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Comparison of Intubating Conditions with 0.6 mg/kg and 0.9 mg/kg Rocuronium Bromide for Rapid Sequence Intubation

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ABSTRACT

Introduction: *Dose of rocuronium bromide usually used for rapid sequence intubation (RSI) allows rapid paralysis but the duration of action is prolonged making it unsuitable for short duration surgeries. Theoretically, use of low doses of neuromuscular blocking agents shortens the time for recovery from neuromuscular blockade (NMB). Hence we studied the intubating conditions of rocuronium bromide at 2 × ED95 dose (0.6 mg/kg) in comparison with 3 × ED95 dose (0.9 mg/kg).* ***Methods:*** *Sixty patients aged 18-60 years, ASA PS 1 and 2 posted for elective surgeries requiring GA with endotracheal intubation were studied. Patients were randomized into two groups of 30 each (Group A and B), to receive either 0.6 mg/kg rocuronium bromide or 0.9 mg/kg rocuronium bromide. Intubating condition was assessed at 60 seconds. Onset and clinical duration were recorded and data analysed using independent sample t-test and chi-square analysis.* ***Results:*** *There was a significant difference in the intubating conditions between the groups (p=0.001) with 28 patients (93.3%) having excellent intubating conditions and 2 (6.6%) having good intubating conditions in Group B whereas 16 patients (53.3%) had excellent intubating conditions and 12 (40%) had good intubating conditions in Group A. None had inadequate conditions for intubation. There was significant difference (p<0.0001) between the mean clinical duration of NMB in group A (29.37 min ± 5.73 min) and Group B (50.10 min ± 6.69 min).* ***Conclusion:*** *We concluded that rocuronium bromide at 0.9 mg/kg provided good to excellent intubating conditions at 60 seconds but at the cost of prolonged duration of NMB. Whereas rocuronium bromide at 0.6 mg/kg provided adequate intubating conditions for RSI at 60 seconds and hence could be used at this dose in situations where succinylcholine is contraindicated and a shorter duration of NMB is preferred.*

Keywords: Rocuronium bromide, rapid sequence intubation, neuromuscular blockade, intubating conditions

INTRODUCTION

Rapid sequence intubation (RSI) is performed to secure the patient's airway rapidly and smoothly minimizing chances of aspiration of gastric contents. The conventional neuromuscular blocking drug (NMBD) still used in RSI is succinylcholine because of its quick onset of action and excellent muscle relaxation. However, it is associated with many adverse effects like myalgia, cardiac dysrhythmias, hyperkalaemia, increase in intragastrical, intracranial and intraocular pressures [1-5]. Succinylcholine is contraindicated in patients with major burns and major crush injuries (after 48 h), severe abdominal sepsis, denervation syndromes, and major nerve or spinal cord injuries. This is in account of the risk of hyperkalaemia due to its depolarizing action, possibly leading to fatal cardiac arrhythmias [6,7]. It is also contraindicated in patients with a history of malignant hyperthermia or previous allergic reaction [8]. Considering its potential to cause serious adverse effects, quests began for an alternative NMBD with a short onset of blockade to replace succinylcholine, especially in RSI. The onset time of rocuronium is shortest among all the available NMBDs [9,10]. It has minimal cardiovascular effects, [11,12] and histamine release [13]. Hence, it could be utilized in compromised patients in whom haemodynamic or other effects should be limited.

Dosage of rocuronium commonly used for RSI (≥ 3 ED95) causes rapid paralysis but the clinical duration is prolonged making it inappropriate for short duration surgeries. Theoretically, use of low doses of NMBDs shortens the time for recovery from neuromuscular blockade (NMB). The ED95 dose of rocuronium is 0.3 mg/kg. But intubating conditions may be compromised at low doses. Hence, we decided to study the intubating conditions of rocuronium bromide at 2 × ED95 dose (0.6 mg/kg) in comparison to 3 × ED95 dose (0.9 mg/kg).

The primary objective of the study was to compare the intubating conditions with 0.6 mg/kg and 0.9 mg/kg body weight rocuronium bromide at 60 seconds for RSI using criteria of Goldberg et al. The secondary objectives were to evaluate the clinical duration of NMB of 0.6 mg/kg and 0.9 mg/kg body weight rocuronium bromide and to compare the onset of NMB with 0.6 mg/kg and 0.9 mg/kg body weight rocuronium bromide.

