Clinical Investigation

Effects of pretreatment with different neuromuscular blocking agents on facilitation of intubation with rocuronium: A prospective randomized comparative study

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ABSTRACT

Background and Aims: Priming principle refers to administration of a small dose of non-depolarising blocker, which when followed by a large intubating dose produces a relatively rapid and profound blockade to ensure suitable conditions for endotracheal intubation. We aimed to compare the effects of rocuronium, vecuronium, and atracurium as "pretreatment" drugs on intubating conditions with rocuronium facilitated endotracheal intubation. **Methods:** This double-blinded, randomised controlled prospective study was carried out at a tertiary health care hospital on patients undergoing surgical procedures under general anaesthesia. They were randomly allocated into three groups ($n = 35$) by computer generated randomisation chart to receive either rocuronium (0.06 mg/kg body weight) (Group A); vecuronium (0.01 mg/kg body weight) (Group B) or, atracurium (0.05 mg/kg body weight) (Group C), followed by intubating dose (0.6 mg/kg body weight) of rocuronium. The haemodynamic parameters and intubating conditions were studied and statistically analysed by ANOVA test and Student's *t*-test as applicable using statistical package for the social sciences 16.0 for windows (SPSS Inc., Chicago, IL, USA). **Results:** Excellent intubating conditions were noted in maximum number of patients in Group C (97.41%). No significant differences were observed in the systolic blood pressure in all the three groups at all-time intervals. The mean arterial pressure rose significantly from baseline value to maximum, at '0' min in all the groups; however, no significant difference was observed amongst the groups ($P > 0.05$). **Conclusion:** Pretreatment with rocuronium bromide can facilitate endotracheal intubation in 60 s irrespective of non-depolarising muscle relaxants used for priming; however, it cannot attenuate haemodynamic changes associated with laryngoscopy and intubation.

Key words: Atracurium, intubating condition, pretreatment, rocuronium, vecuronium

INTRODUCTION

Various techniques have been formulated to obtain favourable conditions for intubation and one such technique is the priming technique. Priming principle refers to administration of a small dose of non-depolarising blocker which when followed by a large intubating dose after 2-4 min produces a relatively rapid and profound blockade to ensure a suitable condition for endotracheal intubation.[1] The theory behind this principle is that a small dose of non-depolarizing agent can block large number of acetylcholine receptors at the neuromuscular junctions (NMJ) before appreciable clinical reduction in neuromuscular transmission. The second larger dose blocks the remaining receptors and effects more rapid onset of intubating conditions. When using the priming principle to accelerate the onset of neuromuscular blockade, the initial dose should not exceed 10% of the drug's ED95.[2]

The priming technique is considered clinically superior to the bolus method and is preferred in

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all elective cases and in those patients in whom succinylcholine is contraindicated.[3] The effects of pretreatment of three different non-depolarising muscle relaxants, rocuronium, vecuronium and atracurium on the facilitation of endotracheal intubation with rocuronium are compared as also the haemodynamic changes and adverse effects, if any.

METHODS

A double-blinded, randomised controlled prospective study was conducted at a tertiary health care hospital between September 2010 and August 2012. After obtaining approval by the Institutional Ethics Committee, 105 patients of American Society of Anaesthesiologists physical status I and II aged between 20 and 60 years, both sexes, undergoing surgeries under general anaesthesia, were selected. Patients with renal diseases, hepatic diseases, neurological disorders and neuropathies, cardiovascular diseases and respiratory problems with anticipated airway difficulties, any known allergy to study drugs were excluded from the study.

Based on previous studies,[4] it was calculated that a sample size of 28 patients would be required per group to demonstrate a clinically significant difference among the groups for improving intubating conditions, at $\alpha = 0.05$ with a power (1-β) of 80%. In order to improve the weight of the results, of the study, 35 patients were enrolled for each group. Patients were randomly allocated into three groups by computer generated randomisation chart to receive the drugs during the study as follows: Group A ($n = 35$) - rocuronium (0.06 mg/kg body weight), Group B ($n = 35$) - vecuronium (0.01 mg/kg body weight) and Group C ($n = 35$) - atracurium (0.05 mg/kg body weight).

