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Original Research Article

Evaluation of the Effect of Ketamine on the Onset Time and Intubating Properties of Rocuronium Bromide

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Abstract

Background: The utilization of ketamine before induction agents to expedite the onset time of neuromuscular blockade with rocuronium bromide holds potential value in anesthesia practice. Objective: The objective of this study was to assess the impact of administering Ketamine and normal saline before induction on the onset time and intubating conditions associated with Rocuronium bromide.

Methods: Patients undergoing elective surgeries with ASA I/II categories were selected for the study. They were divided equally into two groups of n=25 each. Group I received 5ml normal saline and group II received Ketamine 0.5 mg/kg. Intubation was conducted at 60 seconds, with conditions assessed using criteria outlined by Cooper et al. including jaw relaxation, vocal cord position, and diaphragmatic movements, graded as excellent, good, fair, or poor. Cormack and Lehane grading determined intubating conditions. Hemodynamic changes in systolic, diastolic, and mean arterial blood pressure were recorded at baseline, premedication, test drug administration, induction, intubation, and post-intubation at 1, 3, and 5 minutes, alongside heart rate variations for comparison.

Results: Neuromuscular Blockade: Ketamine administration (Group II) was associated with a significantly faster onset time for Rocuronium-induced neuromuscular blockade compared to saline (Group I). Blood Pressure: Both groups experienced similar trends in Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), and Mean Arterial Pressure (MAP) throughout the procedure: Group I tended to have slightly higher average SBP and MAP compared to Group II, but the differences were minimal. The baseline heart rate was slightly higher in the Ketamine group (Group II). Both groups experienced an increase in heart rate after induction, with a larger increase in the Ketamine group. At 5 minutes after induction, the control group (Group I) had a higher heart rate compared to the Ketamine group.

Conclusion: Our study suggests that pre-administration of a low dose of Ketamine before induction significantly accelerates the onset time of Rocuronium bromide while ensuring stable hemodynamics. Although 88% of cases demonstrated satisfactory intubating conditions with Ketamine, our findings did not indicate a statistically significant difference in mean arterial pressure between the Ketamine and saline groups during induction.

Keywords: Rocuronium Bromide, Ketamine, Intubation, Hemodynamics.

Introduction

There are various methods to administer general anesthesia to patients, with endotracheal intubation being the most commonly used approach for controlling ventilation artificially. The occurrence of significant complications, such as aspiration and hypoxia, particularly in emergency surgery, obese patients, or during cesarean sections requiring rapid sequence induction, depends greatly on the speed at which an anesthesiologist can secure the airway. [1] This, in turn, relies on the onset time of optimal intubating conditions. Achieving satisfactory intubating conditions involves employing a range of drugs and techniques. The most prevalent method involves using an induction agent in combination with suxamethonium for muscle relaxation. [2] Although suxamethonium yields excellent intubating conditions with a very rapid onset, it has certain limitations. It is contraindicated or best avoided in patients with conditions such as hyperkalemia, pseudocholinesterase deficiency, burns, penetrating eye injury, allergic reactions, and increased intracranial pressure. [3] Additionally, suxamethonium-induced muscle relaxation often results in postoperative myalgia. Recently, rocuronium has emerged as a valuable alternative to suxamethonium for rapid sequence induction, especially in cases where suxamethonium is contraindicated. [4] Rocuronium is an aminosteroid derivative with a very rapid onset of action. However, to use it for rapid sequence induction, it

must be administered at three times its ED95 dosage, which prolongs its duration of action. [5]

Various strategies have been developed to administer a lower dose for rapid sequence induction (RSI), thereby limiting the duration of action. Priming has been employed in numerous studies, yet conclusive results regarding its efficacy remain elusive. [6] Another approach is to reduce the effect site equilibrium time, aiming to accelerate the onset. Extensive research utilizing recirculatory pharmacokinetic models has investigated this aspect. Studies using indocyanine green as a marker have demonstrated that cardiac output affects the pharmacokinetics of rocuronium. [7] Several drugs have been administered before induction to either maintain or enhance cardiac output. Ephedrine has been previously utilized to increase cardiac output and decrease the onset time of rocuronium by up to 26%. [8] The use of ephedrine has also been associated with improved intubating conditions. Conversely, esmolol, a beta blocker known to reduce cardiac output, was found to prolong the onset time. Ketamine, an NMDA antagonist with sympathomimetic properties, has been extensively utilized as an induction agent in cases of hypovolemic shock due to its ability to maintain cardiac output. Additionally, ketamine possesses anesthetic properties that contribute to improved intubating conditions. [9] Based on these findings, we hypothesized that the addition of a low dose of ketamine to propofol and rocuronium induction would expedite the onset time and result in superior intubating conditions.

