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Original article

The effect of ketamine on the onset time of neuromuscular blockade with rocuronium bromide

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ABSTRACT

Background: The role of ketamine given before induction agents in shortening the onset time of neuromuscular blockade with rocuronium bromide can be of use in anesthesia practice.

Aim: The aim of the study was to know the effect of ketamine on the time of onset of neuro-muscular block for intubation with rocuronium bromide.

Method: Fifty patients of age between 18-60 years and ASA grading I/ II undergoing elective surgery under general anaesthesia who gave valid informed consent were selected, After premedication, patients in Group I received normal saline in 10ml syringe, and group-II received Ketamine 0.5 mg kg-1 in 10 ml syringe. After one minute injection rocuronium in the dose of 0.9 mg kg-1 was administered. The primary outcome noted was effect of ketamine on the time for onset of neuro-muscular block and secondary outcomes were any changes in heart rate, systolic and diastolic blood pressure ,mean arterial pressure or pulse oximetry values) due to ketamine with rocuronium bromide and effect on duration of neuromuscular block with ketamine and rocuronium bromide.

Results The mean onset time of neuromuscular block was more in Group I (control) compared to Group II (ketamine) with p value 0.04 .Both groups remained hemodynamically stable.

Conclusion: This study revealed that ketamine reduces the onset time of rocuronium for intubation while maintaining stable haemodynamics.

Keywords: Hemodynamic, Intubation, Ketamine, Neuromuscular block, Rocuronium bromide

INTRODUCTION

Drugs blocking neuromuscular transmission are used for endotracheal intubation for general anesthesia before surgery[1]. Of the non-depolarising neuromuscular blocking group, rocuronium with anon quaternary, amino steroidal structure has a rapid onset of action and thus can be used for rapid-sequence induction (RSI) of anaesthesia where succinylcholine is not indicated. Dose of rocuronium required for appropriate intubation conditions within 60 to 90 seconds is 0.9-1.2 mg kg-1[1].To accelerate the time of onset of neuromuscular block, anaesthesiologists have used priming and also the anesthetic agents which alter the hemodynamic variable like blood pressure, cardiac output and blood supply of muscles.

Ketamine is one such drug as it maintains the hemodynamic stability. Tis a sedative-hypnotic agent that is useful for anaesthesia induction, sedation, and analgesia[4-6]. The clinical ketamine induction dose used in routine practice is 1-2 mg kg-1[7]. Scholars[8-10] have shown that the administration of a sub-anaesthetic dose of ketamine, as an adjuvant agent, results in improved intubation conditions. In addition, the use of ketamine as a sole anaesthesia induction agent with 0.9 mg kg-1of rocuronium has been shown to result in good to excellent intubation conditions compared with other agents[11,12]. Anaesthesiologists have been using many drugs before induction for maintaining or improving cardiac output[13,14]. At the same time, it has anaesthetic properties which can provide good intubation conditions. However, the role of low dose ketamine given before induction with propfol and rocuronium on the intubation condition is less known.[13] for this; we conducted this study to investigate the effect of ketamine on

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the time of onset of blockade with rocuronium bromide.

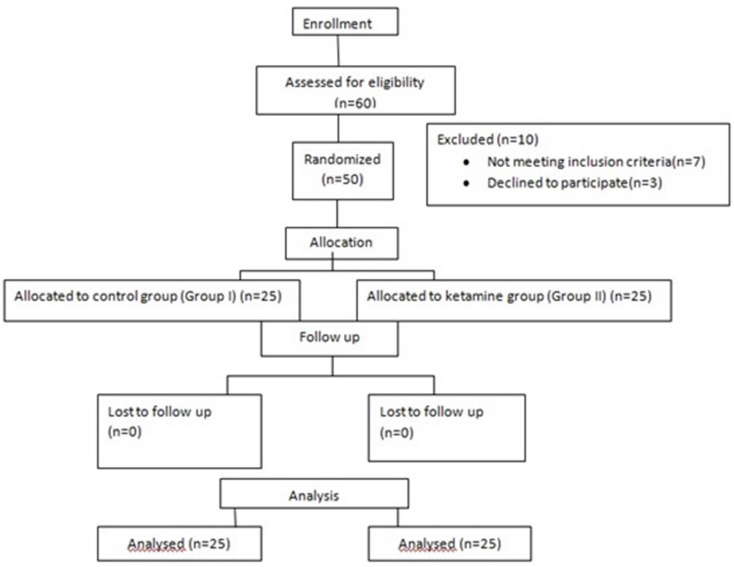
METHODOLOGY:

