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A randomized double blinded comparative clinical study of intubating conditions of rocuronium with priming versus without priming

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Abstract: Background: Rocuronium produces faster neuromuscular blockade compared with other neuromuscular blocking drugs. It produces intubating condition similar to succinylcholine, but does not have the short duration of action. Objective: to compare the onset time of intubation and intubating condition of rocuronium with priming versus without priming.
Methods: Sixty patients of ASA physical status I and II, aged between 18-60 years, of both the sexes, grouped randomly and divided into priming group (group P) and control group (group C) of 30 subjects each. Priming group (Group P) receives 0.06mg/kg of rocuronium and control group (group C) receives normal saline. All patients received inj. Fentanyl 1mcg/kg, followed by inj. thiopentone 5mg/kg for induction. Intubating dose of rocuronium 0.54mg/kg for priming group and 0.6mg/kg for control group administered 3min after priming.
Results: The present conducted study shown that onset time of intubation was 56.4($\pm$6.43) sec in priming group (group P) with 3 min priming interval, 117.6($\pm$16.78) sec in non priming group (group C) with clinically acceptable intubating conditions were obtained in both groups without any adverse effects.
Conclusions: Priming with the rocuronium provide excellent intubating condition in less than 60 sec when compare to non priming group and is a safe alternative to succinylcholine.

Keywords: Endotracheal intubation; Intubating condition; Priming; Rocuronium.

1. Introduction

Securing the airway is the primary importance in all patients undergoing surgery under general anaesthesia. The protective airway reflexes are blunted in anesthetized patients leaving him/her vulnerable to regurgitation of gastric content and aspiration. Therefore endotracheal intubation prevents the aspiration and also secure the airway.

Succinylcholine has long been standard neuromuscular blocking agent used for facilitation of endotracheal intubation. Succinylcholine is a depolarizing neuromuscular blocking agent with a rapid onset and short duration of action. When administered intravenously, it produces excellent intubating conditions with profound relaxation within 60 seconds followed by rapid recovery of blockade. Hence, Securing airway using succinylcholine is an established technique in patients at risk of pulmonary aspiration of gastric content.

However, succinylcholine is associated with a number of undesirable side effects such as myalgia, Hyperkalemia [1], Bradyarrhythmia [2], Increased intragastric pressure, Anaphylaxis, Increased intracranial pressure [3], Malignant hyperthermia, Masseter spasm and succinylcholine is contraindicated in several conditions like Intracranial bleed [4], Recent burns, Open eye injury, Glaucoma, Spinal cord injury [5], Raised intracranial pressure. The above side effects and contraindications prompted the use of non depolarizing muscle relaxants [6].

Rocuronium bromide is an aminosteroid non-depolarizing muscle relaxant has been shown to provide adequate intubating conditions with rapid onset, intermediate duration of action and no obvious side effects. Which is somewhat similar to succinylcholine.

Rocuronium bromide has the shortest onset time among all the non depolarizing neuromuscular blocking agents currently available [7,8]. Rocuronium bromide onset time of action comparable to succinylcholine when used in higher dose of 0.9-1.2mg/kg 9,10,11, but the higher dose increases the duration of action. Therefore to overcome from this limitation various techniques used such as a combination of relaxants [12], Timing principle [13] or priming technique.

Priming principle is a divided dose technique of neuromuscular blocking drug which produces a rapid onset of neuromuscular blockade and suitable intubation conditions. Thus, this study was taken up to study the intubating condition of rocuronium with priming versus without priming.

2. Material and methods

The study was conducted in 60 patients aged between 18 – 60 years of either sex, who were admitted and coming for surgeries under general anaesthesia in Krishna Rajendra hospital and Cheluvamba hospital attached to Mysore Medical College and Research Institute, Mysore. The study was conducted from November 2019 to June 2021. After obtaining approval from 'Institute Ethics committee' and with informed consent, On the previous day, a thorough pre anaesthetic evaluation (PAE) of all the subjects of the two groups, with necessary basic investigations will be done and their informed consent will be taken. All the subjects will be given Alprazolam 0.5 mg and Omeprazole 20 mg orally, on the night before surgery and will be kept nil per oral 6 hours for solids and 2 hours for clear fluids. On arrival to the operation theater (O.T), IV access will be taken using 18G cannula on the non-dominant hand. Infusion of balanced salt solution [500ml] will be started 30 minutes prior to induction. All the subjects will be connected with the multiparameter monitor (EDAN iM80), for recording SPO2, non-invasive Blood pressure (NIBP) and heart rate (HR). Subjects will be premedicated with Inj. Midazolam 0.03mg/kg was given intravenously to all patients in both groups 10 min prior to priming dose. Blood pressure cuff tied to contralateral upper limb. After explaining about the nerve stimulation technique, supramaximal threshold was set with peripheral nerve stimulator. In group C 2ml of normal saline was taken in 2ml syringe. Total intubating dose of rocuronium bromide 0.6mg/kg was diluted to 5ml.

