variables, and Chi-square was used for nonparametric variables. $p<0.05$ was considered as statistically significant.

RESULTS

No statistical difference was found between the groups according to surgery times and demographic data (Table 2).

The onset time of Group S was 163.6±32.6 sec and the onset time of Group K was 116.4±30.8 sec. The difference between the groups was significant ($p<0.001$). There was no significant difference between the intubation quality scores of the groups ($p>0.05$) (Table 3). Intubation quality was found to be excellent in 28 patients in Group S and in 29 patients in group K.

TABLE 2: A comparison of demographic data and surgery times of the study groups (Mean ±SD).

Variables	Group S (n=30)	Group K (n=30)
Age (years)	40.4±12.3	40.8±13.9
Weight (kg)	68.4±13.1	73.8±14.3
Surgery time (min)	131.8±66.9	139.6±52.0
Gender (F/M)	18 /12	16 /14

p >0.05: Group S vs Group K.

Group S: Saline group, Group K: Ketamine group.

TABLE 3: The intubation condition scores of the study groups.

Intubation Quality	Group S n (%)	Group K n (%)
Excellent	28 (93.3%)	29 (96.7%)
Good	2 (6.7%)	1 (3.3%)

p >0.05: Group S vs Group K.

TABLE 4: The comparison of the neuromuscular block charactheristics of rocuronium block in both groups (Mean ± SD).

Intubation Quality	Group S n (%)	Group K n (%)
Excellent	28 (93.3%)	29 (96.7%)
Good	2 (6.7%)	1 (3.3%)

*p<0.001 : Group S vs Group K.
**p<0.05 : Group S vs Group K.
***p >0.05 : Group S vs Group K.
Group S: Saline group, Group K: Ketamine group

The clinical duration of the first dose of rocuronium, recovery index and spontaneous recovery time of Group K were longer than those of Group S ($p<0.001$, $p<0.001$, $p<0.05$, respectively). There was no difference between the groups according to clinical durations of repeated doses of rocuronium (Table 4). No significant difference was observed between the groups according to peroperative and postoperative drug consumption. Complications such as postoperative nystagmus, headache, dizziness and laryngospasm were not observed in any of the groups.

Total muscle relaxant consumption was 63.0± 17.6 mg in Group S and 63.2±14.1 mg in Group K, and the difference was not statistically significantly ($p>0.05$).

None of the study groups needed additional analgesics. When the mean HR values of the groups were compared, all values of Group K were higher than those of Group S except control and 60th min values ($p<0.001$) (Figure 1). The control values of both groups were significantly lower than the rest of values in each group ($p<0.001$). There were no significant differences between the groups for MAP values ($p>0.05$) (Figure 2), recov-

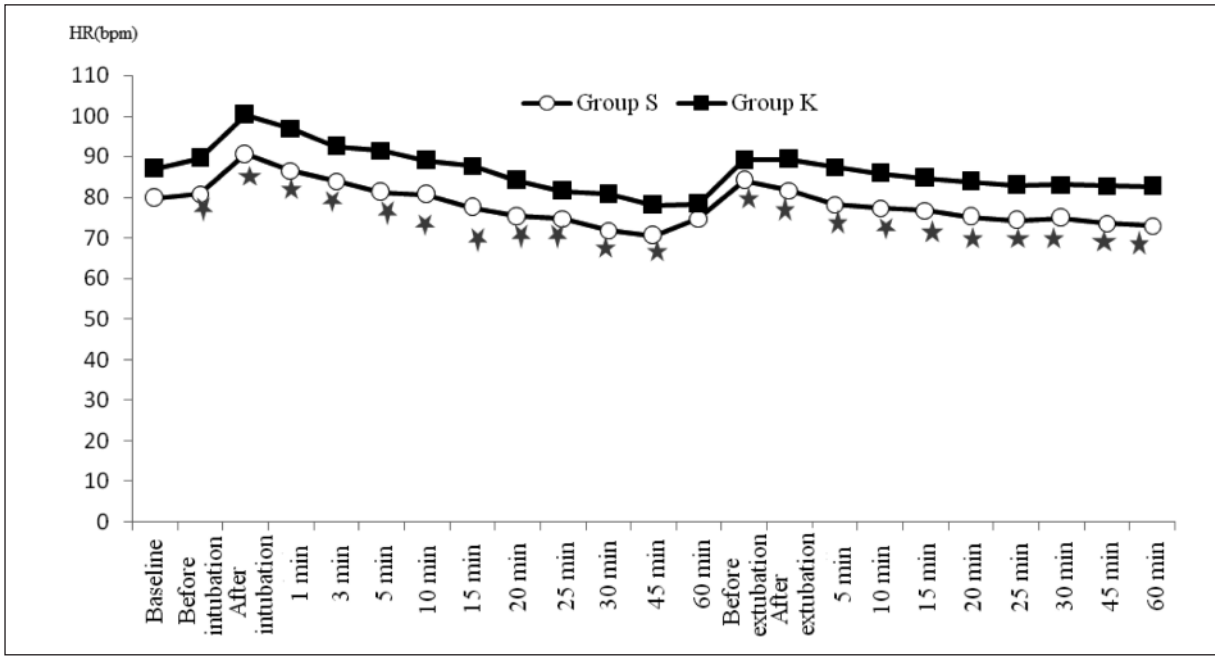

FIGURE 1: The comparison of the mean heart rate (HR) values of the study groups . Group S: Saline group, group K: Ketamine group.
*p< 0.001: Group S vs Group K.