MATERIALS AND METHODS

It was a prospective, randomized, controlled, double blinded study conducted at Lourdes hospital, Kochi, a tertiary care centre, after approval by the appropriate ethics committee and after obtaining informed written consent from the subjects. Study population consisted of 60 American society of anaesthesiologists physical status (ASA PS) 1, 2 patients between 18-60 years, posted for elective surgeries requiring general anaesthesia with endotracheal intubation. Patients with history of known neuromuscular-hepatic-renal diseases, those on drugs affecting NMB, those with allergy to the study drug, pregnant and patients with anticipated difficult airway were excluded.

After a standard preoperative evaluation, and relevant investigations 60 eligible and consenting patients were selected and Investigator A randomized the sample into two study groups using computer software (MedCalc 13.2.2) generated randomization method. Thus 30 patients each were allocated to Group A and Group B and were assigned a serial code. Investigator B prepared the drugs, who loaded Inj. rocuronium bromide at doses 0.6 mg/kg and 0.9 mg/kg body weight according to the study group labelled as Dose X and Dose Y respectively. Group A (n=30), received inj. rocuronium bromide at 0.6 mg/kg body weight diluted to 10 ml of normal saline, (Dose X) and Group B (n=30), received inj. rocuronium bromide at 0.9 mg/kg body weight diluted to 10 ml of normal saline, (Dose Y).

Investigator C who was blinded to the study group did direct laryngoscopy for all the patients and assessed the intubating conditions as per Goldberg criteria to standardize the grading. Data regarding intubating conditions, onset and clinical duration were collected in predefined pro forma from each patient identified only by his/her serial code and was subjected to statistical analysis comparing Dose X versus Dose Y administered to Group A and Group B respectively. The identity of the drug doses was revealed to the investigator only after the statistical study was completed.

After OR preparation, patients were shifted with a working 18G I.V cannula. In addition to standard monitoring including ECG, Non-invasive blood pressure, end-tidal CO_2 ($ETCO_2$) and oxygen saturation using pulse oximeter, neuromuscular monitor to assess adductor pollicis response to train of four (TOF) stimulus was attached. Calculated doses of inj. fentanyl (2 µg/kg), inj. glycopyrrolate (0.004 mg/kg) and inj. midazolam (1 mg) were administered 5 min prior to induction. All patients were pre-oxygenated with 100% O_2 using Bain's circuit and anatomical face mask for 3 min before induction. Modified rapid sequence induction [14] with calculated dose of propofol 2 mg/kg was carried out and ability to bag and mask confirmed. We used a fixed dose of propofol to avoid any confounding effects on intubating conditions.

After confirming loss of consciousness, a control response to a supramaximal single twitch stimulus was obtained. Group A received rocuronium bromide 0.6 mg/kg (Dose X) and Group B received rocuronium bromide 0.9 mg/kg (Dose Y). Time of administration of the drug was recorded. Investigator C performed direct laryngoscopy at 60 seconds (s) using laryngoscope with Macintosh blade and intubated the patient with well lubricated appropriate sized endotracheal tube. Anaesthesia was maintained with air, oxygen (at a 1:1 ratio) and isoflurane. We monitored NMB by visual and tactile evaluation of the evoked mechanical response of adductor pollicis muscle to TOF stimulus given at an interval of 10 seconds. Patient was continuously mechanically ventilated to maintain a target $ETCO_2$ of 35 mm of Hg. Adequate warming measures were taken to prevent hypothermia. At the end of procedure all patients were reversed with inj. neostigmine 0.05 mg/kg and inj. glycopyrrolate 0.01 mg/kg body weight (Tables 1 and 2).

Table 1 Grading of intubating conditions

Score	Ease of laryngoscopy	Vocal cords	Intubation response

1	Good	Open full	None
2	Fair	Open midway	Diaphragmatic movement
3	Difficult	Moving	Moderate coughing
4	Poor	Closed	Severe coughing

This gives a total point value of 12 with 3 representing excellent, 4 to 6 represents good, 7 to 9 represents poor and 10 to 12 represents inadequate intubating conditions.