In group P 0.5 ml of rocuronium taken in 5 ml syringe and diluted to 2ml with normal saline and remaining 4.5 ml of rocuronium diluted to 5ml with normal saline. Drugs were loaded and labelled.

After 3 min of preoxygenation the priming dose of rocuronium 0.06mg/kg [10% of intubating dose] or normal saline to be given 3 min prior to intubation dose as per randomization. The patients were enquired about ptosis, double vision, difficulty in swallowing and difficulty in breathing. 1 min after the priming dose, Inj. Fentanyl 1mcg/kg to be given intravenously. 2.5 min after the priming dose patient is induced with Inj. Thiopentone 5mg/kg B/W I.V slowly. The intubating dose of rocuronium bromide to be injected 3 min after priming or normal saline injection. After giving intubating dose of rocuronium, a supramaximally set Train Of Four stimuli was applied over ulnar nerve at the wrist through surface electrode and repeat for every 10 sec and asses visual loss of adduction of thumb and disappearance of T1 OF TRAIN OF FOUR stimuli. The time interval between the intubating dose and loss of T1 of TOF is considered as onset time of intubation. After loss of T1 stimuli, trachea is intubated and intubating condition s noted. score recorded using in COOPER SCORING SYSTEM [14].

Table 1. Cooper scoring system

Jaw	Relaxation	Vocalcord response to intubation	Grading	Score
Good	Open	None	Excellent	8-9
Good	Open	Slight diaphragmatic	Good	6-7
		Movement or cough	fair	3-5
Moderate	Moving	Severe coughing or bucking	Poor	0-2

2.1. Assesment of intubating condition

2.1.1. Excellent

Good jaw relaxation, vocal cords open, no response to intubation.

2.1.2. Good

Good jaw relaxation, vocal cords open but minimal reaction to intubation.

2.1.3. Poor

Moderate jaw relaxation, moving vocal cords, intubation requiring pressure accompanied by coughing and bucking.

All the subjects will be intubated with appropriate sized cuffed ET tube with gentle laryngoscopy, the time of intubation and intubating conditions were noted in the 2 groups and tracheal position of the tube confirmed by end tidal carbon dioxide (EtCO2). Anesthesia will be maintained with Oxygen+ Nitrous oxide + Ing rocuronium +0.5% Isoflurane.

All patients were monitored with electrocardiogram, non-invasive blood pressure oxygen saturation with pulse oximetry. Data noted it includes onset of intubation, intubating conditions at the time of intubation- heart rate, mean arterial pressure, oxygen saturation will be recorded at baseline immediately after induction 1min and 5 minutes after endotracheal intubation.

Any untoward complications such as hypotension and bradycardia during induction will be noted. Hypotension will be treated with graded dosage of Inj. Mephentermine (> 20% fall of BP from baseline). Bradycardia (HR<60) will be treated by Inj. Atropine 0.6mg IV stat. At the end of the surgery, Isoflurane will be stopped 5 minutes prior to the closure of skin and N20 will be stopped at the end. The muscle relaxants will be reversed with Inj Glycopyrolate 0.01mg/kg body weight and Neostigmine 0.05mg/kg body weight. The patients will be extubated after return of consciousness, good muscle power with protective airway reflexes. The study drugs will be given by an anesthesiologist who is not involved with the study and the subject and the observer are blinded for the study drugs.

2.2. Inclusion criteria

- Age between 18- 60 years.
- Both males and females.
- ASA physical status 1 and 2.
- Weight between 50- 100kgs.
- Surgeries under general anaesthesia.