Material and Methods

This prospective study was conducted in the Department of Anesthesiology, Government Medical College, Akola. Maharashtra. Institutional Ethical approval was obtained for the study as per the protocol for human research. Written consent was obtained from all the participants of the study after explaining the nature of the study in the vernacular language.

Inclusion criteria

1. Age:18 – 60 years
2. ASA: I & II
3. Patients undergoing elective surgery.
4. Who have given valid informed consent.

Exclusion criteria

1. Patients with anticipated difficult intubation
2. Increased risk of regurgitation
3. History of cardiorespiratory illness
4. Neuromuscular disorders
5. Hepatic disease
6. Renal disease
7. known sensitivity to the drugs
8. Pregnant females
9. Emergency surgery

Onset Time: Following induction, the ulnar nerve of the patient underwent stimulation, and the supramaximal stimulus was observed. The duration between the administration of Rocuronium and the achievement of a Train-of-Four (TOF) count of zero was considered as the onset time.

Intubation Conditions: Intubation was performed at 60 seconds, and the conditions were evaluated based on criteria outlined by Cooper et al. The assessment criteria include jaw relaxation, vocal cord position, and diaphragmatic movements, graded as excellent, good, fair, or poor. If vocal cord adduction occurred, the attempt was halted, and another attempt was made after 60 seconds. Cormack and Lehane grading was graded as utilized to determine the intubating conditions. [10]

The hemodynamic alterations in the form of systolic blood pressure, diastolic blood pressure and mean arterial blood pressure were noted at various stages, baseline, at the time of administration of premedication, at the time of administering test drug, after induction, after intubation, 1 minute, 3 minutes and 5 minutes after intubation. Heart rate variations during the same period were also noted for comparison.

Procedure: After obtaining written informed consent, 50 patients aged between 18 and 60 years, classified as ASA I and II, and meeting our inclusion criteria, were selected and randomly assigned to 2 groups of n=25 each using the closed envelope method. Group I received 5ml of normal saline (Control group), while Group II received Ketamine 0.5 mg/kg. Baseline values were recorded after connecting basic monitors including ECG, NIBP, SpO2, and temperature. Intravenous access was established using an 18-gauge venous cannula. Before induction, all patients received 10 ml/kg of normal saline. Premedication consisting of Inj. Glycopyrollate 5 mcg/kg, Inj. midazolam 1 mg, Inj. Fentanyl 2 mcg/kg, and Inj. ondansetron 4 mg IV was administered to all patients. Preoxygenation with 100% Oxygen was performed for 5 minutes. Two minutes before induction, Group I received 5 ml of normal saline, while Group II received Ketamine 0.5 mg/kg. Induction was initiated with 2.5 mg/kg of propofol. Upon loss of consciousness, the supramaximal stimulus was calibrated by ulnar nerve stimulation and adductor pollicis muscle contraction. Train-of-Four (TOF) monitoring was performed every 10 seconds. Inj. Rocuronium at a dose of 0.6 mg/kg was administered once the patient became apneic. Subsequently, the patient was ventilated with 100% oxygen at 6 liters per minute and 2% sevoflurane. Laryngoscopy was conducted at the 60^{th} second after muscle relaxant administration. Intubation was attempted at the 60^{th} second using an appropriate size oral endotracheal tube, and intubating conditions were assessed according to the criteria established by Cooper et al.

[11] If vocal cord adduction occurred or if intubating conditions were deemed poor, intubation was aborted. Patients were ventilated with 100% oxygen and 2% sevoflurane for an additional minute. Reintubation was attempted after 60 seconds if necessary.