The study was done in the Department of Anaesthesiology, in elective general and ENT surgeries under general anaesthesia in OT (operation theatre) at hospitals attached with XXX with permission from Institutional Ethical Committee and Research Review board and with written informed consent of patients. It was a hospital based analytical study, 50 patients of either sex of age between 18 to 60 years with either ASA I or ASA II, who were satisfying inclusion criteria were selected. Patients with anticipated difficult intubation, history of cardiorespiratory disease, neuromuscular disorder, known sensitivity to the drugs used and pregnant females were not included. The selected patients were randomly allocated into either of the two groups using closed envelope method.

All patients were given anxiolytic drug (tablet alprazolam 0.5mg) at night before surgery. Venous access was obtained with a18 gauge intravenous cannula and inj. Ringer lactate infusion was started in OT. After connecting basic monitors-Electrocardiography (ECG), non-invasive Blood Pressure (NIBP), Pulse oximetry (SpO_2), capnography and temperature monitoring, the baseline values in all patients were noted.

All patients were given inj. glycopyrrolate 5 mcg kg^{-1}, inj. midazolam 0.25mg kg^{-1}, inj. fentanyl 2mcg kg^{-1} IV as premedication and were pre-oxygenated with 100% oxygen for 3 minutes. After this, Group I received normal saline in 10ml syringe, and group-II received injection Ketamine 0.5 mg kg-1 in 10 ml syringe which was prepared by assisting anesthesiologist.After 1minute in both the groups, patients were induced with propfol in the dose of 2.5 mg kg^{-1} IV.

Just when the patient lost consciousness, supramaximal stimulus was calibrated by stimulating the ulnar nerve and contraction of the muscle adductor policies. TOF (train of four) monitoring was done at every 10 seconds. All patients received injection rocuronium 0.9mg kg^{-1} IV. The patients were ventilated with 100% oxygen at 8 litre per minute using Bains circuit. All patients were intubated at TOF (train of four) count of zero with appropriate size oral endotracheal tube. The hemodynamic variables including heart rate (HR),systolic blood pressure (SBP),diastolic blood pressure (DBP), mean arterial pressure (MAP) were observed at the time of giving premedication and ketamine. Same vitals were recorded after induction, intubation, and then at 1,3 and 5 minutes following the intubation. Maintenance of general anaesthesia was done with inhalational agent sevoflurane at 2-2.5% according to MAC (minimum alveolar concentration) and rocuronium 0.2 mg kg^{-1} at TOF count of 1-2. At the end of surgery, before extubation, ondansetron 4mg IV was given and for reversal neostigmine 0.05mg kg^{-1} was given with glycopyrrolate 0.2 mg for each 1 mg neostigmine at TOF count of 2-3. At TOF count of four, all patients were extubated after regaining of consciousness and spontaneous breathing. [Figure1]



FLOW CONSORT DIAGRAM

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After shifting the patient in recovery room, Ramsay's sedation score was noted. [Figure-2]

Awake levels	Patient anxious or agitated or both	1
	Patient cooperative, oriented and tranquil	2
	Patient responds to commands only	3
Asleep levels	A brisk response to a light glabellar tap	4
	A sluggish response to a light glabellar tap	5
	No response	6

RAMSAY SEDATION ASSESSMENT SCALE

STATISTICAL ANALYSIS: -

Sample size was calculated to include 25 patients in either group. This was considering 0.05 level of significance and 90% power to find minimum 50% difference between the control group and any other group with respect to best intubation conditions. Collected data was arranged in tabular and graphical forms for further analysis. Continuous measurements were presented as Mean and SD (Min-Max) and categorical data were presented in Number (%) with the help of Microsoft Excel 2007. Statistical analyses were performed using the Statistical Package for the Social Sciences (IBM SPSS of statistics 22.0 Inc., Chicago, IL, USA)To find any significance, Student's t test was used to compare study characteristics on continuous scale between two groups for metric parameters and Chi-square for parameters on categorical scale. Ap value < 0.05 was considered statistically significant.

RESULTS:

Out of 60 participants enrolled for the study;7 patients were excluded and 3 denied to participate in the trial. A total of 50 patients were finally analysed [Figure2]. Demographic profile, age and gender were similar in both the groups [Table -1]. The mean HR ,SBP, DBP and MAP at baseline, aftergiving premedication,the test drug administration, and after induction, at intubation andat 1,3 and ,5 min thereafterremainedcomparable inthe two groups.