2.3. Exclusion criteria

- Patient refusal.
- All ASA grade III and IV patients.
- Patients with significant hepatic, renal, metabolic disorder, neuromuscular disease.
- Those receiving medications known to influence neuromuscular function.
- Those with known allergy to rocuronium.
- Those with anticipated difficult airway (obesity, thyromental distance < 6 cm, Mallampati grade 3 or 4) neuromuscular diseases.
- Psychiatric illness, patients on antipsychotics, anxiolytics and antiepileptic drugs.
- Obesity (BMI>30kg/m2) and sleep disorders.
- Drug allergy.
- Pregnant and lactating women.
- Hepatic and renal diseases.

2.4. Statistical analysis

Descriptive statistics for continuous variables such as age, sex, weight, height, body mass index and onset time of intubation were presented as mean and standard deviation. Categorical data were measured using

percentage. One way ANOVA test was used to compare the time of intubation between the three groups and for comparing intubating conditions among the groups. Statistical significance was considered if p<0.05.

3. Results

Mean age in group C with ASA 1 is 13(43.33%), ASA 2 is 17(56.67%) and group P with ASA 1 is 11(36.67%), ASA 2 is 19(63.33%). With p 0.792 value. There was no statistically significant difference in the weight between two groups.

Mean age in group C was 32.7(±10.76), in group P 33.6(±12.81) yrs. With p value of the 0.77 groups are comparable with respect to age.

With the p value of 0.292, the gender distribution between the two groups was statistically insignificant.

The mean height in group C 154.17(±6.13) was, group P 153.37(±5.2) with P value 0.59. There was no statistically significant difference in the height between two groups.

The mean weight in group C 59.7(±7.55) was, group P 58.23(±7.28) and P value 0.45. There was no statistically significant difference in the weight between two groups.

Table 2. BMI distribution between two groups

Group1C/2P	Group C	Group P	p value- Student t test
BMI (kg/m2)	25.23(±3.21)	24.75(±3.01)	0.55

Mean age in group C 25.23(±3.21), and group P 24.75(±3.01). With p 0.55. There was no statistically significant difference in the weight between two groups.

Table 3. Comparison of onset time of intubation between two groups

Group1C/2P	Group C	Group P	p value-Student t test
Time interval B/W Intubating dose and loss of T1 in TOF stimuli(sec)	117.6(±16.78)	56.4(±6.43)	0.001

The time of intubation in group C was 117.6(±16.78) and group P was 56.4(±6.43), with P value 0.001. The intergroup comparison showed a P value of <0.001 which was statistically significant. Thus the group P with priming of rocuronium and a priming interval of 3 min showed the less time for intubation when compared to group C.

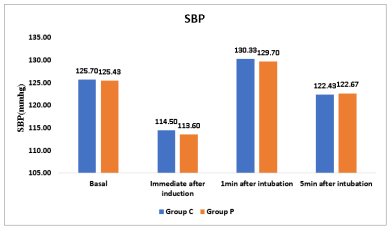
Table 4. Comparison of intubating conditions between two groups

Intubating condition	Group1C/2P		Total	p value
	Group C	Group P		
Excellent	27(90%)	26(86.67%)	53(88.33%)	1
Good	3(10%)	4(13.33%)	7(11.67%)	Fishers exact
Total	30(100%)	30(100%)	60(100%)	

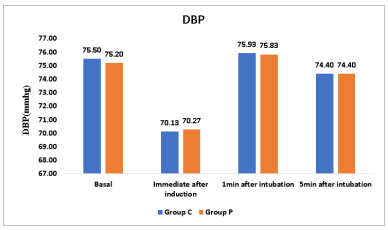
Intubating condition was excellent in 90% and good in 10% of the patients in group C, with the onset time of intubation was 117.6(±16.78) sec. In group P intubating condition was excellent in 88.33% and good in 11.67% patients. that onset time of intubation was 56.4(±6.43) sec.

Overall excellent to good intubating conditions were obtained in all patients in the two groups. There is no statistically significant difference seen in intubating condition between two groups.

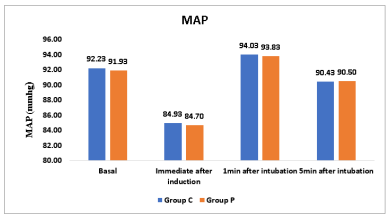
Hemodynamic variables like SBP, DBP, MAP, HR and SpO2 showed no statistically significant difference among two groups.