On arrival at the operation theatre, the patients were connected to the monitors for measuring the heart rate (HR), blood pressure (BP), electrocardiogram, peripheral oxygen saturation (SpO_2), and the baseline values of these variables were recorded. For neuromuscular monitoring, a peripheral nerve stimulator (Train of Four watch®-Organon Infar, Netherland) was used.

Then, a priming dose of the test drug (10% of the ED95), which was prepared and loaded in a syringe by an assistant not involved in the assessment, was administered. This was followed by preoxygenation with 100% oxygen over 2 min and the anaesthesia was induced with injection thiopentone sodium until the loss of eye lash reflex. 90% (0.54 mg/kg body weight) of the calculated intubating dose (0.6 mg/kg body weight) of rocuronium was administered to facilitate endotracheal intubation. The ulnar nerve was stimulated percutaneously at the wrist joint immediately after administering the intubating bolus dose. The electromagnetic response of single twitch contractions (0.1 Hz) of adductor pollicis muscle obtained by stimulation of ulnar nerve with supra maximal stimulus of 0.2 ms duration was recorded.

Oxygenation was continued and endotracheal intubation was attempted at 60s from the end of rocuronium injection. The single twitch height was first recorded immediately after the administration of the intubating dose of rocuronium and at the end of 60s; another single twitch response was recorded. The intubating condition was assessed by the scale of Cooper *et al*.,[5] consisting of a total score of 9 in relation to jaw relaxation, condition of the vocal cords and response to intubation, which are graded as excellent (if score is 8-9), good (if score is 6-7), fair (if score is 3-5) and poor (if score is 0-2]). After successful intubation, a uniform anaesthetic technique was followed in all the patients. Vital haemodynamic parameters were recorded at 0, 1, 2, 3, 4, 5 and 10 min following intubation. '0' minute was defined as the point of time where the remaining 90% of the intubating dose of rocuronium was administered following the priming dose. Patients were extubated after the return of airway protective reflexes and monitored in post anaesthetic care unit (PACU) before transfer to the PACU.

The parameters and patient data were recorded and entered in Microsoft Excel sheet (Microsoft Office 2007 Professional) and compared among the three groups using ANOVA test for categorical variable, Student's *t*-test for continuous variables, and $P \leq 0.05$ was deemed significant. Statistical package for social sciences (SPSS) for Windows version 16.0 software, Chicago, SPSS Inc. was used for statistical analysis.

RESULTS

The age, weight, and sex distribution of the three groups were uniform and comparable [Table 1]. The HR [Figure 1] rose from the baseline value reaching its maximum value at 1 min and thereafter receded even though it did not come down near the baseline value in all three groups. The three groups when compared showed no significant difference in HR at different time intervals ($P > 0.05$).

The systolic blood pressure (SBP) in all the three groups rose from the baseline value reaching its maximum in the '0' min even though the rise was highly significant throughout all the time intervals [Figure 2]. The values reached the baseline at 10th min. The changes in SBP when the three groups were compared by F test at different time intervals showed no significant difference ($P > 0.05$). The variation in SBP from the baseline value till the first 5 min was significant within all three groups.

The changes in the mean arterial BP [Figure 3] followed the same trend as that of SBP. The rise was maximum in the '0' min in all the three groups and declined till '10' min but baseline wasn't reached even at '10' min. The three groups when compared together at different time intervals showed no significant differences (not statistically significant) among the groups.

Single twitch height measured just before the intubation (T2) showed significant change when compared with baseline (T1), noted immediately after administration of intubating dose of rocuronium in all the three groups as shown in Table 2. When the twitch heights were compared in between the groups, significant difference was noted only between the twitch heights at intubation, of Groups B and C.

Grading of the quality of intubating conditions is shown in Table 3. Maximum number of 'excellent intubating conditions' was observed in Group C. Intubating conditions were excellent in 85.71%, 88.57%, and 97.14% in Groups A, B, and C respectively. Fair intubating conditions were seen in only 1 patient from Group A.