The time of onset of blockade was determined by noting the time in seconds from administration of drug to TOF count of 0. Clinical duration of blockade, which was taken as the time in minutes from abolition of all four twitches to return of first twitch in TOF sequence, was also recorded. Data was collected, tabulated, coded, and then analysed using IBM SPSS® software version 22.0.0 with independent sample t-test for comparison of means of age, weight, onset and clinical duration and Chi-square analysis for comparison of gender, ASA PS and intubating conditions.

RESULTS

Table 2 Demographic parameters

Patient characteristics	Group A (n=30)	Group B (n=30)	p-value
Age (years)	40.63 ± 7.23	37.43 ± 9.78	0.155*
Sex (male/female)	13/17	14/16	0.795*
Body weight (kg)	65.17 ± 10.99	62.20 ± 7.89	0.235*
ASA PS 1/2	15/15	20/10	0.190*
Values expressed as mean ± SD. ASA PS- American Society of Anaesthesiologists Physical Status; n- Number of patients; SD- Standard deviation; * Not significant			

The two groups were homogenous and comparable with respect to age, sex, body weight and ASA PS with no significant statistical difference with respective p-values (p>0.05).

Ease of laryngoscopy

All the patients in group A and 28 patients (93.3%) in group B had a well relaxed jaw facilitating easy laryngoscopy. The difference was not statistically significant with p>0.05. Laryngoscopy was difficult in none of the patients in both groups.

Vocal cord status

Twenty patients (66.7%) in Group A had vocal cords in fully apart position when compared to 30 patients (100%) in Group B. Eight patients had vocal cords in open mid-way position and 2 patients had moving vocal cords in Group A. None of them had closed vocal cords. There is statistically significant difference in the status of vocal cords between the two groups (p=0.001).

Response to intubation

Nine patients (30%) in Group A had diaphragmatic movement on intubation compared to 2 patients (6.67%) in Group B. There is statistically significant difference in response to intubation among the two groups with p=0.042. None of the patients in both groups had moderate or severe coughing/bucking response to intubation.

Intubating conditions

In Group B, 28 patients (93.3%) had excellent intubating conditions with relaxed jaws allowing an easy laryngoscopy, fully open cords and no coughing/bucking or diaphragmatic movement on intubation. The remaining 2 patients (6.6%) had good intubating conditions (score of 4) with easy laryngoscopy, fully open cords but slight diaphragmatic movement on intubation. In Group A, 16 patients (53.3%) had excellent intubating conditions. Twelve patients (40%) fell into the good intubating condition group among which 8 had vocal cords at open midway position and 6 had slight diaphragmatic movements. Two patients (6.6%) had poor intubating conditions with slight vocal cord movement. But none of the patients had inadequate conditions for intubation. P=0.001 (<0.05) indicates statistically significant difference in the intubating conditions between the two groups.

Comparison of onset

The mean onset of NMB in group A patients who received 0.6 mg/kg of rocuronium bromide was 101.53 s ± 20.84 s in comparison with 78.27 s ± 13.04 s in group B who received 0.9 mg/kg of rocuronium bromide. $p<0.0001$ indicates high level of statistical significance.

Comparison of clinical duration of NMB

The mean clinical duration of NMB in group A patients received 0.6 mg/kg body weight of rocuronium bromide was 29.37 min ± 5.73 min when compared to mean duration of 50.10 min ± 6.69 min in group B who received 0.9 mg/kg body weight of rocuronium bromide. The difference is highly significant statistically with $p<0.0001$.

DISCUSSION

The dose of NMBD is usually determined in terms of ED95 value. ED95 is the dose of a relaxant needed to produce 95% depression of a single twitch response. Employing multiples of ED95 has been suggested as a technique to improve relaxation and hasten the onset of action of NMBD [15]. Classical RSI technique involves securing the airway within one minute of administration of muscle relaxant which demands a quick onset of NMB.

Rocuronium bromide at ≥ 3 × ED95 creates excellent intubating conditions but with a disadvantage of prolonged duration [9]. Hence, we conducted a study comparing the intubating conditions between 3 × ED95 and 2 × ED95 doses of rocuronium bromide at 60 s.