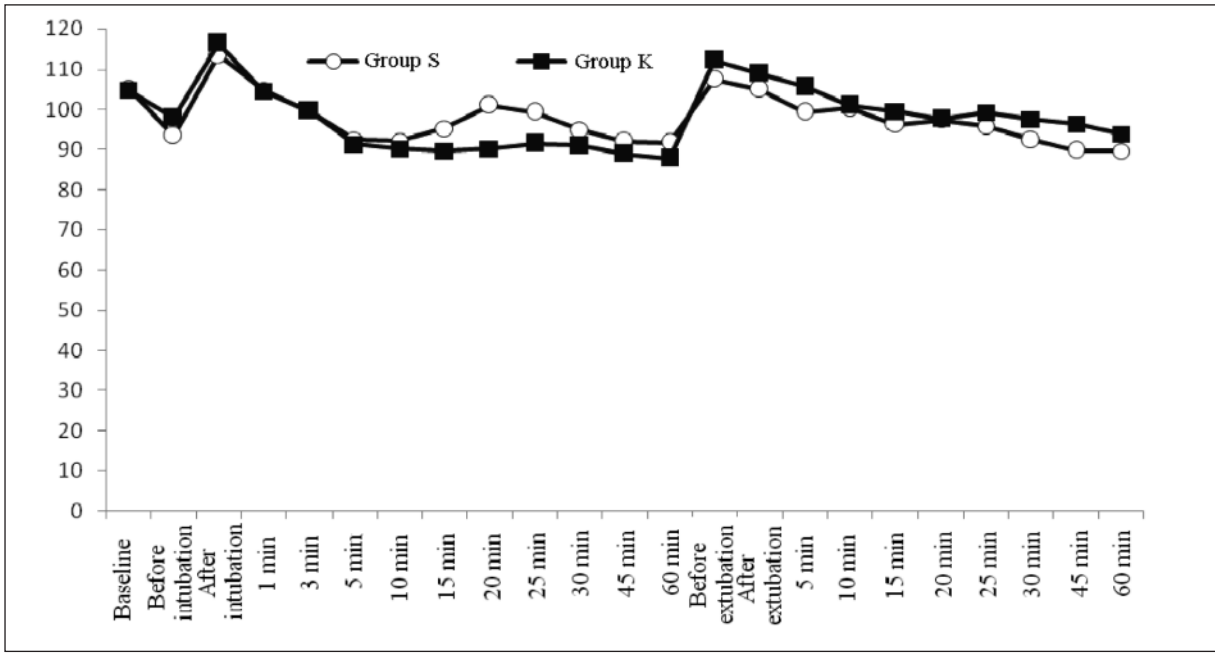

FIGURE 2: The comparison of the mean arterial blood pressure (MAP) values of the study groups. Group S: Saline Group and Group K: Ketamine Group. Group S vs Group K not statistically significantly (p> 0.05).

ery times (p>0.05), VAS scores (p>0.05) or Ramsay sedation scores (p>0.05). Recovery times were 11.5±6.1 min in Group S and 14± 7.1 min in Group K (p>0.05).

Power analysis: Our primary endpoint was the onset time of rocuronium. Power analysis estimation was based the onset time of Group S (163.6± 32.6 sec) and Group K (116.4±30.8 sec.) in our

study. With an α error of 0.01 and sample size of 30 patients per group, we calculated the power of our study as 99.9%. The power analysis of our study was performed using Power Calculator (http://www.dssresearch.com/KnowledgeCenter/toolkitcalculators/statisticalpowercalculators.aspx).

DISCUSSION

In our study, we demonstrated that rocuronium block onset times were significantly longer in Group S when compared to Group K; however intubation quality did not differ between the study groups. According to these results, ketamine administered in a subanesthetic dose (0.5 $mg.kg^{-1}$) prior to induction with rocuronium and propofol shortens intubation time without changing intubation quality. Similar to our study; Topcuoglu et al. reported that onset time of neuromuscular block was shortened with ketamine in a subhypnotic dose (0.5 $mg.kg^{-1}$).[11] Ketamine may shorten rocuronium onset time with its sympathomimetic effect. According to Donati,[12] the onset time of the neuromuscular block is affected by the reaching speed of the drug to the neuromuscular junction and nicotinic receptors, and this is directly related to cardiac output. Ezri et al. also pointed out the effect of hemodynamic changes on the onset time of rocuronium in their study performed with ephedrine and esmolol.[13] Although there was no difference between the study groups according to MAP values, the finding of significant increase in heart rate may support this approach in our study.