DISCUSSION

Since the first report of the priming principle as a method to accelerate the onset of neuromuscular block as well as to provide excellent intubation conditions, many investigations directed to optimise the priming technique have been performed. Several workers[6,7] used small doses of vecuronium (0.015 mg/kg) and proved that administration of vecuronium in divided doses gave satisfactory intubating conditions in majority of patients. Recently Rao *et al*.[8] proved that priming with rocuronium provides excellent intubating conditions in <60s with no adverse effects.

Table 1: The distribution of patient's demographic profile in three groups

Patient's parameter	Group A	Group B	Group C
Age in years (mean±SD)	34.91±10.66	39.77±10.36	39.40±10.90
Body weight in kg (mean±SD)	50.97±8.23	53.89±8.84	53.34±9.01
Sex (male:female)	10:25	11:24	17:18

P>0.05; not significant. SD – Standard deviation

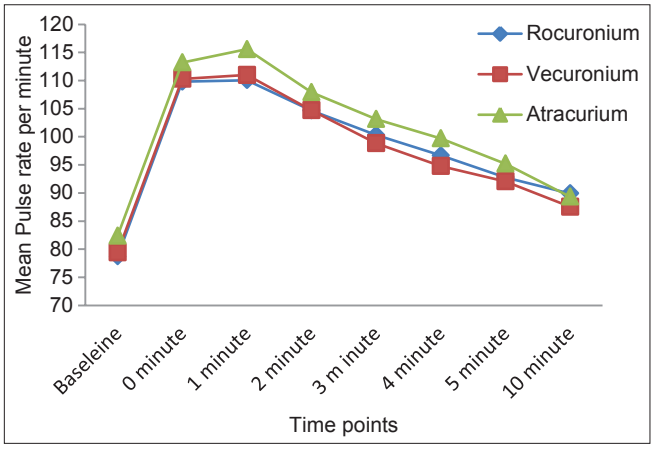

Figure 1: The distribution of pulse rate (rate per minute) in the three groups at different time intervals

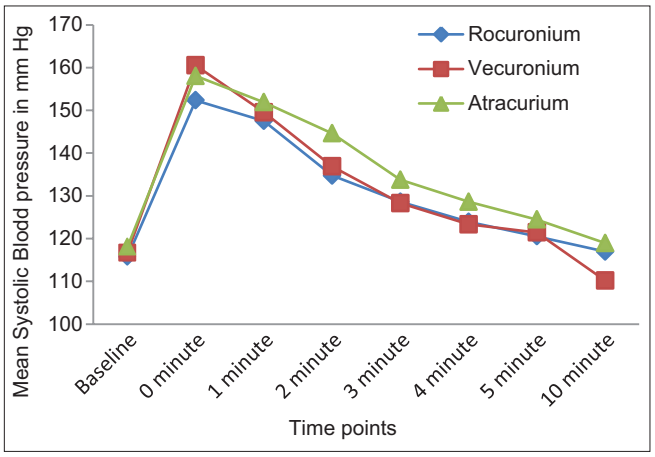

Figure 2: The distribution of systolic blood pressure (in mmHg) in the three groups at different time intervals

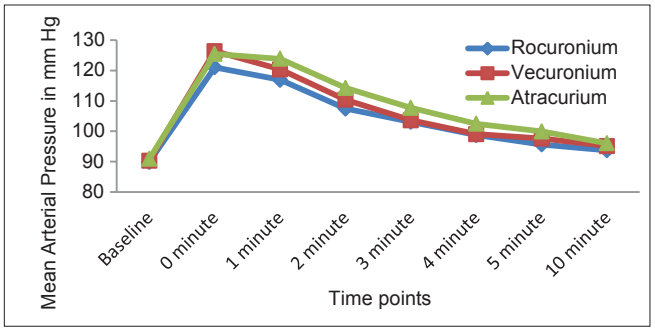

Figure 3: The distribution of mean arterial pressure (in mmHg) in the three groups at different time intervals

