Comparison of Intubating Conditions of Rocuronium Bromide and Vecuronium Bromide with Succinylcholine Using "Timing Principle"

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ABSTRACT

Background: Rapid and safe endotracheal intubation is of paramount importance in general anaesthesia. The aim of this study was to compare the intubating conditions of succinylcholine with rocuronium bromide and vecuronium bromide using "Timing principle". The timing principle entails administration of a single bolus dose of nondepolarizing muscle relaxant, followed by an induction drug at the onset of clinical weakness.

Patients & Methods: 75 patients were divided into three groups of 25 each. Patients allocated to Groups A and B received rocuronium 0.6 mg kg⁻¹ and vecuronium 0.12 mg kg⁻¹ respectively. At the onset of clinical weakness (ptosis), anesthesia was induced with propofol 2.5 mg kg⁻¹; intubation was accomplished after 60 seconds of induction agent in both groups. Patients in Group C received propofol 2.5mg kg⁻¹ followed by succinylcholine 2mg kg⁻¹ and their tracheas were intubated at 60s. Train of four count was assessed at adductor pollicis muscle using nerve stimulator at intubation and time to loss of TOF was observed. In group A and B, intubating conditions were assessed according to a grading scale and haemodynamic variables were compared at 1, 3 and 5 minutes after intubation.

Results: Intubating conditions were either excellent (84% in group A, 48% in group B and 88% in group C) or good (16% in group A, 48% in group B and 12% in group C) and only 4% pt had poor intubating conditions in group B. Patients were interviewed postoperatively, and all were satisfied with the technique of induction of anesthesia. Rocuronium and Vecuronium are haemodynamically stable drugs as compared to Succinylcholine.

Conclusion: Rocuronium 0.6 mg kg⁻¹ provides good to excellent intubating conditions at 60 s comparable to succinylcholine after the induction of anesthesia using the timing principle.

KEYWORDS: Rocuronium, Vecuronium, Timing Principle, Nerve stimulator

The ease with which endotracheal intubation is performed depends upon degree of muscle relaxation, depth of anaesthesia and skill of anaesthesiologist. One characteristic of the ideal muscle relaxant is a rapid onset of action. Succinylcholine reliably produces muscle relaxation within 60 seconds of its administration, but it can produce serious side effects and is contraindicated in certain patients. Different techniques that have been used to decrease the effective onset time of nondepolarizing muscle relaxants include priming and the administration of large doses. A technique that uses the “timing principle” has been applied to rapidly produce good intubating conditions. When this technique is used, a single bolus dose of a muscle relaxant is administered, and anesthesia is induced at the onset of clinical weakness. In this way, the time from the induction of anesthesia to complete muscle relaxation is reduced, and the peak effect of the muscle relaxant and IV induction drug may more closely coincide. Rocuronium is a steroidal nondepolarizing muscle relaxant with an onset time (after 3-4 x the 95% effective dose) not different from that of succinylcholine. In this prospective, randomized, double-blind clinical trial, we evaluated the intubating conditions 60 s after the induction of anesthesia using Rocuronium and vecuronium with the timing principle, and compared them with those after the administration of succinylcholine and haemodynamic variables were compared at 1, 3 and 5 minutes after intubation.

PATIENTS AND METHODS

After obtaining institutional ethical committee approval and a written informed consent from seventy five patients aged 18-50 years of ASA Grade I and II, scheduled to undergo various surgeries under general anaesthesia were selected. Exclusion criteria were: increased risk of pulmonary aspiration, neuromuscular disease, Mallampatti grade III and IV, medications known to influence neuromuscular function, anticipated difficulty with airway management, and contraindications to succinylcholine. The patients were
divided randomly into three groups of 25 each as follows: 

GROUP-A - Patients received rocuronium bromide 0.6mg kg⁻¹ intravenously and anaesthesia was induced at the onset of clinical weakness using propofol 2.5mg kg⁻¹. 

GROUP-B - Patients received vecuronium bromide 0.12mg kg⁻¹ intravenously and anaesthesia was induced at onset of clinical weakness using propofol 2.5mg kg⁻¹. 