Scheufler et al. made a different interpretation on the effect of ketamine by claiming that independent CMAP modulation of S (+) ketaminefrom corticospinal D- and I- wave-mediated facilitation at or distal to spinal alpha-motor neuron might play a role on neuromuscular transmission, and stated that further studies were needed.[14] In vitro environments, the effects of ketamine on the neuromuscular properties of certain neuromuscular blocker agents were attributed to the blockade of ketamine in open conformations of Ach-dependent ion channels of motor end plates.[1-6,15] Ketamine may potentialize the effects of d-tubocurarine, pancuronium, atracurium and vecuronium depending on the dose in primates; however, these effects on acetylcholine receptors were found to occur before the junction.[1,16] Maleque et al.[7] concluded that the open forms of ionic channels that were activated with acetylcholine in frogs, interacted with ketamine and blocked neuromuscular transmission.

The clinical duration of the first dose of rocuronium is between 15-40 minutes.[17] The extension of this time to 55.2 minutes in Group K may be related to ketamine effect. We could not observe this extension with the repeated doses which might be due to relatively short activation time of a subhypnotic dose of ketamine.

The volatile agents have an augmentation effect on the neuromuscular characteristics of nondepolarising blockers. According to Wulf et al., inhalational anesthetics prolong the duration action and recovery times of mivacurium.[18] Desflurane was founded to delay the onset of rocuronium block, but did not affect clinical duration and recovery.[19] However, the effect of sevoflurane in our study may be underestimated as anesthesia was maintained with sevoflurane in both groups.

In the beginning of our study, we expected less muscle relaxant consumption in the ketamine group. However, there was no significant difference between the groups with respect to total muscle relaxant consumption. We attributed this to the longer surgery time as well as the higher body weight of patients in this group, although the differences were not statistically significant. In our opinion, this is an important limitation of our study.

Ketamine may provide good intubation quality besides early intubation. Baraka et al. and Hans et al. showed that ketamine provided better intubation conditions than thiopental.[20,21] However, the ketamine doses used in these studies were 1.5 mg kg^{-1} and 2.5 mg kg^{-1}, respectively. Ledowski and Wulf[22] found that the intubation conditions of 0.6 $mg.kg^{-1}$ rocuronium were better in ketamine-etomidate induction group; however, arterial blood pressure and heart rate were also higher in this group. Leykin et al. administered ketamine 1 $mg.kg^{-1}$ or thiopentone 4 mg kg^{-1} after a priming dose of

rocuronium and found out that intubation conditions of priming and ketamine combination was better.[23] Kim et al. showed that 0.5 mg kg^{-1} ketamin improved intubation conditions without neuromuscular block during sevoflurane induction in children.[24] The induction agents such as etomidate and ketamine are known to improve intubation conditions by maintaining cardiac output and blood pressure and accelerating the onset time of rocuronium.[11,21,25] Although our study is in accordance with these studies as Group K has had higher heart rates and shorter onset times than those of Group S, we could not demonstrate better intubation quality scores in Group K. We related this situation to the relatively smaller dose of ketamine used in our study.

Administration of ketamine in a subanesthetic dose during induction may prolong recovery and discharge from recovery room (Aldrete score >8).[26] The time needed for recovery is related to the dosage of ketamine. Higher doses need longer periods for mobility, preparation for discharge, and real discharge times.[27] Ketamine as a single dose of 0.5 mg.kg^{-1} in our study did not cause a difference in the recovery times between the groups (Group S: 11.5 min and Group K: 14 min). In addition, propofol may have prevented ketamine-related side effects such as hypertension, delirium, nightmares and hallucination.

However, in our study, ketamine combination did not provide an advantage for the prevention of hypotension due to propofol induction except higher heart rates. In their study examining the injection pain intensity of proposal, Özkoçak et al. showed that pretreatment with 0.5 mg kg^{-1} ketamine prevented hypotension during propofol induction.[28] Lu et al. concluded that ketamine in a dose of 1 mg kg^{-1} could attenuate the hemodynamic responses to propofol.[29]

In conclusion, we have demonstrated that ketamine in subhypnotic doses before induction shortens the onset time and prolongs the clinical duration of rocuronium block. Thus, administration of ketamine in a subhypnotic dose before induction may have the advantages of fast intubation and longer clinical durations with rocuronium without a delay in postoperative recovery profile. In this study, we could not determine an effect of 0.5 mg kg^{-1} ketamine on clinical duration of repeated doses of rocuronium, therefore we need further dose-studies with ketamine in order to achieve a reduction in total consumption of nondepolarizing neuromuscular blockers.

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