Table1 Demographics

VARIABLES	GROUP I	GROUP II	P value
AGE (Years)	31.84 +_11.01	32.24+_10.78	0.89(NS)
SEX Male: Female (%)	13:12 (52:48)	14:11(56:44)	0.77(NS)

NS- Non significant

We found no statistically significant difference in the above hemodynamic parameters [Table 2]. No change in mean duration of neuromuscular blockade after adding ketamine with rocuronium was seen.

TABLE2 Comparison of onset,duration of neuromuscular blockade, and Ramsay sedation scoring in both groups

VARIABLES	GROUP I	GROUP II	P VALUE
ONSET TIME (seconds)	95.72±15.88	84.52±17.88	0.0234(S)
DURATION OF NM BLOCKADE (Minute)	34.28±2.01	34.52±2.06	0.67(NS)
RAMSAY SEDATION SCORE	1.96±0.2	1.96±0.22	0.99

NM- Neuromuscular Blockade, S- Significant, NS- Non-significant

Also, thepost operative mean Ramsay sedation score was not significaintly raised with ketamine at this dose.[Table-3]

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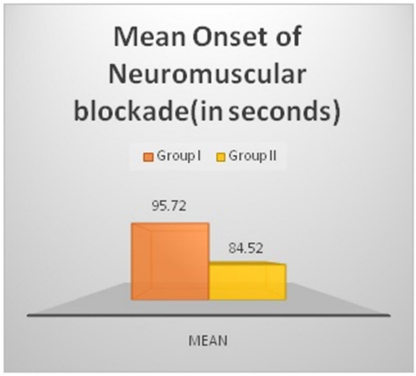
TABLE3 COMPARISION OF HAEMODYNAMIC PARAMETERS BETWEEN THE GROUPS

Duration	Group I				Group II			
	Heart rate (bpm)	SBP (mm Hg)	DBP (mm Hg)	MBP (mm Hg)	Heart rate (bpm)	SBP (mm Hg)	DBP (mm Hg)	MBP (mm Hg)
Baseline	80.12±4.29	128±9.9	81±3.4	97±5.1	80.76±3.81	125±8.2	80±4.6	91±9.7
After premed	80.44±4.06	126±7.6	78±4.7	94±4.3	80.52±3.50	122±7.9	78±4.2	93±4.8
After ketamine	80.84±4.11	125±6.3	78±4.5	94±3.8	81.28±3.13	126±7.9	79±4.8	95±4.1
After induction	80.8±2.61	122±6.3	77±3.8	92±3.3	81.24±2.44	122±6.7	78±3.4	93±3.8
After intubation	84.56±3.71	125±5.7	79±2.9	94±2.7	83.04±2.15	127±6.9	80±4.0	96±4.3
1 min after intubation	87.36±3.73	126±4.5	80±2.6	95±2.2	85.84±3.46	128±6.19	80±4.1	96±3.6
3 min after intubation	87.44+_2.63	126+_4.3	80+_2.0	95+_2.1	86±2.50	124±5.3	80±3.1	95±2.6
5 min after intubation	86.64+_2.96	122+_4.9	79+_2.6	93+_2.3	85.36±2.66	123±4.9	80±3.2	94±2.7
P value	>0.05(NS)	>0.05(NS)	>0.05(NS)	>0.05(NS)	>0.05(NS)	>0.05(NS)	>0.05(NS)	>0.05(NS)

bpm- beats per minute, SBP- systolic blood pressure, DBP- diastolic blood pressure, MBP- mean blood pressure, NS- non significant

A difference in the mean onset of neuromuscular blockade between the control and ketamine group was found in our study, as evident from the p value. (0.0234). The mean onset time was 84.52±17.8 seconds in ketamine group and 95.72±15.88 seconds in the control group showing that it takes significantly less time for onset of neuromuscular block with the additon of ketamine.[Figure 3]



MEAN ONSET TIME (IN SECONDS) OF NEUROMUSCULAR BLOCKADE IN CONTROL (GROUP I) AND KETAMINE GROUP(GROUP II)