Table 2: The distribution of single twitch height in the three groups

Group	Mean±SD	*t* value	*P* value
Group A			
T1	102.77±30.83	13.33	0.000
T2	35.37±24.97		
Group B			
T1	92.94±32.45	12.45	0.000
T2	28.23±20.00		
Group C			
T1	100.51±32.88	10.65	0.000
T2	40.80±25.79		

T1 – Immediately after administration of intubating dose of rocuronium;
T2 – After 60s of administration of intubating dose of rocuronium;
SD – Standard deviation

Table 3: The distribution of intubating condition level-wise in the three groups

Intubating condition (scores)	Group A (%)	Group B (%)	Group C (%)	χ^2 value	*P* value
Poor (0-2)	0	0	0	4.27	0.37
Fair (3-5)	1 (2.85)	0	0		
Good (6-7)	4 (11.42)	4 (11.42)	1 (2.85)		
Excellent (8-9)	30 (85.71)	31 (88.57)	34 (97.14)		
Total	35	35	35		

Group A – Rocuronium; Group B – Vecuronium; Group C – Atracurium

The synergistic effect of rocuronium when combined with itself or with various other non-depolarizing muscle relaxants have been observed in priming studies.[9] In a retrospective study by Patanwala *et al*.,[10] first attempt successful intubation with rocuronium (72.6%) and succinylcholine (72.9%) were similar. In this study, surprisingly, 100% first attempt successful intubations were seen 60s after administering the bolus dose. The least possible dose of rocuronium (0.6 mg/kg) was used as bolus for intubation as against higher doses used by some studies and excellent intubating conditions were achieved. Kopman *et al*.[2] were of the opinion that, when using the priming principle to accelerate the onset of neuromuscular blockade, the initial dose shouldn't exceed 10% of the drug's ED95. Schwarz *et al*.,[6] Van Aken *et al*.,[7] Taboada *et al*.,[11] Naguib *et al*.[12] respectively used 0.015 mg/kg vecuronium, 0.015 mg/kg vecuronium, (0.01 mg/kg) vecuronium and 0.05 mg/kg atracurium as priming doses. Accordingly, the priming dose used in this study was guided by the above mentioned studies. Though the onset time was not studied, the priming interval of 3 min was adopted as done by Yavascaoglu *et al*.[13] and endotracheal intubation performed 60s after the bolus dose. This is a shorter priming interval when compared with that of Tripathi and Pandey *et al*.[14] who advocated a priming interval of not <5 min. Takaya *et al*.[15] used a 4-6 min. priming interval and Naguib *et al*.[16] accomplished intubation 90 s after the intubating dose.

Several workers[17,18] explained the entropy suppression and haemodynamic stability respectively provided by rocuronium at optimum doses and was hailed as the drug of choice with optimum dose and a preferable drug for intubation for avoiding the side effects of succinylcholine. Wierda *et al*.[19] observed limited increase in HR without change in MAP and attributed this effect to the weak vagolytic activity of rocuronium. In the present study, there was statistically insignificant change in MAP in the three groups at all-time intervals. However, statistically significant but clinically insignificant increase in MAP at 0 and 1 min was observed. This increase in MAP at 0 min could be due to the haemodynamic responses induced by rocuronium injection pain,[20] and the increase at 1 min could be due to the sympathetic stimulation produced due to laryngoscopy and intubation.[21] Simultaneously, there were no statistically significant differences in the HR, even though it increased from the baseline value in all the groups till the 3rd min. This rise in HR following intubation as found in all the groups may be the result of the usual responses to laryngoscopy and intubation. Even though the study of haemodynamic changes was not the primary aim, it was studied as a secondary outcome of the study, and we observed an increase in haemodynamic parameters at various time intervals in all the three study groups after the bolus dose of rocuronium. These findings are in concurrence with the study of Verma *et al*.[21]

No significant differences were observed between the quantitative values of each component of intubating score in the present study. All the patients could be intubated at 1 min after the bolus dose of rocuronium was given. This is in agreement with the study by Cooper *et al*.[5] who explained the rapid onset of neuromuscular block to be due to the low potency of rocuronium, which results in a high molecular load being present at the NMJ, producing an initial high concentration gradient and transfer of molecules of the drug to the biophase. Similar findings were observed by different workers[8,13,22] and this could be because of the fact that when rocuronium is combined in equipotent doses with other non-depolarizing agent, it acts synergistically in the early part of blockade.