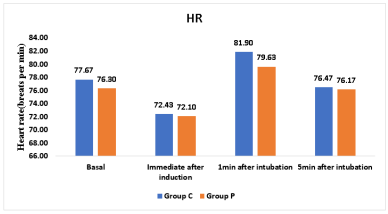
(a) SBP



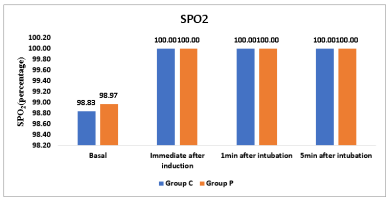
(b) DBP



(c) MAP



(d) HR



(e) SPO2

Figure 1. Comparison of hamodynamiacl variables like SBP, DBP, MAP, HR and SpO2 between two groups

4. Discussion

Succinylcholine has long been standard neuromuscular blocking agent used for facilitation of endotracheal intubation. Succinylcholine is a depolarizing neuromuscular blocking agent with a rapid onset and short duration of action. When administered intravenously, it produces excellent intubating conditions with profound relaxation within 60 seconds followed by rapid recovery of blockade. hence, Securing the airway using succinylcholine is an established technique in patients at risk of pulmonary aspiration of gastric content. However, succinylcholine is associated with a number of undesirable side effects.

Rocuronium bromide is an aminosteroid non-depolarizing muscle relaxant has been shown to provide adequate intubating conditions with rapid onset, intermediate duration of action and no obvious side effects. Which is somewhat similar to succinylcholine.

Rocuronium bromide onset time of action comparable to succinylcholine when used in higher dose of 0.9-1.2mg/kg [9–11], but the higher dose increases the duration of action. Therefore to overcome from this limitation various techniques used such as a combination of relaxants [12], Timing principle [13] or priming technique.

Hence, the present study is conducted to compare the onset time of intubation and intubating condition of rocuronium with priming versus without priming. In our study we have selected total of 60 patients who was posted for neck surgeries, abdominal, thoracic surgeries and upper limb surgeries were enrolled for our studies.

Recommended dose of rocuronium bromide is 0.6-1.2mg/kg. In our study we have used 0.6mg/kg of rocuronium like Friedrich K. Puhringer et al. [15]. Based on the above study we have used priming dose 0.06mg/kg followed by intubating dose 0.54mg/kg after 3min interval in Group P and normal saline followed by intubating dose 0.6mg/kg after 3min in Group C. Intubating condition and onset time of intubation were compared between two groups. In some studies they have taken 2 min interval between priming and intubating dose of rocuronium Karl E Griffith et al [16]. Some studies have taken 1.5mg/kg of intubating dose of rocuronium Mark et al. [17].

Patients in our study belonging to American Society of Anaesthesialogists (ASA) physical status class 1 and class 2 posted for surgeries under general anaesthesia were devided in 2 groups of 30 patients each.

Mean age in Group P was 33.6+ 12.81 as compared to Group C 32.7+10.76 years with p value 0.77. Data was also comparable with respect to sex distribution with M: F ratio of 10:20 in Group P and 14:16 in Group C with p value of 0.292. Mean weight of patients in Group P was 58.23+ 7.28 as compared to Group C 59.7+7.55 kg with p value 0.45. Mean height of patients in Group P was 153.37+ 5.2as compared to Group C 154.17+6.13cms with p value 0.59. Mean BMI of patients in Group P was 24.75±3.01 as compared to Group C 25.23±3.21 with p value 0.55.

There was no significant difference regarding the age, gender, height, weight, BMI, between two groups. Hence we ensured that the demographic parameters did not confound our results.

Onset time of rocuronium is 60-90 sec with a dose of 2*ED95. But priming has shown to accelerate the onset of block of nondepolarizing relaxants by 30-60 seconds with the result that intubation can be performed within 90-120 seconds after the intubation dose.

In our study the onset time of intubation in group C was 117.6(±16.78) and group P was 56.4(±6.43), with P value 0.001. The intergroup comparison showed a P value of <0.001 which was statistically significant. Thus the group P with priming of rocuronium and a priming interval of 3 min showed the less time for intubation when compared to group C.