GROUP-C - Patients were induced with propofol 2.5mg kg⁻¹ followed by succinylcholine hydrochloride 2mg kg⁻¹. 

Baseline parameters like Pulse rate, SpO₂, systolic and diastolic blood pressure, heart rate, ECG, were noted. All patients received intravenous midazolam 0.04mg kg⁻¹ and Inj. Butorphanol 40 μg kg⁻¹ on arrival in the operating room. Patients were preoxygenated for 3 minutes. 

Patients allocated to group-A received rocuronium bromide 0.6mg kg⁻¹ intravenously over 5 seconds through rapidly running infusion placed in forearm. Patients were asked to keep their eyes open as long as possible and closely observed for first clinical signs of weakness, specifically, the onset of ptosis (furrowing of forehead). Time from injection of rocuronium bromide to onset of clinical weakness (in seconds) was recorded. At the onset of clinical weakness (ptosis), anesthesia was induced with propofol 2.5 mg kg⁻¹. Neuromuscular monitoring using train of four count at adductor pollicis muscle was commenced from time of loss of eyelash reflex using train of four (TOF) pattern of stimulation viz, supra maximal square wave stimuli applied to the ulnar nerve at the wrist at 2Hz for 2 seconds. The TOF stimulus was repeated at 12 second intervals until TOF count became 0 and this time was noted. In group-A TOF count at 60 second after administration of propofol was recorded and tracheal intubation performed by observer unaware of the group to which patient belonged. Time to loss of response to TOF stimulation. Patients in group-B followed similar procedure with vecuronium 0.12mg kg⁻¹ given instead of rocuronium. Patients in group-C were given propofol 2.5mg kg⁻¹ and intravenous succinylcholine 2mg kg⁻¹ was administered rapidly over 5 seconds. Sixty seconds after succinylcholine, tracheal intubation was performed by observer blinded to the procedure. TOF monitoring was not done in group C. 

Systolic BP, diastolic BP, heart rate and spo2 were recorded 1, 3 and 5 minutes after intubation and thereafter every 10 minutes throughout the surgical procedure in all the groups. 

Intubating conditions were assessed as excellent, good and poor according to grading scale described by International Consensus Conference held in Copenhagen in 1994 (Table no.1). Patients having difficult intubating conditions were managed according to difficult airway management protocol. 

Patients were interviewed by investigator who was blinded to study for following questions:- 

1. Did you feel weak or have any discomfort immediately before going to sleep for your operation? 
2. Did you feel short of breath immediately before going to sleep for your operation? 
3. Do you have pain in the muscles now? 

The data from the present study was systematically collected, compiled and statistically analyzed to draw relevant conclusions. 

Parameters like Age, Weight, Time to intubation, Time between relaxant and intubation were analyzed with Anova test. Intubating conditions, Train of four count at intubation were analyzed statistically with Chi-square test. Haemodynamics were analyzed with Anova with post hoc test and paired t test was used for- Time to onset of clinical weakness, Time to loss of Train of four. Differences were considered to be significant if p value was < 0.05, highly significant when p<.01, very highly significant when p<.001. 

**RESULTS**

There were no significant demographic differences among groups with respect to age, weight and sex (Table no 2). The mean and standard deviation of the time to onset of clinical weakness was 18.20±2.10 seconds and 40.64±5.15 seconds in the Group A and Group B respectively. The difference between the two groups were statistically significant with early onset in Group A as compared to Group B. 

The intubating conditions were graded as excellent in21 (84%), 12(48%) and 22(88%) and good in 4(16%), 12(48%) and 3(12%) patients of group A, B and C respectively (Table no 3). The difference was statistically significant between group A and B (p<0.05) and the group B and C (p<0.05) but not significant between A and C.
Poor intubating conditions were seen only in 1 case in B group.