Heart rate, blood pressure, and mean arterial pressure were recorded at the time of premedication administration and test drug administration. The same parameters were monitored after induction, after intubation, and at 1, 3, and 5 minutes following intubation.

Statistical analysis: The data collected was analyzed using a statistical package for social sciences (SPSS version 15). All qualitative variables were compared using the chi-square test and differences between the mean values were compared with the student's t-test p values of (<0.05) were considered as significant.

Results

Out of n= 50 cases selected in this study for group I there were 14(males and 11 females. Similarly, for group II there were 13 males and 12 females. Table 1 compares various demographic characteristics of the two groups. Age: Both groups have similar average ages (Group I: 33.65 years, Group II: 32.94 years) with a high p-value (0.875), indicating no statistically significant difference. Weight: The average weight is slightly higher in Group I (58.93 kg) compared to Group II (57.31 kg), but the p-value (0.335) suggests this difference is not statistically significant. Height: Similar to age and weight, both groups have comparable average heights (Group I: 160.35 cm, Group II: 161.57 cm) with a high p-value (0.812), indicating no significant difference. Body Mass Index (BMI): The average BMI is slightly higher in Group II (23.66 kg/m²) compared to Group I (22.68 kg/m²), but the p-value (0.192) is not statistically significant at a conventional level (often set at 0.05). This table suggests that the two groups have similar demographic characteristics in terms of age, weight, height, and BMI. Based on the p-values, there are no statistically significant differences between the groups in these parameters.

Table 1: Showing the parameters recorded in the cases of the study

Variable	Frequency	Mean	± SD	P values
Age distribution in years				
Group I	25	33.65	8.84	0.875
Group II	25	32.94	10.25	
Weight distribution in Kgs				
Group I	25	58.93	8.66	0.335
Group II	25	57.31	6.71	
Height distribution in cms				
Group I	25	160.35	8.95	0.812
Group II	25	161.57	9.19	
BMI (Kg/m^2)				
Group I	25	22.68	1.27	0.192
Group II	25	23.66	1.10	

Modified Mallampatti Score (MMS): Figure 1 shows the distribution of MMS scores in each group. Both groups have a similar distribution with a high proportion of MMS I and II scores (easy to intermediate visualization of airway structures).

Overall distribution: Both groups have a similar distribution of MMS scores. MMS I (easy visualization): Group I: 12 patients (48%), Group II: 13 patients (52%). MMS II (intermediate visualization): Group I: N=11 patients (44%), Group II: N=11 patients (44%). MMS III (difficult visualization): Group I: 2 patients (8%), Group II: 1 patient (4%).