Intubating conditions

We found excellent or good intubating conditions with 0.6 mg/kg rocuronium at 60 s in 28 (93.3%) subjects. This finding corroborates with the study by Cooper et al. [16] who reported excellent or good intubating conditions in 95% of cases. Our observation was also in concurrence with studies by several other previous authors [17-22] all of whom had obtained similar conditions in 100% of the study population. We observed excellent intubating conditions in 16 of our subjects (53.3%) which is in accordance with previous studies [22-24]. Good intubating conditions were found in 12 cases (40%) which are similar to the results obtained by Crul et al. [22] and McCourt et al. In 2 of or subjects (6.6%) we found poor intubating conditions, concurrent with results of Cooper et al. [16], with slight vocal cord movement. In contrast, 25% of patients in the study by McCourt et al. [23] and 20% of patients in a study by Aparna Shukla et al. [24] had poor intubating conditions. Both these authors had used thiopentone sodium as the induction agent which causes less suppression of laryngeal reflexes than propofol [25], which might have increased the incidence of vocal cord movements.

Table 3 Intubating conditions with 0.6 mg/kg rocuronium bromide

Authors	Excellent	Good	Poor	Inadequate
Puhringer (n=20) [17]	17 (85%)	3 (15%)	-	-
Magorian (n=10) [20]	10 (100%)	-	-	-
Cooper (n=20) [16]	13 (65%)	6 (30%)	1 (5%)	-
Crul (n=20) [22]	10 (50%)	10 (50%)	-	-
Fuchs-Buder (n=35) [19]	29 (83%)	6 (17%)	-	-
Naguib (n=10) [18]	7 (70%)	3 (30%)	-	-
McCourt (n=57) [23]	16 (28%)	27 (47%)	14 (25%)	-
Aparna Shukla (n=20) [24]	10 (50%)	6 (30%)	4 (20%)	-
Present study (n=30)	**16 (53.3%)**	**12 (40%)**	**2 (6.6%)**	**-**

In patients who had received 0.9 mg/kg rocuronium we noted that 28 subjects (93.3%) had excellent intubating conditions with remaining 2 patients (6.6%) having good intubating conditions. Good or excellent intubating conditions were obtained in 100% of cases in studies by several previous investigators [18-20,22,26]. using 0.9 mg/kg of rocuronium bromide. None of the patients had poor intubating conditions. This was in contrast to study by McCourt et al. [23] who had used thiopentone sodium at 5 mg/kg as the induction agent (Tables 3 and 4).

Table 4 Intubating conditions with 0.9 mg/kg rocuronium bromide

Author	Excellent	Good	Poor	Inadequate
Magorian (n=10) [20]	8 (80%)	2 (20%)	-	-
Crul (n=19) [22]	17 (89.5%)	2 (10.5%)	-	-

Fuchs-Buder (n=35) [19]	33 (94%)	2 (6%)	-	-
Naguib (n=10) [18]	10 (100%)	-	-	-
Weiss (n=45) [26]	38 (84.4%)	7 (15.5%)	-	-
McCourt (n=55) [23]	32 (58.2%)	20 (36.3%)	3 (5.5%)	-
Present study (n=30)	**28 (93.3%)**	**2 (6.6%)**	**-**	**-**

Onset

Our observation pertaining to the onset of action of rocuronium bromide at 0.6 mg/kg is concurrent with those obtained in previous studies [14,17,20,21,23,27,28] as shown in Tables 5 and 6. Again, Cooper [16] had obtained a shorter onset probably due to the confounding effect of halothane.

Table 5 Onset of action of rocuronium bromide at 0.9 mg/kg

Author	Onset of action in seconds
Cooper (n=20) [16]	45.5 ± 11.05
Magorian (n=10) [20]	75 ± 28
Fuchs-Buder (n=35) [19]	118 ± 23
Hemmerling (n=45) [27]	99 ± 31
Present study (n=30)	**78.27 ± 13.04**

In our study, we observed the onset of action of 0.9 mg/kg of rocuronium bromide to be 78.27 s ± 13.04 s which corroborates with studies by Magorian [20], Hemmerling [27] and Fuchs Buder T [19] Contrasting result was found in the study by Cooper [16] in which patients were maintained on 0.5% to 0.75% halothane following induction prior to administration of muscle relaxant. Inhalational agents have been found to interact and potentiate effect on nondepolarizing muscle relaxants at neuromuscular junction [29-33].