Table 2
Table Showing Demographic Variables of Patients in Different Groups

| Parameter       | Group A (Rocuronium) | Group B (Vecuronium) | Group C (Succinylcholine) | P-value |
|-----------------|----------------------|----------------------|---------------------------|---------|
| Age (years)     | 35.24±9.39           | 35.92±8.63           | 32.88±9.62                | 0.478   |
| Weight (kg)     | 56.04±10.24          | 56.08±8.02           | 57.08±8.38                | 0.911   |
| Gender (Male/Female) | 7/18                | 10/15                | 12/13                     | NS      |

The train of four counts were recorded at the time of intubation in group A and group B. 12 patients in group A and 13 in group B failed to produce an acceptable level of neuromuscular blockade at the adductor pollicis but 3 patients in group A and none of the patient in group B had complete blockade at adductor pollicis respectively (Table no 4).

The time to loss of train of four was recorded and compared in Group A and B. Time to loss of train of four was significantly shorter (109.44±21.60 seconds) in Group A as compared to Group B (254.44±26.80 seconds) showing early onset in Rocuronium as compared to Vecuronium group (Table 5).

Heart rate, systolic and diastolic blood pressure were significantly more in all the three groups at 1 minute after intubation(p<.05). All the haemodynamic variables had decreased at 3 minutes after intubation in all groups. But at 5 minutes after intubation all the haemodynamic parameters had come near baseline in group A and B. The results between Group A and B are not statistically significant (p>.05) but on comparison with Group C in which all the parameters were significantly increased from baseline as p<.05 (Figure no. 1, 2, 3).

All patients were satisfied with the induction technique used in this study and none of them complained of any discomfort or shortness of breath during induction of anaesthesia. There was no complaint of muscle pain in the postoperative period in group A and B but 1 patient complained of muscle pain in group C.
DISCUSSION

Muscle relaxation is used to serve two purposes: one to facilitate endotracheal intubation and other to provide surgical relaxation. The ideal neuromuscular blocking agent is one which has brief duration of action, provides profound relaxation and is free from haemodynamic changes. Succinylcholine reliably produces muscle relaxation within 60 seconds of its administration, but it can produce serious side effects like hyperkalemia, malignant hyperthermia, bradycardia and cardiac dysrhythmias and is contraindicated in certain patients. As a result an alternative muscle relaxant suitable for intubation that has the same advantages of rapid onset and good to excellent intubating conditions as succinylcholine, but fewer side effects is desirable. Keeping this objective in mind we undertook this comparative study of rocuronium, vecuronium and succinylcholine in terms of intubating conditions and haemodynamic changes.

The time interval from the suppression of protective reflexes by induction, to accomplishment of intubation is a critical period, during which regurgitation and transbronchial aspiration of gastric contents can occur most frequently. Different techniques that have been used to decrease the effective onset time of nondepolarizing muscle relaxants include priming and the administration of large doses. A new technique that uses the "timing principle" has been applied to rapidly produce good intubating conditions with atracurium and rocuronium. When this technique is used, a single bolus dose of a muscle relaxant is administered, and anesthesia is induced at the onset of clinical weakness. In this way, the time from the induction of anesthesia to complete muscle relaxation is reduced, and the peak effect of the muscle relaxant and IV induction drug may more closely coincide.

In the present study, rocuronium administered in the dose of 0.6mg kg\textsuperscript{-1} using TIMING PRINCIPLE and tracheal intubation was performed at 60 seconds after induction with propofol provided intubating conditions that were excellent to good in all patients (21-excellent, 4-good) and this was comparable to succinylcholine 2mg kg\textsuperscript{-1} (22-excellent, 3-good) and the difference was statistically insignificant. None of the patient had poor intubating conditions with both the drugs. This is consistent with the study done by Seiber TJ et al who evaluated intubating conditions 45 and 60 seconds after administration of intravenous induction agent following rocuronium 0.6mg kg\textsuperscript{-1} in 45 patients who were randomly assigned to three groups. He concluded that rocuronium 0.6 mg kg\textsuperscript{-1} provides good to excellent intubating conditions 45 and 60 s after the induction of anesthesia using the timing principle.

In a study done by Koh KF et al atracurium when used with TIMING PRINCIPLE produced excellent to good intubating conditions which were comparable to succinylcholine group.

The mean onset time to clinical weakness was 18.2±2.10 seconds observed with rocuronium in our study. This time is consistent with a study by Nelson JM et al who after allowing a fixed 20 second delay b/w administration of rocuronium and thiopentone sodium, obtained intubating conditions 60 seconds after anaesthetic induction that were comparable with succinylcholine.