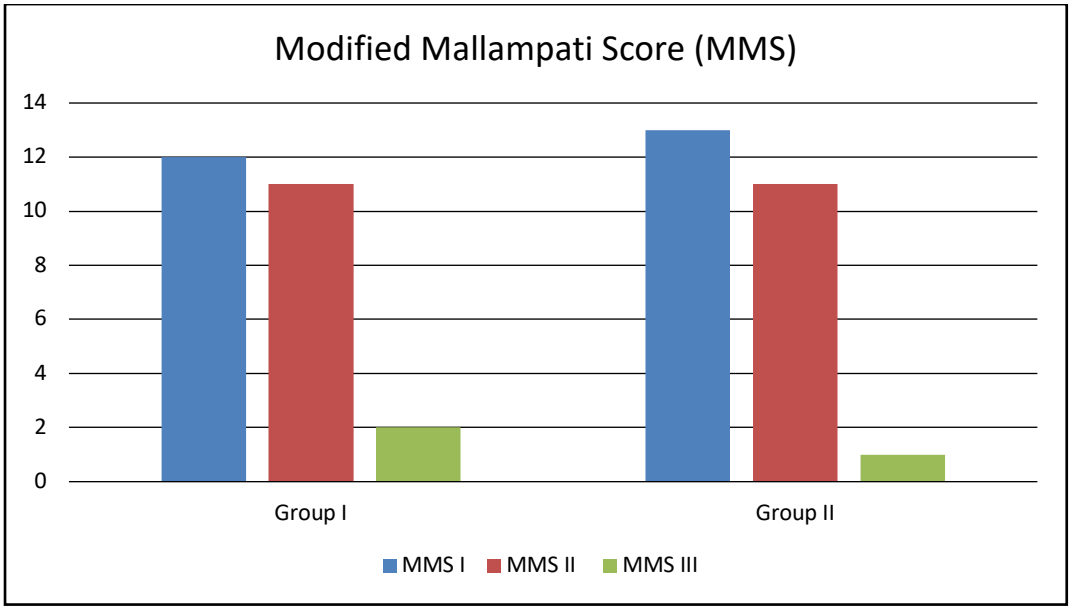

Figure 1: Showing Modified Mallampati Score (MMS) distribution in two groups of cases

Table 2 compares the intubating conditions between two groups (Group I and Group II) likely undergoing a medical procedure requiring endotracheal intubation. The Cormac-Lehane (CL) grading system was used to assess the visualization of the vocal cords during laryngoscopy, which helps predict ease of intubation.

Grading system: The Cormac-Lehane grade is categorized as I: Full visualization of the vocal cords (easiest intubation), IIA: Partial visualization of the vocal cords, IIB: Only the epiglottis visualized (most difficult intubation).

Group I (control): Achieved grade I visualization in 12 patients (48%), Had grade II A visualization in 9 patients (36%), and Faced grade II B visualization in 4 patients (16%).

Group II (Ketamine): Achieved grade I visualization in 14 patients (56%), Had grade II A visualization in 10 patients (40%), and Faced grade II B visualization in only 1 patient (4%).

Table 2 Shows the intubating conditions based on CL grade in two groups

Cormac and Lehane Grades	I		II A		II B	
	N	%	N	%	N	%
Group I	12	48	9	36	4	16
Group II	14	52	10	40	1	4

Intubating conditions comparison: Patients underwent intubation at the 60-second mark, and intubation conditions were assessed according to Cooper's criteria. Using appropriately sized McIntosh blades and endotracheal tubes, all patients were successfully orally intubated within this timeframe. Our findings were as follows: Excellent intubating conditions were observed in 13(52%) patients in the saline group and 16(64%) patients in the Ketamine group. Good intubating conditions were noted in 6(24%) patients in the saline group and 7(28%) patients in the Ketamine group. Fair intubating conditions were observed in 6(24%) patients in the saline group and 5(20%) patients in the Ketamine group. Neither group exhibited any instances of poor intubating conditions.

Table 3: Time required for onset of neuromuscular blockade

Group	Frequency	Mean	± SD	P value
Group I	25	126.98 sec	46.33 sec	
Group II	25	94.54 sec	sec	0.001

Mean Onset Time: Group I: 126.98 seconds (average time to achieve neuromuscular blockade) with a standard deviation (SD) of 46.33 seconds. Group II: 94.54 seconds (average time to achieve neuromuscular blockade) with a standard deviation (SD) of 33.25 seconds. p-value (0.001) is statistically significant, indicating a strong difference between the two groups. The Ketamine group (Group II) had a significantly faster onset time (mean of 94.54 seconds) compared to the control group (Group I) with a mean of 126.98 seconds.

Figure 2 shows the changes in Systolic Blood Pressure (SBP) measured in mmHg at different time intervals for two groups. Both groups experience a

slight decrease in SBP after induction of anesthesia (After induction). SBP increases after intubation (After intubation) in both groups, likely due to the stress response associated with the procedure. SBP gradually decreases over time following intubation (1 minute, 3 minutes, 5 minutes) in both groups.