Table 6 Onset of action of rocuronium bromide at 0.6 mg/kg

Authors	Onset of action (Seconds)
Puhringer (n=20) [17]	72 ± 30
Cooper (n=20) [16]	58.5 ± 12.95
Magorian (n=10) [20]	89 ± 33
Abouleish (n=40) [28]	98.1 ± 9.4
Hemmerling (n=45) [27]	145 ± 48
Schlaich (n=30) [21]	136 ± 35
Aparna Shukla (n=20) [24]	80.1 ± 5.42
Ramkumar (n=25) [14]	156 ± 54.5
Present study (n=30)	**101.5 ± 20.85**

Intubating conditions are more dependent on the degree of NMB at the laryngeal adductors than that at the adductor pollicis [29]. Total NMB of the larynx or diaphragm may not be necessary for acceptable intubating conditions. The onset of NMB is much quicker in the muscles that are required to achieve good intubating conditions, than in the usually monitored muscle [9]. Just two of our subjects had some amount of vocal cord movement during intubation. Six patients had slight diaphragmatic movement as intubation response. Since diaphragm is one of the most resistant muscles to both depolarizing and nondepolarizing NMBD it requires 1.4 to 2.0 times the dose of muscle relaxant when compared to adductor pollicis for a similar degree of NMB [30].

Duration of action

We used recovery to first twitch response to TOF stimulus as the endpoint to clinical duration as employed by Cooper et al. [16] and Ramkumar et al. [14]. We obtained clinical duration ranging from 20 min to 44 min when 0.6 mg/kg rocuronium bromide was used which concur with the studies of previous authors [14,16-21,23,27,32,34] as summarized in Tables 7 and 8.

Table 7 Clinical duration of action of rocuronium bromide at 0.6 mg/kg

Authors	Duration of action (minutes)
Friedrich K Puhringer (n=20) [17]	25.3 ± 5.0
Huizinga (n=30) [34]	24 ± 4

Toni Magorian (n=10) [20]	37 ± 15
Cooper (n=20) [16]	34 ± 7.4
Fuchs Buder (n=35) [19]	21 ± 4
Naguib (n=10) [18]	23.7 ± 5.1
Hemmerling (n=45) [27]	35 ± 12
Schultz (n=60) [32]	28.2
Schlaich (n=30) [21]	38 ± 10
Aparna Shukla (n=20) [24]	30.8 ± 3.17
Ramkumar (n=25) [14]	48 ± 19.75
Present study (n=30)	**29.37 ± 5.7**

Table 8 Clinical duration of action of rocuronium bromide at 0.9 mg/kg

Authors	Duration of action in minutes
Magorian (n=10) [20]	53 ± 21
Cooper (n=20) [16]	54.5 ± 9.2
Fuchs-Buder (n=35) [19]	34 ± 11
Naguib (n=10) [18]	36.4 ± 7.4
Hemmerling (n=45) [27]	53 ± 22
Schultz (n=60) [32]	41.6
Present study (n=-30)	50.1 ± 6.7

On evaluating the clinical duration of action of 0.9 mg/kg rocuronium bromide the value obtained was in accordance with results obtained by previous investigators [16,18-20,27,32].

We observed that even though rocuronium bromide at a dose of 0.9 mg/kg provided excellent intubating conditions in 93.3% of subjects, it has a statistically significant prolongation of duration of action compared to that at 0.6 mg/kg. This is a definite disadvantage in terms of prolonged apnoea time and in the context of short duration surgeries, sugammadex still not being available in our scenario.

CONCLUSION

We concluded that rocuronium bromide at 0.9 mg/kg provided good to excellent intubating conditions at 60 s but at the cost of prolonged duration of NMB. Rocuronium bromide at 0.6 mg/kg provided adequate intubating conditions for RSI at 60 s. Hence it could be employed at this dose in situations where succinylcholine is contraindicated and a shorter duration of NMB is preferable like in short duration surgeries, provided a difficult airway is not anticipated.

CONFLICT OF INTEREST

None declared.

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