The mean onset time of clinical weakness in Vecuronium group in dose of 0.12mg kg\textsuperscript{-1} was 40.64±5.15s which was consistent with the study done by Koyama K et al in which the time after vecuronium administration to onset of clinical muscle weakness was 57.6 ± 7.8 sec in 0.15 mg.kg-1, and 42.2 ± 2.2 sec in 0.2 mg kg\textsuperscript{-1} group.

When the timing principle is used, the initial signs of clinical weakness precede loss of consciousness. A potential risk, therefore, is that patients would experience an uncomfortable feeling during the induction sequence. In our study, no patient demonstrated restlessness at the time when ptosis was observed. This suggests that patient satisfaction with the manner in which they went to sleep (in response to the postoperative questionnaire) was not because of amnesic effects of anesthetics, but because the degree of muscle weakness present was not associated with discomfort.

In the present study train of four was 4/4 in 12 patients in group A and 13 patients in group B showing inadequate neuromuscular blockade at adductor pollicis muscle at the time of intubation. This study is consistent with the results shown by Meistelman et al who showed that monitoring the adductor pollicis during onset of blockade to determine the time required for good intubating conditions could be misleading because paralysis of the adductor pollicis lags behind onset of neuromuscular blockade at the vocal cords. Donati et al showed that the onset of neuromuscular

![Figure 4](image_url)

Showing Changes in Diastolic Blood Pressure at 1, 3 and 5 Minute after Intubation in Different Groups
block at the Adductor pollicis lags behind the onset at the laryngeal adductor muscles\(^{11}\).

Koh and Chen\(^{11}\) also used ptosis (rather than handgrip strength) as the marker for the onset of clinical weakness, postulating that onset time for neuromuscular block at levator palpebrae superioris would be similar to that in orbicularis oculi and, therefore, that in the diaphragm\(^{7}\).

Employment of the timing principle necessarily implies that anaesthesia is induced only at the onset of clinical weakness. This might result in patients experiencing breathing difficulties or discomfort due to partial weakness just before they become unconscious. This problem has been circumvented by pretreatment with 0.03 to 0.06 mg kg\(^{-1}\) of midazolam or 1µg kg\(^{-1}\) of fentanyl prior to administration of muscle relaxant. A combination of midazolam and fentanyl was also found to be effective in avoiding patient discomfort. Our choice of combination of 0.04mg kg\(^{-1}\) of midazolam and 40µg kg\(^{-1}\) of Butorphanol at the start of preoxygenation to provide patient comfort was successful as no patient complained of pain on injection, discomfort, shortness of breath or weakness prior to becoming unconscious.

In our study in concern of haemodynamics, in group A, B and C the haemodynamics were increased at 1 minute after intubation due to stress response of intubation but the heart rate, systolic Blood pressure and diastolic Blood pressure in group A and B returns back to baseline at 5 minutes but not in Group C showing that rocuronium and vecuronium when used with TIMING PRINCIPLE produces minimal circulatory changes and are haemodynamically stable drugs as compared to Succinylcholine which shows increase in all the parameters at 5 minute and this change was statistically significant. This was consistent with a study done by Koyama et al\(^{12}\) who also observed that increase in systemic blood pressure, heart rate and rate pressure product were significantly lower in patients in timing principle group than in those in SCC group. Intubating conditions were almost excellent in both groups, and there were no complications in this study.

To conclude using the TIMING PRINCIPLE with rocuronium bromide 0.6mg kg\(^{-1}\) produces intubating conditions that are comparable to succinylcholine hydrochloride 2mg kg\(^{-1}\). Rocuronium and vecuronium are haemodynamically stable drugs as compared to succinylcholine. So rocuronium may be considered a suitable alternative for succinylcholine especially in patients who are at risk of adverse effects of succinylcholine. Vecuronium is also a haemodynamically stable drug with no adverse effects but for its delayed onset of action cannot be considered as a better alternative to rocuronium and succinylcholine. Train of four count at adductor Pollicis muscle is not a good indicator of laryngeal muscle relaxation for intubation.

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