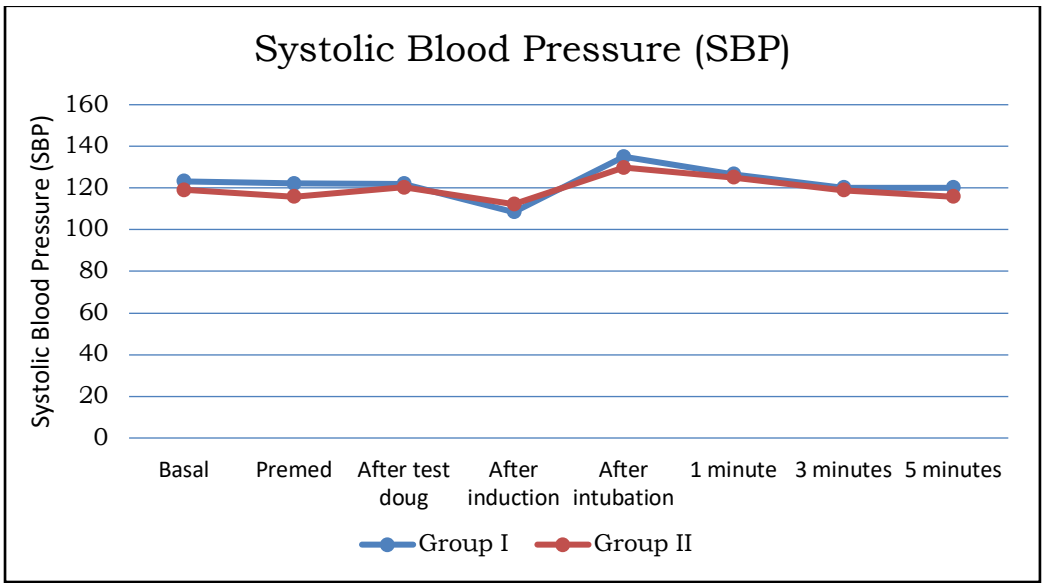

Figure 2: Mean systolic blood pressure in mmHg recorded at various intervals in two groups

Figure 3 shows the average (mean) diastolic blood pressure (DBP) in mmHg measured at various time intervals for two groups. Time Points: DBP is measured at baseline (basal), after premedication (premed), after test drug administration, after induction of anesthesia, after intubation, and 1, 3, and 5 minutes following intubation. General Trends: Both groups experience similar patterns of DBP changes: A slight decrease after anesthesia induction. Increase after intubation. Gradual decrease following intubation.

Group Specific Observations: Group I tends to have slightly higher DBP compared to Group II, but the differences are minimal. Overall, the table suggests similar trends in DBP changes during anesthesia for both groups. Group I has a slightly higher average DBP, but a more comprehensive analysis would require the full study for details on the missing information.

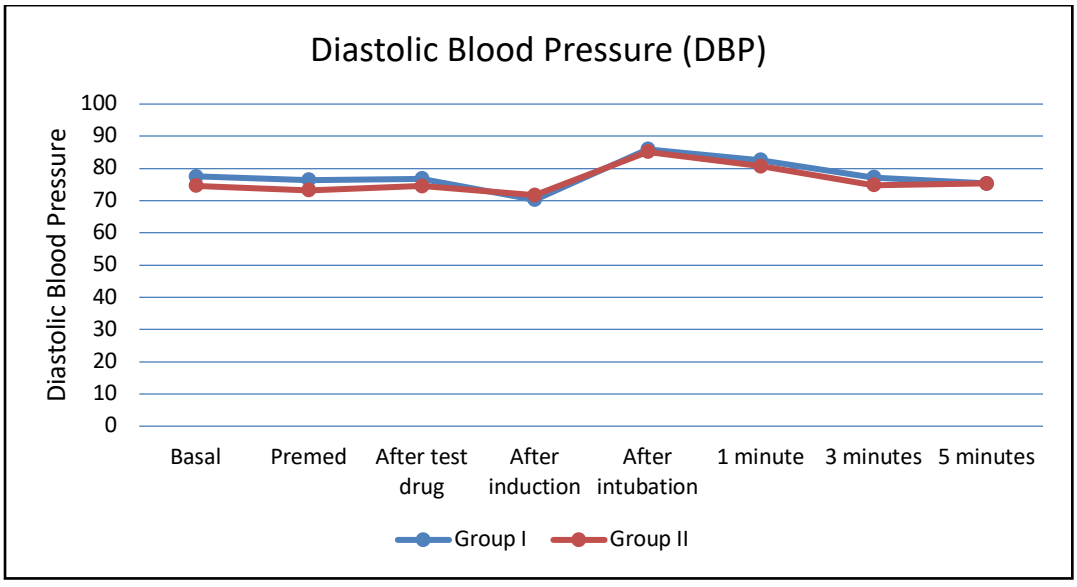

Figure 3: Mean diastolic blood pressure in mmHg recorded at various intervals in two groups