This findings are consisted with the study of. Sindhu K Shridhar et al. [14]. where onset time of intubation was 57.4 sec in group A, and 123.9sec in group C. Intubating conditions were clinically acceptable in all groups. In the study of Anisha Puri et al. [18] onset time of intubation in priming group is 61.97sec and in nonpriming group 114.5 seconds with excellent intubating condition both groups. Hanumnatha Rao et al. [19]. where the onset time of intubation was 50.67sec in priming group and 94.00sec in control Group, with excellent intubating conditions in both groups and without any adverse effects.

The study concluded that, the priming interval of 3 min with rocuronium provides excellent intubating condition in less than 60 sec Thus, rocuronium with priming can be used as safe alternative to succinylcholine.

The phenomenon underlying the shortening of time interval between intubating dose and achieving intubating conditions by priming can be explained by two mechanisms 20. First, the priming dose occupies a proportion of post synaptic nicotinic receptors, hence reducing margin of safety of neuromuscular transmission. The intubating dose, thus blocks more rapidly that critical mass of receptors necessary for clinical paralysis. In this theory, it follows that the size of the priming dose is of fundamental importance (in order to occupy a critical mass of receptors), as is the time separating priming and intubating doses (in order to maximize receptor occupancy). The second theory suggests that the priming dose blocks presynaptic nicotinic receptors, reducing the mobilization and release of acetylcholine such that the intubating dose produces paralysis more rapidly. It has been advised that a total of 2 to 3 times the ED95 of a non depolarizing agent (slightly more than without priming) may be used for intubation when priming principle is utilized.

Jaw relaxation, position of vocal cords, response to intubation (coughing, bucking or muscular movements) and absence of twitches to train of four stimuli were assessed just before intubation and intubating conditions were graded as excellent, good and poor depending upon the COOPER scoring system. All the patients in our study had Intubating condition was excellent in 90% and good in 10% of the patients in group C, In group P was excellent in 88.33% and good in 11.67% patients. Overall excellent to good intubating conditions were obtained in all patients in the two groups without any adverse effects. There is no statistically significant difference seen in intubating condition between two groups. Excellent to good intubating conditions which was clinically acceptable. This was similar to the results of studies by, Hanumantha Rao et al. [19], Karl Griffith et al. [16].

But priming dose (10% of intubating dose), small enough to cause any unpleasant side effects and large enough to cause moderate inhibition of neuromuscular transmission is used. After 3min, rest of the intubating dose of drug is administered to produce neuromuscular blockade.

One of the major drawback of priming dose is the occurrence of adverse effects such as weakness, diplopia, dysphagia, generalized discomfort and breathing difficulties. no such adverse effects are occured in our study. Naguib et al.[21] conducted a study to compare the effects of priming rocuronium (0.54mg/kg) with rocuronium(0.06mg/kg) or mivacurium(0.015mg/kg).

Their onset time after priming with rocuronium was 73 sec which was higher when compared to our study. Thus, we found a shorter onset time of intubation of 56.4±6.43sec in the priming group with 3 min priming interval and 117.6±16.78s in the control group. The intubating conditions were excellent to good in all the groups in our study. There was fall in systolic and diastolic blood pressure in both Group P and Group C immediately after induction, but statistically not significant fall in SBP, DBP and MAP seen in both the groups.

In our study there is no significant increase or decrease in heart rate and no fall in saturation seen immediately after induction, 1min and 5min after intubation in both the groups.

5. Conclusion

Rocuronium bromide produces comparable intubating condition between priming and non priming groups. Excellent in 90%, good in 10% of group C patients. In group P intubating conditions were excellent in 88.33% and good in 11.67% patients. Overall excellent to good intubating conditions were obtained in all patients in the two groups without any adverse effects. The onset time of intubation after priming with 10% (0.06mg/kg) of an intubating dose (0.54mg/kg) of rocuronium and a priming interval of 3 min was 56.4±6.43 sec. which is significantly lower than non priming group (117.6±16.78s). Priming with the rocuronium provide excellent intubating condition in less than 60 sec when compare to non priming group and rocuronium with priming can be used as a safe alternative to succinylcholine to secure the airway in rapid sequence induction or whenever succinylcholine is contraindicated.

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Conflicts of Interest: The authors declare that they do not have any conflict of interests.

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