Though statistically insignificant, establishment of excellent intubating conditions in 97.14% of patients

in atracurium primed group as against 88.57% vecuronium and 85.71% rocuronium primed group may suggest a greater synergism between two drugs belonging to structurally different groups-atracurium being a non-steroidal benzylisoquinolone compound and rocuronium a mono quaternary steroid.

Though single twitch response was recorded just before intubation, it was not used as the guiding parameter. The baseline twitch height was 98.74% (recorded after administering bolus dose) and 34.80% just before intubation. Intergroup comparison showed significant difference only between the single twitch response recorded in vecuronium and atracurium groups just before intubation. However, when the intubating grades were compared, more number of patients in the atracurium primed group had excellent intubating conditions. Withdrawal response was seen in 3, 2 and 1 patient in rocuronium, vecuronium and atracurium groups respectively. This could be attributed to the pain on rocuronium injection. A study by Borgeat and Kwiatkowski[23] has shown that injection of rocuronium is associated with severe, burning pain of short duration responsible for spontaneous movements in the arm observed after induction of anaesthesia. However, intubating conditions were excellent in all these patients.

Priming technique alleviated the withdrawal responses associated with intravenous administration of rocuronium as only 6 patients (0.05%) showed withdrawal response to rocuronium injection. This is in agreement with the study by Lee *et al*.[24] who found similar results. No symptoms of muscle weakness were observed which may be compared with the findings of Abdulatif *et al*.[4] There were a few limitations in this study which included the following: The priming effect of the various agents could have been assessed at a shorter point of time than the predetermined time of 60s. The pharmacokinetics of the agents along with the economical aspect of the study could have been assessed. The confounding effects of rocuronium injection and laryngoscopy and intubation on haemodynamic responses could have been further addressed.

CONCLUSION

There is a strong possibility that endotracheal intubation could have been successfully performed earlier than 60s as it is possible to do so when the intubating conditions were only 'good', a presumptive event which might have happened before the establishment of excellent conditions in almost 90% of cases at 60s. However, we were guided by the recommendation that intubation should be performed at 60s with rocuronium (0.6 mg/kg). Though the study did not prove a significant difference in intubating conditions among the three groups, it explains the efficacy of using priming principle for attaining excellent intubating conditions proved by numerous studies.

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Announcement

CALENDAR OF EVENTS OF ISA - 2014

Certain important dates are given here for the members. All the applications should be sent by registered post (with Acknowledgement Due)

Date	Name of the Award/Post	Application has to be sent to
30th June 2014	Bhopal Award for Academic Excellence	Hony. Secretary, ISA
15th August 2014	Prof. A. P. Singhal Life Time Achievement Award	Hony. Secretary, ISA
31st October 2014	Dr. (Mrs.) Rukmini Pandit Award - Publication format along with Conference Presentation Certificate	Hony. Secretary, ISA
31st October 2014	Y. G. Bhoj Raj Award - Best Review Article in IJA	Hony. Secretary, ISA
31st October 2014	Dr. Kop's Award	Chairman Scientific committee of ISACON with a copy to Hony Secretary ISA
27th November 2014	Dr. TN Jha Memorial & Dr. KP Chansoriya Travel grant	Hony. Secretary, ISA
27th November 2014	Late Dr. Venkata Rao Memorial Oration	Hony. Secretary, ISA
27th November 2014	Ish Narani Best Poster Award	Chairman Scientific Committee ISACON
28th November 2014	ISA GOLDCON QUIZ Competition	Chairman Scientific Committee ISACON
28th November 2014	Awards for 1. Best City Branch 2. Best State Branch 3. Best Metro Branch 4. Public Awarness Individual 5. Public Awarness City 6. Public Awarness State 7. Ether Day State 8. Ether Day City 9. Membership Drive % (State) 10. Membership Drive No.s (State) 11. Individual Drive	Hony. Secretary, ISA

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