Figure 4 shows the changes in Mean Arterial Pressure (MAP) measured in mmHg at different time intervals for two groups. Both groups experience a decrease in MAP after induction of anesthesia (Induction). MAP increases significantly after intubation (Intubation) in both groups, likely due to the stress response associated with the procedure. MAP gradually decreases over time

following intubation (1 minute, 3 minutes, 5 minutes) in both groups.

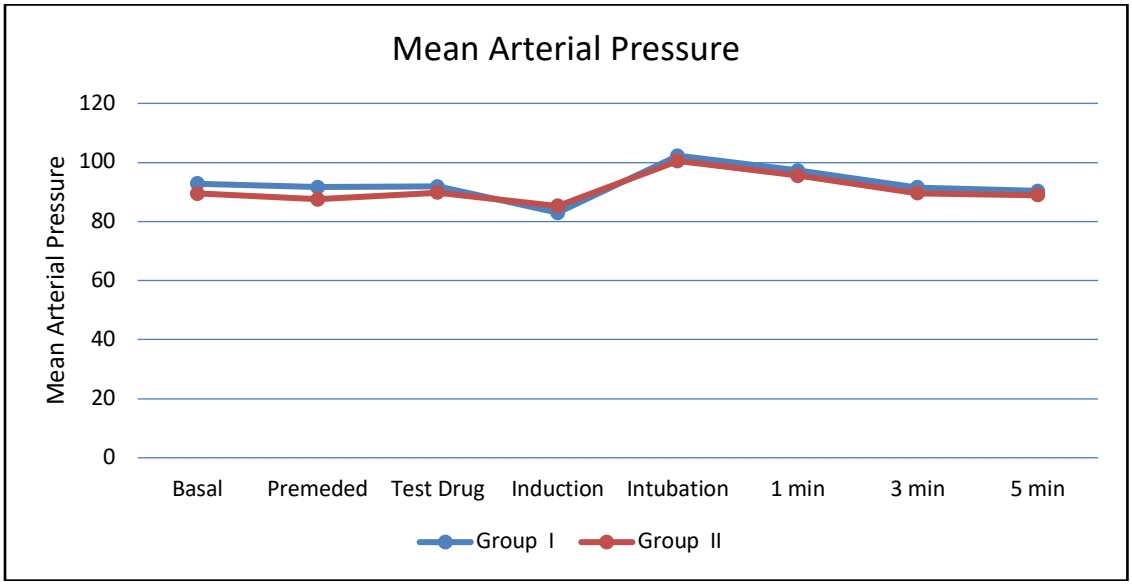

Figure 4: Mean Arterial pressure in mmHg recorded at various intervals in two groups

Table 4 compares heart rate (HR) at baseline, induction, and 5 minutes after induction between two groups (Group I and Group II) Baseline HR: Group II (85.61 bpm) has a slightly higher average HR than Group I (83.66 bpm). Induction HR: Both groups experience an increase in HR after induction. Group II (91.22 bpm) has a larger increase compared to Group I (88.46 bpm). 5 minutes HR: Group I (90.32 bpm) has a higher HR compared to Group II (85.61 bpm) at 5 minutes after induction.

Table 4: Comparison of heart rate in the cases of the study.