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DISCUSSION

Our study was done to know the effect of ketamine on the time taken for the onset of block, changes in hemodynamic parameters and duration of NM blockade with rocuronium bromide. The onset time of a neuromuscular blocking drugs is a significant factor in deciding the ease with which the tracheal intubation is performed[1,2]. The addition of ketamine at 0.5 mg kg^{-1} IV given before induction with propofol 2.5 mg kg^{-1}IV was shown to decrease the onset time of NM blockade for intubation with rocuronium 0.9 $mg.kg^{-1}$. Intubation time is considered to depend on various factors affecting the onset of neuro-muscular block including cardiac output, mean circulation time, and physiological factors like blood supply of muscles in the body[3,8,10]. Induction agents like ketamine and etomidate have been shown to shorten the onset of neuromuscular block with rocuronium by maintaining blood pressure and cardiac output values, thereby improving the intubation conditions[13,14]. In one such study, ketamine at high dose resulted in quicker onset of block with rocuronium due to increase in cardiac output[13]. In our studytotal 50 patients were assessed, most of the patients were of 30-42 years of age(ASA grade 1 or 2) with 52% males in Group I and 56% males in Group II.

The mean heart rate increased in both the groups with time upto 3 min after intubation and mean systolic blood pressure and mean arterial pressure increased till 1 min after intubation in either group withno significant difference(p value >0.05). In the study by T Ledowskiet al[14]who compared the effect of ketamine and fentanyl on intubation with induction of anaesthesia using etomidate and rocuronium ,blood pressure and HR both were significantly increased in the ketamine group (P <0.01). With their study PelinTrajeet al[8] concluded that decline in mean blood pressure after induction was found to be less in ketamine group compared to control and priming groups (P = 0.001) but the difference in heart rate among ketamine, control and priming groups (P = 0.095) was not significant. In our study also we found that decrease in mean arterial blood pressure after induction was less in ketamine group as compared to control group although not statistically significant.

Similar studies conducted with ketamine and rocuronium by Ferguson etal (2022)[15] compared fentanyl and placebo with ketamine along with rocuronium. Hypotension was found to be more common with fentanyl and hypertension with placebo group. But in our study no case of either hypotension or hypertension was reported among the study population. Baraka et al[12]studied the time for 50% neuromuscular block and time to maximum onset of NM block between thiopentone with rocuronium and ketamine with rocuronium and concluded that the time was more with thiopentone (45±10) and less with ketamine (42±14).Our findings were similar to this study where most of the patients had the onset of neuromuscular blockade in less than 80 seconds in the ketamine group. Similarly, in the study by PelinTraje et al[8], Ketamine was shown to decrease onset time of NM blockade (P = 0.001).Another study conducted by Kang's et al[16]patientscompared onset ofrocuronium with saline or ketamine. Onset time of rocuronium was 201 ± 103 sec in saline group, and 136 ± 48 sec in the group who received ketamine in the dose of 0.25 mg kg-1 drug, and 139 ± 36 sec in the group who received 0.5 mg kg-1 of ketamine. The saline group had the slowest onset of block (P < 0.05).

Intubation conditions can be influenced by factors like cardiac output and blood supply of muscles.[1-3] Drugs such asephedrine, ketamine or etomidate can maintain cardiac output. Baraka et al[12] identified that 1.5 mg kg^{-1} ketamine provided good intubation conditions. PelinTrajeetal[8] found that ketamine improved intubation conditions at dose of 0.5 mg kg-1 and decreased the onset of block with rocuronium. Our results were in conformation with above studies using ketamine along with rocuronium bromide to fasten the onset of NM blockade. Dose of rocuronium can be reduced to avoid prolong duration of NM block by using ketamine in induction. Also, with use of this dose of ketamine haemodynamic parameters were maintained, and either hypotension or hypertension was avoided. The reasons for better intubation conditions could be that ketamine could compensate the hemodynamic changes resulting from bradycardia and hypotension by maintaining heart rate and blood pressure. Some studies have suggested that ketamine may increase cardiac output, resulting in increased muscle blood flow, and thereby accelerating neuromuscular block. The results of our study no significant difference in Ramsay Sedation Score between ketamine and

control group which are similar to the study by Mustafa et al.[17]

CONCLUSION

This present study revealed that ketamine decreases the onset time of neuromuscular block by rocuronium, while maintaining stable haemodynamics and thus could be added safely before induction of anesthesia.

LIMITATIONS

The study was performed in patients who did not require rapid sequence induction. The effect of study drugs need to be studied in this scenario. Monitoring of depth of anesthesia could not be done. Besides, further studies can be conducted with different doses of ketamine and with detailed Train of Four (TOF) records.

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