Groups	Frequency	Heart Rate		
		Baseline	Induction	5 minutes
Group I	25	83.66 ± 5.65	88.46 ± 10.32	90.32 ± 6.28
Group II	25	85.61 ± 6.33	91.22 ± 8.98	± 5.52

Discussion

In our current study, we found that administering Ketamine at a dosage of 0.5 mg/kg before induction led to a reduction in Rocuronium onset time at a dose of 0.6 mg/kg. Although we achieved satisfactory intubation conditions, with approximately 64% of cases rated as excellent when ketamine was used, we did not detect any significant statistical variance compared to the control group. Rapid sequence induction necessitates the use of agents with the shortest onset of action to minimize the risk of hypoxia and aspiration. Traditionally, suxamethonium is the preferred choice for rapid sequence induction. However, rocuronium is an alternative treatment when suxamethonium is contraindicated. Nevertheless, at doses ranging from 0.9 to 1.2 mg/dl, the duration of action of rocuronium was prolonged. To address this issue, various strategies have been devised to reduce the onset time and enhance intubation conditions while using a lower dose of 0.6 mg/dl. One such strategy involves maintaining cardiac output during induction. Audibert G et al. [12] in their study, concluded that for low-potency drugs like Rocuronium, onset primarily depends on maintaining circulation to the muscle rather than local factors.

The study conducted by Wang YG et al. [13] on hyperthyroid patients, where cardiac output was elevated, further supports the effectiveness of this approach. They observed that the time of onset in hyperthyroid patients was shorter than that in euthyroid patients. In our study, we used low-dose Ketamine (0.5 mg/kg) to stimulate sympathetic outflow. This approach aims to attenuate the decrease in blood pressure induced by propofol and sustain cardiac output. Additionally, by elevating catecholamine levels, ketamine enhances blood flow to the muscles by increasing beta 2 activity. Hence, its mechanism of action is two-fold. In our study, we observed a significant reduction in onset time when ketamine was used. The onset time in the Ketamine group was 94.54 ± 33.25 seconds compared to 126.98 ± 46.33 seconds in the saline group, with a 'p' value of 0.001. These findings are consistent with those reported by Topcuoglu et al. [14], who found that ketamine was associated with a significantly shorter onset time ($p = 0.001$), whereas priming did not exhibit a significant effect ($p = 0.94$). We observed that the onset time was shorter in both

groups than that in their study. This discrepancy may be attributed to the use of fentanyl and sevoflurane during induction. Several studies have suggested that sevoflurane can accelerate rocuronium onset [15, 16]. Ahn et al. [17] compared the effects of Ketamine and priming on the onset time of cis-atracurium, which also correlates with our findings. The onset time was the shortest in the ketamine priming group (76.4 ± 8 s), showing high significance with a p-value of < 0.008. Both Ketamine and priming alone also decreased the onset time of cis-atracurium compared with that in the control group.

Leykin Y, et al. [18], however, could not discern any difference between the thiopentone group and the Ketamine group in terms of onset time. They administered a total dose of 0.4 mg/kg), approximately equivalent to one ED95. Considering that the onset time is influenced by the number of molecules at the neuromuscular junction, particularly for low-potency drugs such as rocuronium, the use of a dose twice the ED95 (0.6 mg/kg) in our study might have contributed to the decreased onset time. AS Baraka et al. [19] conducted a study that diverged from ours. They investigated the effect of different induction agents on the onset time of rocuronium in pregnant women. Their findings did not reveal any significant differences between the thiopentone and ketamine groups. The duration from rocuronium injection to a T1/control ratio of 50% blockade, as well as the time to maximum blockade (onset time), did not exhibit any variance. Given that pregnant patients already experience heightened cardiac output owing to altered physiology, it is plausible that the addition of ketamine did not influence the onset time [20]. Similar to Ketamine, Ephedrine, an indirect-acting sympathomimetic, enhances cardiac output and is anticipated to reduce onset time.

Conclusion

Our study suggests that pre-administration of a low dose of Ketamine before induction significantly accelerates the onset time of Rocuronium bromide while ensuring stable hemodynamics. Although 88% of cases demonstrated satisfactory intubating conditions with Ketamine, our findings did not indicate a statistically significant difference in mean arterial pressure between the Ketamine and saline groups during induction. However, arterial blood pressure and heart rate remained comparable between the groups at other times throughout the study.

References

1. Lamon AM, Habib AS. Managing anesthesia for cesarean section in obese patients: current perspectives. Local Reg Anesth. 2016 Aug 16; 9:45-57.
2. Gupta S, Kirubahar R. A comparative study of intubating conditions of rocuronium bromide and suxamethonium in adult patients. Anesth Essays Res. 2010 Jan-Jun;4(1):15-19.
3. Hovgaard HL, Juhl-Olsen P. Suxamethonium-Induced Hyperkalemia: A Short Review of Causes and Recommendations for Clinical Applications. Crit Care Res Pract. 2021; 2021:6613118.
4. Bohringer C, Moua H, Liu H. Is There Still a Role for Succinylcholine in Contemporary Clinical Practice? Transl Perioper Pain Med. 2019;6(4):129-35.
5. Kim YB, Sung TY, Yang HS. Factors that affect the onset of action of non-depolarizing neuromuscular blocking agents. Korean J Anesthesiol. 2017 Oct;70(5):500-10.
6. Avery P, Morton S, Raitt J, Lossius HM, Lockey D. Rapid sequence induction: where did the consensus go? Scand J Trauma Resusc Emerg Med. 2021 May 13;29(1):64.
7. Kuipers JA, Boer F, Olofsen E, Bovill JG, Burm AG. Recirculatory pharmacokinetics and pharmacodynamics of rocuronium in patients: the influence of cardiac output. Anesthesiology. 2001 Jan;94(1):47-55.
8. Kim KS, Cheong MA, Jeon JW, Lee JH, Shim JC. The dose effect of ephedrine on the onset time of vecuronium. Anesth Analg. 2003 Apr;96(4):1042-46.
9. Simonini A, Brogi E, Cascella M, Vittori A. Advantages of ketamine in pediatric anesthesia. Open Med (Wars). 2022 Jul 6;17(1):1134-1147.
10. Cormack RS. Laryngoscopy grades. Anesthesia. 1999 Sep;54(9):911-12.
11. Cooper R, Mirakhur RK, Clarke RS, Boules Z. Comparison of intubating conditions after administration of ORG 9426 (rocuronium) and suxamethonium. Br J Anaesth. 1992; 69:269–73.
12. Audibert G, Donati F. The onset of rocuronium, but not of vecuronium or mivacurium, is modified by tourniquet inflation. Anesth Analg. 1996 Apr;82(4):848-53.
13. Wang YG, Song XJ, Feng SW, Ge YL, Yang JJ, He LL. Hyperthyroidism patients have shorter onset and duration time of rocuronium than euthyroidism patients. J Pharm Pharm Sci. 2007;10(1):53-60.
14. Topcuoglu PT, Uzun S, Canbay O, Pamuk G, Ozgen S. Ketamine, but not priming, improves intubating conditions during a propofol-rocuronium induction. Can J Anaesth. 2010 Feb;57(2):113-19.
15. Lowry DW, Mirakhur RK, McCarthy GJ, Carroll MT, McCourt KC. Neuromuscular effects of rocuronium during sevoflurane, isoflurane, and intravenous anesthesia. Anesth Analg. 1998 Oct;87(4):936-40.

16. Lee S, Ro YJ, Koh WU, Nishiyama T, Yang HS. The neuromuscular effects of rocuronium under sevoflurane-remifentanil or propofol-remifentanil anesthesia: a randomized clinical comparative study in an Asian population. BMC Anesthesiol. 2016 Aug 22;16(1):65.
17. Ahn BR, Kim SH, Yu BS, Lim KJ, Sun JJ. The effect of low-dose ketamine and priming of cisatracurium on the intubating condition and onset time of cisatracurium. Korean J Anesthesiol. 2012 Oct;63(4):308-13.
18. Leykin Y, Pellis T, Lucca M, Gullo A. Intubation conditions following rocuronium: influence of induction agent and priming. Anaesth Intensive Care. 2005 Aug;33(4):462-68.
19. Baraka AS, Sayyid SS, Assaf BA. Thiopental-rocuronium versus ketamine-rocuronium for rapid-sequence intubation in parturients undergoing cesarean section. Anesth Analg. 1997 May;84(5):1104-07.
20. Baraka A, Jabbour S, Tabboush Z, Sibai A, Bijjani A, Karam K. Onset of vecuronium neuromuscular block is more rapid in patients undergoing cesarean section. Can J Anaesth. 1992 Feb;39(2):135-38.